Author's response to reviews

Title: Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure

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Version: 3 Date: 26 April 2012

Author's response to reviews:

26, April, 2012

Professor Eugenio Picano
Cardiovascular Ultrasound
Editor-in-Chief
Italy

Please find enclosed our corrected manuscript (blue type) entitled “Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure” by Eros da Mota Dias, Luiz Tadeu Giollo Jr. Débora Dada Martinelli, Camila Mazeti, Heitor Moreno Júnior, José Fernando Vilela Martin, and Juan Carlos Yugar-Toledo for consideration by the Journal.

We can assure you that It has not been published in this or any similar form (in print or electronically, including on a web site), nor accepted for publication elsewhere, nor is it under consideration for publication elsewhere.

Personally, I would be very happy to have this manuscript published in the Cardiovascular Ultrasound. Please, let me know the Editorial decision.

Best Regards

Juan Carlos Yugar-Toledo, MD PhD.
Rua: Las Vegas 200
Response to reviewer

Dear, Prof Lorenzo Ghiadoni

Cardiovascular Ultrasound

Italy

We completed the revision of the paper entitled: entitled “Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure”, and we can assure that it was a pleasure to receive the very interesting suggestions and criticisms. Significant changes were done carefully when necessary.

Title: Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure

Version: 1 Date: 5 January 2012

Reviewer: Lorenzo Ghiadoni

Reviewer’s report:

This study aimed to evaluate the relationship between hypertension and cognitive deficiency (CD), determining the association with markers of early vascular disease and CD in 150 hypertensive patients, with CD (HCD) or without CD (HNCD) and 50 normotensive controls (NT). Carotid intima-media thickness (IMT) and central systolic BP were significantly different between the HCD and HNCD while radial Augmentation Index was not different.

Major comments:

1. It is unclear how patients were recruited (consecutive or selected?). It should be clearly stated, as well as the blood pressure cut-off used to include/exclude participants.

R. Two hundred male and female individuals aged between 40 and 80 years old were evaluated in this cross-sectional study.

One hundred and fifty stage II hypertensive patients according to JNC VII (1) were selected from the specialized hypertension center of the Faculty of Medicine of São José do Rio Preto (FAMERP). Of these, 42 hypertensive patients had CD (HCD group) and 108 hypertensive patients had no CD (HNCD group).
The control group was selected from subjects referred to investigate stage I primary hypertension whose blood pressures proved to be normal after standard measurements.

This study was approved by the Research Ethics Committee of the Post Graduation Program in Health Sciences of the Medicine School in São José do Rio Preto (FAMERP). Informed written consent was obtained from all participants before their enrollment in the study.

The inclusion criteria of the hypertensive patients in this study were: aged between 40 and 80 years, treated stage II hypertension - VII JNC, optimal response to pharmacological treatment (BP < 140/90 mmHg), The exclusion criteria were presence of the atherosclerotic plaque defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface, no acute medical illness in the past month and the ability to understand, verbalize and answer questions related to the study.

Participants were submitted to clinical evaluations, physical examinations and investigations of their family history for cardiovascular disease. Blood pressure of the right arm was measured during the morning by a trained healthcare professional with the patient in the seated position and using an appropriate cuff size.

The age, gender, weight, height, an electrocardiogram and the results of biochemical blood tests for these individuals were recorded on a questionnaire. Patients with secondary hypertension, those taking anticholinesterase drugs, those that had suffered strokes, had diagnosis of dementia or had recently had an acute infection were excluded in order to rule out cases of acute confusional state. Additionally, patients with family history of Alzheimer's disease (parents and siblings), and history of psychiatric illness or substance abuse were excluded.

2. It is unclear the cut-off of MMSE used to identify subject with cognitive deficits. This a major issue since a cut-off value for MMSE of 24 might exclude subjects with early cognitive impairment which represent the first clinical expression of hypertension related-cognitive damage).

R. We agree with the reviewer, but recent reports consider a cut-off value of 24 because the high sensitivity and acceptable specificity in an older study population (2)

3. Patients with cognitive impairment are older than hypertensive patients without cognitive impairment. This represents a major confounding factor for the increase in central systolic BP and IMT.

R. We agree with the reviewer, a multivariate analysis was made to reduced
4. Hypertension-related cognitive impairment depend on the intensity of the exposure of high blood pressure which in turn is related to the duration of hypertension. These data are lacking and they should be considered.

R. We agree with the reviewer, the data about the duration of the exposure to hypertension was added in Table 1. No significant differences between the two groups were found in relation to the duration of hypertension (HCD = 15.03 ± 9.74 vs. HNCD 15.73 ± 9.57 p = 0.40)

5. Different antihypertensive treatment might differently affect cognition. This topic has not been considered.

R. Really this information is important and will be included in the table.

6. Mean and SD of MMSE score suggest that some subjects had MMSE > 30 while the maximum value to be considered is always 30 also if the score results higher than 30 after correction for education degree.

R. The necessary corrections were made and the maximum value remained higher than 30; the SD was recalculated after corrections.

7. Different distribution in gender distribution could explain the lack of difference in augmentation index between HCD and HNCD. Data on central PP and DBP should be also given to interpret results in NT. Moreover data on PWV and cognitive function should be discussed (Scuteri A et al. J Hypertens 2007 May;25(5):1035-40).

R. We agree with the reviewer, The Scuteri report was added and discussed appropriately

Minor points

1. Revise acronyms: HA-CI, AH-CI, HA-AD References are not correctly reported through the text

R. The necessary corrections were made.

2. Figure 1 is redundant.

R. Figure 1 was deleted.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
No conflict of interest exists

Reference


Response to reviewer 2

Dear, Prof Eva Gerdts

Cardiovascular Ultrasound

Italy

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Reviewer’s report

Title: Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure

Version: 1 Date: 25 December 2011

Reviewer: Eva Gerdts

Reviewer’s report:

The authors aimed to identify factors associated with cognitive impairment in hypertension, in particular the relation with increased carotid intima-media thickness (IMT) and central blood pressure. A total of 150 hypertensive patients
and 50 control subjects were recruited for this cross-sectional analysis. Cognitive impairment is a major and costly health problem, so the topic is important and interesting. However, the actual data set is insufficiently explored, limiting the interpretation of results. In particular, the following points should be addressed:

1. No abstract is presented.
   R. The abstract was included.

2. The references are out of order.
   R. The necessary corrections were made.

3. The abbreviation CI should not be used for cognitive impairment. You also use the same for confidence interval, which may be disturbing for the reader.
   R. We agree with this interesting observation and we changed the abbreviation to CD (cognitive deficiency).

4. Detailed information on how these study participants were recruited should be provided. In particular it is unclear how normotensive controls were recruited as they were significantly younger than the hypertensive patients which may flaw the study analysis.
   R. Two hundred male and female individuals aged between 40 and 80 years old were evaluated in this cross-sectional study.

One hundred and fifty stage II hypertensive patients according to JNC VII (1) were selected from the specialized hypertension center of the Faculty of Medicine of São José do Rio Preto (FAMERP). Of these, 42 hypertensive patients had CD (HCD group) and 108 hypertensive patients had no CD (HNCD group).

The control group was selected from subjects referred to investigate stage I primary hypertension whose blood pressures proved to be normal after standard measurements.

This study was approved by the Research Ethics Committee of the Post Graduation Program in Health Sciences of the Medicine School in São José do Rio Preto (FAMERP). Informed written consent was obtained from all participants before their enrollment in the study.

The inclusion criteria of the hypertensive patients in this study were: aged between 40 and 80 years, treated stage II hypertension - VII JNC, optimal response to pharmacological treatment (BP < 140/90 mmHg), The exclusion criteria were presence of the atherosclerotic plaque defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface, no acute medical illness in the past month and the ability to understand, verbalize and answer
questions related to the study.

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The age, gender, weight, height, an electrocardiogram and the results of biochemical blood tests for these individuals were recorded on a questionnaire. Patients with secondary hypertension, those taking anticholinesterase drugs, those that had suffered strokes, had diagnosis of dementia or had recently had an acute infection were excluded in order to rule out cases of acute confusional state. Additionally, patients with family history of Alzheimer's disease (parents and siblings), and history of psychiatric illness or substance abuse were excluded.

5. It is well known that antihypertensive treatment influences IMT and central blood pressure, and differences among drug classes have been reported. Information on antihypertensive treatment should be added to table 1 and treatment should be included among the covariates in a revised multivariate analysis.

R. We agree with the reviewer, the data about the antihypertensive therapy was added in another table and the multivariate analysis was made to reduce confounding factors and the results discussed in the discussion section.

6. The inclusion criterion ‘regularly attending medical consultations’ should be explained and probably rephrased.

R. The necessary corrections were made.

7. The importance of measuring blood pressure correctly is stressed by the authors. It should be clarified if clinical blood pressure was measured in the sitting or supine position. Furthermore, the lack of ambulatory blood pressure should be included in the discussion and in study limitations.

R. Blood pressure of the right arm was measured during the morning by a trained healthcare professional with the patient in the seated position and using an appropriate cuff size.

8. How was 24 hour sodium excretion measured? Include this as well as how microalbuminuria was measured in the method section.

R: Sodium concentrations of urine were measured by flame photometry using modern Instrumentation after 24-hour urine was collected without preservatives. 50 mL was submitted to flame photometry. Blood samples were collected from each of the subjects for measurement of plasma creatinine on one of the days of food and urine collection, to permit calculation of creatinine clearance.
Microalbuminuria was measured by the conventional immunoturbidimetry test utilizing antibodies to human albumin in an automated immunoprecipitin analysis system.

9. The method used for assessing carotid IMT should be better described in the text including if only the common carotid artery was analyzed and if both near and far field wall was included in the analysis. Both mean and peak IMT and the prevalence of carotid plaque should be included. When the text is adequately revised, figure 1 can be omitted.

R: The figure 1 was deleted.

The carotid intima-media thickness (IMT), the mean thickness of the anterior and posterior walls of the left and right carotid arteries, was evaluated using high resolution ultra-sound. Patients were always examined between 7:00 a.m. and 11:00 a.m. in the supine position with the head at a 45° angle on a support.

This method is established and standardized according to the report of the "34th Bethesda Conference Task Force #3 Noninvasive Atherosclerosis Measurement" and a sample protocol outlined by the American Society of Echocardiography (2).

The ultrasound analysis was performed by a physician experienced in vascular studies certified by the Cardiovascular Imaging Department of the Brazilian Society of Cardiology blind to the patient’s clinical data. The examination was carried out according to a previously established protocol (3) standardized for both carotid arteries. Images were acquired at end diastole (defined as the R wave of an electrocardiogram) using a 7-12 MHz linear transducer and high resolution ultra-sound (Philips, HD 11 XE, Andover MA – USA). The intima-media thickness was measured over a segment of the artery that was 1 cm long, located approximately 0.5 cm below the carotid-artery bulb and considered not to contain any plaque (i.e., not to have any perceivable protrusion of the artery wall into the lumen) (4-5).

The IMT data were analyzed offline by two independent observers using computer program analysis (M'ATH - Metris, France) which allows automated measurement of the IMT from images obtained during four cardiac cycles identified by the R wave of ECG. The analysis, based on the tone of the gray scale and a specific algorithm to recognize tissue, is automatic. The average measurements from the near and far walls of the left and the right common carotid arteries were used to compare the results between the three study groups. The variability between the IMT measurements should be less than 2%, as in this study.

10. Figure 1 suggests that the internal carotid artery was not studied. If so, please include this factor in the discussion. Is it possible that atherosclerosis in the internal carotid artery may reflect cerebral circulation and function even better than IMT in the common carotid?
Re: Associations of risk factors with the mean CCA and maximum ICA IMT are slightly different, and both are independently associated with prevalent CVD. Their value for predicting incident cardiovascular events needs to be compared in outcome studies. (6)

We chose the mean CCA IMT because it uses a method that scans a 1cm long segment of the common carotid artery. Polak et al., (7) in a recent report noted that although the maximum ICA IMT is more strongly associated with prevalent CVD than CCA IMT, the relative effect of a 1-mm change in CCA IMT is more significant than an equivalent 1-mm increase in ICA IMT. This is in part explained by the larger values and wider range for ICA IMT compared with CCA IMT.

11. The guidelines advocate that central blood pressure should be estimated from carotid or aortic pulse wave analysis. In the current study radial pulse wave analysis was used. Why was this suboptimal strategy chosen? Possible influence on study results should be discussed.

Re: Central (aortic and carotid) blood pressures are more strongly related to the pathogenesis of cardiovascular disease than peripheral pressures. (8) It is the aortic systolic pressure that the left ventricle encounters during systole (afterload), and the aortic pressure, during diastole, is a determinant of coronary perfusion. Furthermore, the distending pressure in the large elastic-type arteries (aorta and carotid) is a key determinant of the degenerative changes that characterize accelerated aging and hypertension. In contrast, the muscular peripheral arteries, such as the brachial and radial arteries, are less influenced by these changes. (9)

Because of pulse pressure amplification between central and peripheral arteries, it is inaccurate to use the brachial pulse pressure as a surrogate for aortic or carotid or aortic pulse pressure, particularly in young subjects. And the carotid femoral Pulse Wave Velocity (PWV) is considered the “gold standard” measurement of arterial stiffness. Pulse-wave analysis should be optimally obtained at the central level, i.e. at the site of the carotid artery or the ascending aorta, and either directly recorded or computed from the radial artery waveform using a transfer function. The pulse waveform should be analyzed by three major parameters: central pulse pressure, central systolic pressure, and augmentation index.

Tonometry of the radial artery provides an accurate, reproducible, noninvasive assessment of the central pulse pressure (PP) waveform. Radial artery applanation tonometry (AT) is performed by placing a hand-held tonometer (strain gauge pressure sensor) over the radial artery and applying mild pressure to partially flatten the artery. The radial artery pressure is then transmitted from the vessel to the sensor (strain gauge) and is recorded digitally. A mathematical formula using a fast Fourier transformation algorithm, approved by the Food and Drug Administration of the USA, permits derivation and calculation of central pressure indices from a peripheral brachial blood pressure and concomitant recording of a PP wave with radial AT.
In the Strong Heart Study, an observational study of prevalent and incident cardiovascular disease and their risk factors in American Indians, central aortic pulse pressure and arterial stiffness were more strongly related to vascular hypertrophy and extent of carotid atherosclerosis than the brachial pressure. Furthermore central pulse pressure better predicts outcomes compared to brachial pressure.(8)

12. The statistical approach is not well described. Univariate associations with cognitive impairment should be tested by Pearson’s correlation. Building of the multivariate model should be done based on univariate associations and collinearity diagnostics. Covariates of IMT, central blood pressure and finally cognitive impairment should be presented fully. In particular the realtion between steady and pusatile measures of blood pressure should be explored.

Re: Thank you for this observation. The necessary correction was made.

13. The same results should not be presented both in text and tables.

Re: The duplicate results in the text were deleted.

14. In the result text, 4 different patient groups appear: AH-CI, HA-AD, HA and NT. This differs from the description in methods and the results in the tables. Please clean up, so methods and results are concordant.

Re: Thank you for this observation. The necessary correction was made.

15. Units are lacking in table 1. Also use period as decimal separator.

The necessary correction was made.

16. Table 3 and 4 can be taken out as results are presented in Figure 4 and 5.

The necessary correction was made.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I do not have any competing interest in this field as my research is all about hypertensive heart disease.
References


