Author’s response to reviews

Title: The Prevalence and Correlates of High Aortic Stiffness in North China: a Community-based Study

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Author’s response to reviews: see over
Author's covering letter for initial submission

Title: Prevalence of arterial stiffness in North China, and associations with risk factors of cardiovascular disease: a community-based study

Authors:

Version: 1 Date: 13 September 2012

Comments: see over
Response to the reviewers:

First we would like to express our heartfelt thanks to the reviewers and editors for their hard work and valuable comments, which enable us to further our knowledge to a great extent and improve this manuscript.

In this text, we write our responses in cyan color.

Response to the Reviewer 1

- Wang JW et al. evaluated the prevalence and correlates of high baPWV in a community-based study of North China. The strength of this study is the large sample size. However, previous studies have clearly shown the determinants of increase baPWV in various populations, such as old age, SBP, diabetes…. Hence, although this study provides the cutoff values of baPWV in identifying patients with high baPWV in different age groups in North China, the clinical novelty in this study may be limited.

Besides the strength based on the large sample size, the present study has several points of novelty. Firstly, this study is the first epidemiological study designed specially on the prevalence of high baPWV and its determinants based on Chinese general community-based populations. It is true that several previous studies have indicated the determinants of increased baPWV in some populations. They were, however, limited by the highly characteristic study subjects, such as those with old age, diabetes, or coronary heart disease. Furthermore, none of previous studies provided adequate information of baPWV in general Chinese population. We therefore performed such a study and tried to explore these areas. Secondly, in this study, the cutoff values of baPWV to identify people with high baPWV in different age groups were also calculated. It is meaningful not only in designing a further study in this area, but also to be used as a reference for studies based on other populations.

Last but not least, arterial stiffness has been an issue with great interest during the recent years. Many questions in this area are to be answered. Evidence and data are required to be accumulated on the basis of various populations, especially Chinese population, which is the largest in the world. Results yielded by the present study did provide new evidence and data based on Chinese community population, and contribute to clinical risk stratification. Just as what reviewer 2 said, data yielded by this study should help better identify potential risk factors associated with elevated baPWV.

- Although baPWV is highly associated with aortic PWV, baPWV is not a
substitute for aortic PWV, especially no comparison of baPWV and aortic PWV in this study. The authors should avoid the word of “aortic stiffness”. Direct use the terms of “baPWV” or “arterial stiffness” is more appropriate.

The authors much appreciate this useful comment and suggestion. Modifications have been made accordingly where needed in the revised version on page 1-3 and page 8-11.

- It is well known that renal function, nutrition and inflammation are the determinants of arterial stiffness. There are no eGFR, creatinine, hsCRP, and albumin data in this study.

Thanks for this comment.

Both renal dysfunction and elevated level of hsCRP have been proved to be predisposing factors of cardiovascular diseases. Also, previous studies have indicated that eGFR, creatinine, hsCRP are significantly associated with arterial stiffness. Up to now, however, association between plasma albumin level and arterial stiffness and/or baPWV has not been reported. The authors and co-workers understood that adding these variables into the investigation would enhance the strength of this study. However, considering the feasibility with regard to the limited funds and huge additional work in all twenty-three community centers, we finally did not require all participants to receive blood tests of eGFR, creatinine, hsCRP. The authors have described this concern in the limitations section.

In addition, the authors and co-workers have planned to involve more subjects and indices, including eGFR, creatine, hsCRP and etc., in the second part of this study, which is now at the beginning of data collecting stage. Hope our future reports would give an enhanced interpretation regarding these variables.

Response to the Reviewer 2

This interesting study investigated the distribution of brachial-ankle pulse wave velocity (baPWV) in a Northern Chinese population, as well as investigated associations of CVD risk factors with baPWV. As baPWV is a relatively novel and straight-forward measure of arterial stiffness, and has been associated with vascular damage and cardiovascular events, this paper offers contributions to better understand the distribution of baPWV in the Northern Chinese population. Furthermore, it should help better identify potential risk factors associated with elevated baPWV. Specific comments are shown below.

- In the limitations section, please state the likely biases that could result from
having a fairly low participation rate (53.6%), including the impact of this low participation rate on generalizability of the findings.

Generally speaking, a higher response rate contributes to a more robust finding or conclusion. In the present study, however, only those who wanted to take a health examination intended naturally to be volunteers and respond to the questionnaire. Considering this potential problem, we asked community workers to inform each potentially eligible participant and his or her family of the importance of a health examination before this study was performed. Also, the authors and other investigators came to each community center to make presentations of health education for community residents, in order to gain their confidence and, in the meantime, tell them the importance of this epidemiological study. These efforts made sense. Moreover, during the investigation, each participant was provided with a free fast breakfast after blood tests were done. Due to the limited funds, we could not pay each participant. Instead, we paid each community center for their work. In China, today, community workers usually have good and close relationships with the residents. Therefore, the community workers were able to persuade more potentially eligible residents to participate in this investigation by means of various encouragements. As for those who still did not want to respond, study staff telephoned them or came to their families in person, making a final effort to increase the response rate.

With all the work done, we finally achieved a 53.6% response rate, which was yet not fully satisfied but best available. According to the reviewer’s comment, the authors have described the likely bias and impacts in the limitations section. Though there existed such limitations due to the response rate, we believe that the present results based on the large sample size of 23 communities are meaningful.

- Table 6: Please report all tests performed for associations between baPWV with CVD risk factors. It appears that only significant findings are shown (e.g. for heart rate, systolic blood pressure, etc.) Showing null associations is also important for the literature (e.g. associations of total cholesterol, fasting glucose and smoking with baPWV, in males and females; showing other CVD factors that you likely tested such as BMI, diastolic blood pressure, etc. – likely all variables shown in Table 5). As needed please address issues of multiple statistical testing, such as the use of Bonferroni corrections.

According to this comment, modifications have been made in Table 6. Results of insignificant variables have been added. Other tables and annotations have also been partly modified.

As for the statistical analyses, difference in continuous variables between the two groups were tested with student’s t test, including age, baPWV, BMI, MAP, SBP, DBP,
pulse pressure, HR, TC, HDL-C, LDL-C, TG and fasting glucose. Differences in binomial categorized variables between the those with baPWV lower than and those with that higher than cut-off points were analyzed with Person’s χ² test, including hypertension (yes/no), diabetes (yes/no), smoking (yes/no), ischemic heart disease (yes/no), ACEIs usage (yes/no), statins usage (yes/no), CCBs usage (yes/no). Considering the difference between men and women, we performed multiple analyses in two genders separately. The standard used for a variable entering or not entering the multivariate analysis was based on p < 0.10 yielded by univariate analysis, and/or its potential clinical significance on the basis of previous studies and clinical practice. Consequently, in men, variables entering the multiple logistic regression model included SBP (per 1 mmHg), DBP (per 1 mmHg), HR (per 1 beat/min), plasma glucose (per 1 mmol/L), diabetes (yes/no), hypertension (yes/no), CCBs usage (yes/no), ACEIs usage (yes/no), and smoking (yes/no); while in women, the included variables were SBP (per 1 mmHg), BMI (per 1 kg/m²), HR (per 1 beats/min), TC (per 1 mmol/L), LDL-C (per 1 mmol/L), HDL-C (per 1 mmol/L), TG (per 1 mmol/L), plasma glucose (per 1 mmol/L), diabetes (yes/no), hypertension (yes/no), CCBs usage (yes/no), ACEIs usage (yes/no). The multiple backward stepwise logistic regressions were then performed. The criterion for inclusion of variables was p < 0.05, and that for exclusion was p > 0.10.

It should be pointed out that, we did not put age either as a continuous or an ordinal categorical variable into the model, for we had used different cut-off value for different age groups respectively. This was expected to better interpret the confounding effects of age. And in the authors’ opinion, to doing so is more meaningful and scientific than to put age as a variable into the model with using one cut-off point for the studied population as a whole.

Part of the above descriptions has been added into the statistical analysis section.

- Table 6: please state the covariates adjusted for in the regression analyses. It is important that confounders such as age are included in the models.

Please refer to the response to the previous comment, where the reason why age was not used as a variable in multiple logistic regression models is stated. Furthermore, according to this comment, we add a note to Table 6 as below.

* High baPWV was defined based on different cut-off values in different age groups respectively.

- Title: using the term “correlates” suggests that correlation tests were performed. In reality, regression analyses were performed, which is a more sophisticated method. I would recommend removing “correlates” from the title, and consider
using other terms (e.g. association) such as “Prevalence of aortic stiffness in North China, and associations with CVD risk factors.” Also, please change throughout the manuscript (including the abstract) any reference to “correlates”, being sure that term is only used to reflect tests of correlation rather than regression tests.

The term “correlates” has been replaced by other more proper terms throughout the text where needed. And the title has also been modified.

- Please state whether IRB ethics approval was obtained for this study, and if so, which organization provided the IRB approval.

The name of the organization that provided IRB approval was Institutional Review Board of Capital Medical University, which was established in May 2006, and then officially registered to DHHS (U.S. Department of Health & Human Services) and OHRP (Office for Human Research Protection) in November 2006. The authors have now stated this claim as below in paragraph 1 on page 4 in the revised manuscript.

Approval of this study was granted by Institutional Review Board of Capital Medical University.

- Please state the reasons for excluding participants with the following factors:
  a) Previous percutaneous coronary intervention and/or coronary artery bypass grafting;
  b) aortic valvular heart disease;
  c) aortic aneurysm;
  d) serious myocardial dysfunction with an ejection fraction of <30%;
  e) peripheral arteriosclerosis obliterans with an ankle-brachial index (ABI) of <0.9.

The reasons were the followings:

1. Aortic valve diseases and aortic aneurysm often associates with either reduced arterial compliance or abnormalities of aorta, which significantly affect PWV values. The baPWV measurement is not suitable for these patients in predicting other diseases.
2. PCI procedures may injure the femoral artery and/or radial artery by puncture and catheterization. After the procedures, the artery used may become stenosis to some extent. During CABG, the left internal mammal artery is often harvested, and sometimes the radial artery is also used. Therefore, patients with a history of PCI/CABG may present a modified or unreal result when tested via the automatic device used in the present study. Furthermore, perhaps due to the same
considerations, previous studies also exclude subjects with a PCI and/or CABG history.

3. ABI of 0.9 or less indicates the probability of obstructive arteriosclerosis, which could lead to a decreased PWV value.

4. Those with an ejection fraction of <30% tend to have an increased PWV value.

In short, involving the subjects with above factors will render the results of this study less valid.

The authors did not describe these reasons in detail in the manuscript due to the following reasons:

a) Word limit
b) Similar criteria have been used by previous studies
c) These reasons may be familiar to most readers

- In the methods section, please state more detail on the assay methods that were used to measure total cholesterol, HDL, glucose and triglycerides, including evidence of internal/external quality control, and measures of internal consistency (e.g. coefficients of variation for all assays).

Yes, the authors have rewritten the methods section (Para 2, Page 5) and stated the assay methods and quality control measures in more detail. References for this section have also been added to the Reference section.

Measurements of HDL-C level complied with that described in Manual of Laboratory Operations of the Lipid Research Clinics Program, where the intra-assay coefficient of variation (CV) and inter-assay CV are required to be 1.4% and 2.0% respectively. Levels of plasma glucose (PG) were measured using the hexokinase method, where intra-assay and inter-assay CV are required to be 1.9% and 2.6% respectively. For those with TG < 400 mg/dl, low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation: \( \text{LDL-C} = \frac{\text{TC} - \text{HDL-C} - \text{TG}}{5} \). No participant with TG ≥ 400mg/dl was found in this investigation.

The laboratory center of The Military General Hospital of Beijing PLA was responsible for all the blood tests in this study. The internal and external quality controls procedures were performed in accordance with regulations published by Chinese Laboratory Quality Control.

- For the finding of the highest baPWV founds in the age 50-60 year ages, please add more information in the Discussion section as to why levels were higher in this age compared to older ages. For example, is there evidence (in your study or other studies) that there is a survivor effect (in that the healthiest people with
lower baPWV are more likely to survive past 60 years, and hence be assessed in the cross-sectional study), or is there evidence of cohort effects (e.g. with the epidemiologic transition in diet and other CVD risk factors in China, do those greater than age 60 have fewer CVD risk factors due to more traditional, less CVD-inducing behaviors)? Are there other possible reasons for this finding?

It is true that the prevalence of high baPWV in 50-59 age group was higher than that in other age group in the present study. Proportion of people with high baPWV in >70 age group was lower than that in middle-aged group. Several reasons may contribute to this phenomenon.

Firstly, the cut-off point of different age group was calculated based on population of different age. Therefore, though the average level of baPWV increases with age, it is possible, mathematically speaking, to see a higher prevalence of “high baPWV” in a younger age group. Put another way, the results depends on the definition of “high baPWV”. If the cut-off points for high PWV were defined as the crude 90th percentiles for the health sample as a whole, irrespectively of age, the cut-off points of baPWV would turn to be 1731 cm/s in men and 1760 cm/s in women respectively. Were such thresholds used, the prevalence of “high baPWV” would have gone up sharply with age in both genders. Then rather less people in <50 age group could be considered as those with high baPWV, while the prevalence of high baPWV of >70 age group would be remarkably high, 77.8% and 61% in female and male respectively. In the authors’ opinion, however, to use the cut-off points irrespectively of age is less valid or meaningful.

Secondly, the “survivor effect” mentioned by the reviewer 2 might exist. Previous researches have indicated that those with lower baPWV tend to live longer. A study with 6.5 years follow-up reported that participants in the highest baPWV tertile showed an increased risk of all-cause mortality evidenced by a multivariable adjusted hazard ratio of 6.8 (95% confidence interval: 1.4-32.8) as compared with the lowest tertile. Another study enrolled community population aged 65 or older and found that a high-baPWV level was associated with an increased risk of 3-year total mortality after adjustment for age, sex and systolic blood pressure (hazard ratio for high baPWV vs. low baPWV=2.98, 95% CI=1.25-7.07). Therefore the investigators of that study inferred that the healthiest people with lower baPWV are more likely to survive past 60 years. Consequently, we may infer that, >70 age group in the healthy sample population tended to consist of people who used to be with a lower baPWV when they were younger. This may partly explain the lower prevalence of baPWV in older age group based on age-specific cut-off points.

Furthermore, as we described in the manuscript, participants with hypertension, diabetes, dyslipidemia, cardiovascular diseases, smoking, and/or obesity were excluded from the healthy sample. Based on the findings of this study and previous studies, we know that people with these potential risk factors tend to be with higher
baPWV. In the meantime, most of these risk factors are closely positively correlated to increasing age. Therefore, after these “risky” participants were removed, people in the reference sample tend to be with lower baPWV in each age group, especially in older age groups.

Future stage of this study and other specially designed studies are still needed to further explore this phenomenon.

Part of the above considerations has been added to the Discussion section in the revised manuscript. (para 4, page 9)

- Table 1 – it appears there is an error in the point estimate for baPWV in females for the overall sample (baPWV=15786 cm/s – it should likely be 1578.6 cm/s). Please check and correct as needed.

Yes, sorry for this error. Correction has been made.

In the revised version of this manuscript, only important modifications directly related to the reviewers’ comments or suggestions have been highlighted with color. Besides the modifications mentioned above, according to the editor’s comments, the whole manuscript has also been carefully modified with regard to English writing. Phrases and sentences throughout the manuscript have been checked and reedited to become more logical, fluent, and reasonable. These detailed modifications were not highlighted with color. Hope it will reach the standard of further consideration. Many thanks again for the hard work and contributions made by the reviewers and editors.

Yours sincerely,

The authors