Subtype of hypertension is evidence for preclinical atherosclerosis

A study of carotid artery ultrasonography and biochemical markers

Marwan S. Al-Nimer, *MD, PhD,* ***Ismail I. Hussein,*** *MSc, PhD,* ***Warda S. Lasso,*** *MBChB, MD.*

ABSTRACT

الأهداف: تقييم تصلب الشرايين قبل التشخيص السريري في أنواع ارتفاع ضغط الدم الشرياني باستخدام قياس الشحوم كمؤشر حيوي و نمط B للأشعة فوق السمعية للشرايين السباتية.

الطريقة: بلغ العدد الإجمالي 96 مريض (49 أنثى و 47 ذكر) تتراوح أعمارهم بين 42 و 78 عام تم ضمهم من وحدة الدوبلر الوعائية في مستشفى بغداد التعليمي – بغداد – العراق خلال الفترة من يناير إلى يونيو 2008. تم تقسيم المرضى إلى ضغط الدم الطبيعي (المجموعة الاولى I)، فرط ضغط الدم التقلصي (المجموعة الثانية II)، فرط ضغط الدم الانبساطي (المجموعة الثالثة III) وفرط ضغط الدم التقلصي والانبساطي (المجموعة الرابعة IV).

النتائج: لوحظ تصلب الشرايين قبل التشخيص السريري في المجموعتين الثالثة III والرابعة IV بدلالة تدني مستوى البروتينات الشحمية عالية الكثافة و زيادة مستوى البروتينات الشحمية منخفضة الكثافة ومؤشر التصلب. ارتفع معدل سمك باطن و وسط الشرايين السباتية بدلالة نوعية بالتدرج من المجموعة الأولى I إلى الرابعة IV وكان معدل قيم مؤشر المقاومة في كل من الشرايين السباتية للمجموعة الرابعة IV أعلى من المجموعة الأولى I. لوحظ وجود اللويحة السباتية بنسبة عالية و بدلالة نوعية في المجموعة الرابعة IV (12 من 15)، تليها المجموعة الثالثة III (14 من 31) ثم المجموعة الثانية II (1 من 30).

خاتمة: تعد قيم الشحوم والأشعة فوق الصوتية نمط B للشرايين السباتية من الإجراءات التنبؤية الجيدة لتصلب الشرايين قبل تشخيصها سريرياً ويحسب ذلك إلى فرط ضغط الدم الانبساطي و فرط ضغط الدم التقلصي والانبساطي معاً مقارنة إلى فرط ضغط الدم التقلصي.

Objectives: To assess subclinical atherosclerosis in subtypes of hypertension using lipid profile as a biomarker and B mode ultrasonography of the carotid arteries.

Methods: Ninety-six subjects (49 females and 47 males) aged 42-78 years were recruited from the vascular Doppler unit at Baghdad Teaching Hospital, Baghdad, Iraq from January to June 2008. They were grouped into normotensive (group I), isolated systolic hypertension (group II), isolated diastolic hypertension (group III), and combined systolic and diastolic hypertension (group IV).

Results: Subclinical atherosclerosis was observed in groups III and IV in terms of significantly low levels of high-density lipoprotein, high levels of low-density lipoprotein, and high atherogenic index. The mean intima media thickness was significantly increased with transition from group I to group IV in all carotid arteries, and the mean resistive index value of each carotid artery in group IV was significantly higher than that of group I. Carotid plaque was demonstrated in a significantly higher percent in group IV (12 out of 15) followed by groups III (14 out of 31) and II (1 out of 30).

Conclusion: Lipid profile and high resolution B-mode ultrasonography of the carotids are good predictive measures of subclinical atherosclerosis. Isolated diastolic hypertension and combined systolic-diastolic hypertension accounts for early subclinical atherosclerosis compared with isolated systolic hypertension.

Neurosciences 2010; Vol. 15 (2): 79-83

From the Departments of Pharmacology (Al-Nimer), and Physiology (Hussein), College of Medicine, Al-Mustansiriya University, and the Department of Ultrasound (Lasso), Baghdad Teaching Hospital, Baghdad, Iraq.

Received 10th October 2009. Accepted 15th December 2009.

Address correspondence and reprint request to: Dr. Marwan S. M. Al-Nimer, Professor of Pharmacology, Department of Pharmacology, College of Medicine, Al-Mustansiriya University, PO Box 14132, Baghdad, Iraq. Tel. +964 (1) 5591530. Fax. +964 (1) 5410584. E-mail: alnimermarwan@ymail.com

Hypertension is an important contributor to the morbidity and mortality of cardiovascular disease.[1] Isolated systolic hypertension is a common type of high blood pressure (BP), and can lead to serious health problems such as stroke, heart disease, chronic renal disease, and dementia.[2] It is more common in older people affecting up to 30% of people over 60 years of age.[3] Smoking and obesity are also risk factors for this condition. Large artery stiffness is associated with isolated hypertension, while diastolic high BP tends to predominate if the arterial stiffness is normal or low. Isolated diastolic hypertension does not seem to be a condition of increased cardiovascular risk,[4-6] perhaps because it might be a sign of a general paucity of atherosclerosis. Obesity or metabolic syndrome may be frequent in this group entity.[7] Systolic BP is a better predictor of stroke than diastolic BP, and it has a much greater impact on risk of stroke in younger than in older men.[8,9] Higher resolution B mode ultrasonography focuses on the common carotid artery, and intima media thickness (IMT) is useful for quantifying risk factor relationships to subclinical atherosclerosis. Multiple regression analysis revealed correlations between carotid intima-media thickness and hypertension.[10] Progression of common carotid artery IMT is significantly correlated with coronary artery disease progression measured by serial quantitative angiography.[11,12] The relation between clinical coronary events and progression of carotid IMT is as strong as the relation between coronary events and progression of coronary atherosclerosis determined by angiography. The aim of this study was to assess subclinical atherosclerosis in subtypes of hypertension using lipid profiles as biomarkers, and B mode ultrasonography of the carotid arteries.

Methods. Subjects in this investigation were recruited from the vascular Doppler unit at Baghdad Teaching Hospital, Baghdad, Iraq from January to June 2008. An independent scientific committee revised and approved the study protocol and the information to be provided to the patients. Subjects' written consent was obtained prior to their enrollment in the study. The criterion of inclusion was hypertension. Exclusion criteria included previous history of ischemic stroke, diabetes mellitus, familial hyperlipidemia, history of angina, myocardial infarction, angioplasty, congestive heart failure, aortic stenosis, atrial fibrillation, coronary bypass, carotid or peripheral vascular surgery, or renal insufficiency. Ninety-six subjects (49 females and 47 males) aged 42-78 years were able to comply with the study protocol. Each patient was clinically examined at the time of initiation of the study. Three BP measurements were taken on the right arm using an appropriately sized cuff with the subject in the seated position. Mean values were taken of the second and third BP readings. Subjects were categorized as having subtypes of hypertension into 4 groups: group I (n=20): healthy normotensive subjects with BP <140/<90 mm Hg; group II (n=30): isolated systolic hypertensive patients with BP ≥140/<90 mm Hg; group III (n=31): isolated diastolic hypertensive patients with BP<160/≥90 mm Hg, and group IV (n=15) combined systolic and diastolic hypertensive patients with BP ≥160/≥90 mm Hg. Anthropometric measurements of body weight (kg) and height (m) were carried out. Body mass index (BMI) was calculated using Quetlet's index. Biochemical analysis included lipid profile (fasting lipids and lipoproteins) measurement. The ratio of triglycerides (TG) to high-density lipoprotein (HDL) was calculated to determine atherogenic index as well as the particles of atherogenic low-density lipoprotein (LDL).[13,14] Ultrasonography was performed with B-mode images of a high-resolution ultrasound scanner equipped with a 7 MHz linear array transducer. Anterior, antero-lateral, and postero-lateral projections were used to obtain images of the left and right common and internal carotid arteries. Carotid IMT measurements were carried out 3 times for each artery at each site, and the average of 3 measurements of each carotid artery IMT was taken; the coefficients of variation of these measurements ranged from 1.5-2.3%. The resistive index was calculated according to Pourcelot[15] as follows: 1-[Minimum diastolic velocity/Maximum systolic velocity]. The average of 6 measurements was used for calculation. The pulsed-Doppler volume was carried out in the middle/distal carotid arteries (common and internal) region on both sides with a maximum Doppler angle of 60º with a sampling volume of approximately 3 quarters of the vascular diameter. Neither stenosis at the measurement site, nor a stroke signal was seen in the studied patients.

Statistical analysis. Statistical analysis was carried out using Microsoft Excel 2003. The results are presented as absolute number, percent, median, range, and mean ± SD. The data was analyzed using unpaired, two-tailed Student's t-test and simple correlation test, taking $p \leq 0.05$ as the lowest limit of significance.

Results. **Table 1** summarizes the characteristics of the study group. Healthy normotensive individuals (group I) significantly differed from hypertensive patients (groups II, III, and IV) in respect to age and blood pressure. The mean age of healthy normotensive subjects was significantly less than corresponding hypertensives in groups II, III, and IV. The anthropometric measurements revealed non-significant differences in BMI between the studied groups. There was no significant difference in systolic blood pressure between groups II and III, or in diastolic blood pressure between groups I and

Table 1 - Characteristics of the study groups.

Characteristics	Group I (n=20)	Group II (n=30)	Group III (n=31)	Group IV (n=15)
Gender				
Male	9	16	16	6
Female	11	14	15	9
Age (year)	49.6 ± 5.6	54.3 ± 4.6 (p=0.003)	56 ± 6.2 (p=0.004)	63.9 ± 7.4 (p=0.0000014)
Median duration of high BP (year)	0	7	12	15
SBP (mm Hg)	130.5 ± 5.1	145 ± 5.1 (p=0.000000000023)	143.4 ± 9.2 (p=0.000000053)	164.7 ± 5.8 (p=0.000000000000000054)
DBP (mm Hg)	75.3 ±7.5	78.5 ± 4.9	96.5 ± 6.6 (p=0.0000000000021)	95.7 ± 3.7 (p=0.000000000017)
BMI (kg/m^2)	29.47 ± 3.789	28.986 ± 3.753	30.635 ± 3.924	31.526 ± 3.041
Active smoking	9	12	18	7

The results are expressed as absolute number and mean ± SD, probability values compared with group I
BP - blood pressure, SBP - systolic blood pressure, DBP - diastolic blood pressure, BMI - body mass index

Table 2 - Fasting serum lipids and lipoprotein levels profile.

Lipid/lipoprotein level	Group I (n=20)	Group II (n=30)	Group III (n=31)	Group IV (n=15)
Cholesterol (mg%)	208.8 ± 36.9	205.4 ± 30.5	227.6 ± 44.8	243.5 ± 51.7
Triglycerides (mg%)	161.2 ± 47.8	145.2 ± 41.0	147.5 ± 51.1	159.2 ± 52.4
LDL (mg%)	128.9 ± 33.7	132.8 ± 27.8	157.7 ± 42.7 (p=0.01)	178.7 ± 46.1 (p=0.001)
HDL (mg%)	45.4 ± 8.9	42.7 ± 10.9	40 ± 8.4 (p=0.03)	33.1 ± 6.3 (p=0.000037)
VLDL	33.9 ± 10.3	29.5 ± 8.3	31.2 ± 11	31.8 ± 10.5
TG/HDL ratio	3.645±1.071	3.639 ± 1.508	3.984 ± 1.928	4.964 ± 1.961 (p=0.028)

The results are expressed as mean ± SD, probability values are compared with group I. LDL - low-density lipoprotein, HDL - high-density lipoprotein, VLDL - very low-density lipoprotein, TG - triglycerides

Table 3 - Mean intima-media thickness (mm) of common and internal carotid arteries.

Arteries	Group I (n=20)	Group II (n=30)	Group III (n=31)	Group IV (n=15)
Right CCA	0.545 ± 0.060	0.670 ± 0.121 (p=0.000015)	0.720 ± 0.166 (p=0.0000038)	0.88 ± 0.137 (p=0.000000056)
Left CCA	0.602 ± 0.083	0.704 ± 0.116 (p=0.0007)	0.751 ± 0.136 (p=0.000013)	0.88 ± 0.152 (p=0.0000029)
Right ICA	0.37 ± 0.057	0.436 ± 0.109 (p=0.007)	0.506 ± 0.173 (p=0.0002)	0.54 ± 0.112 (p=0.000032)
Left ICA	0.405 ± 0.075	0.483 ± 0.164 (p=0.04)	0.508 ± 0.196 (p=0.01)	0.546 ± 0.106 (p=0.0002)

The results are expressed as mean ± SD, probability values are compared with group I.
CCA - common carotid artery, ICA - internal carotid artery

Table 4 - Mean resistive index of common and internal carotid arteries.

Arteries	Group I (n=20)	Group II (n=30)	Group III (n=31)	Group IV (n=15)
Right CCA	0.701 ± 0.077	0.726 ± 0.123	0.713 ± 0.063	0.754 ± 0.040 (p=0.01)
Left CCA	0.72 ± 0.052	0.733 ± 0.063	0.738 ± 0.081	0.776 ± 0.076 (p=0.02)
Right ICA	0.652 ± 0.157	0.704 ± 0.073	0.725 ± 0.094	0.779 ± 0.058 (p=0.002)
Left ICA	0.713 ± 0.077	0.751 ± 0.089	0.763 ± 0.079 (p=0.03)	0.788 ± 0.089 (p=0.01)

The results are expressed as mean ± SD, probability values are compared with group I.
CCA - common carotid artery, ICA - internal carotid artery

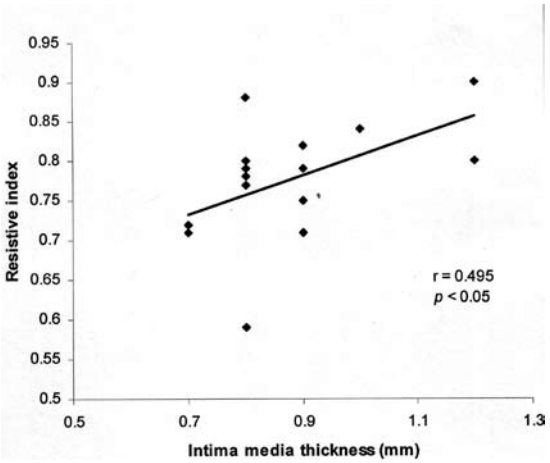

Figure 1 - Correlation between intima media thickness (mm) and resistive index of left common carotid artery of group IV.

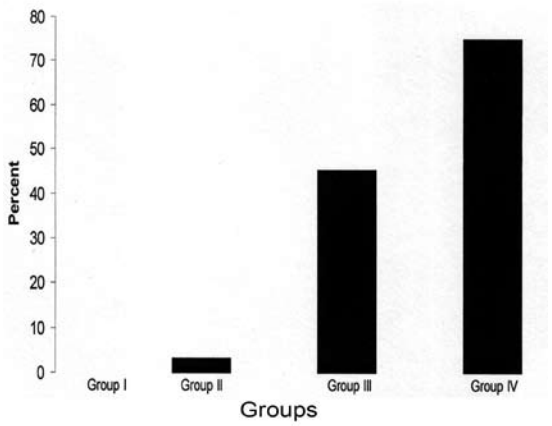

Figure 2 - The distribution of cases according to the presence of carotid plaques in groups I - IV.

II, or between groups III and IV (**Table 1**). Variable numbers of active smoking were found in all studied groups. Lipids (serum cholesterol and triglycerides) and lipoprotein (very low-density lipoproteins [VLDL]) were non-significantly increased with transition from group II towards group IV (**Table 2**). Lipoprotein (LDL) level was significantly higher in groups III and IV compared with group I and II, and the lipoprotein (HDL) was significantly lower in groups III and IV compared with groups I and II (**Table 2**). Neither LDL nor HDL levels in the isolated systolic hypertension group (group II) significantly differed from group I. The TG/HDL ratio was significantly higher in group IV compared with group I (**Table 2**). The mean IMT was significantly increased with transition from group I (healthy normotensives) towards group IV (combined systolic and diastolic hypertensives) in all carotid arteries (**Table 3**). Although the mean resistive index value of each carotid artery in groups II, III, IV was higher than that of group I, the significant differences were only observed in group IV for all carotid arteries and left internal carotid artery of group III compared with group I (**Table 4**). There were non-significant differences between IMT and resistive index for each carotid artery in each studied group except the left common carotid artery of group IV (**Figure 1**). **Figure 2** shows that carotid plaque was demonstrated in a significantly higher percent in group IV followed by groups III and II.

Discussion. The results of this study demonstrate that both lipid profile and high resolution B-mode ultrasonography of carotid artery IMT are useful to discriminate which hypertensive subtype has a much greater impact on risk of atherosclerosis.

Evidence of subclinical atherosclerosis is well observed in patients with combined systolic and diastolic hypertension (group IV) in terms of significantly high LDL, low HDL, high atherogenic index high, TG/HDL ratio, increased thickness of IMT, and resistive index of carotid artery as well as the presence of carotid plaques. The duration of hypertension may have contributed to these findings, but the other associated risk factors including active smoking, and overweight are less likely to contribute directly to these findings. Recently, Sehestedt et al[16] reported that whenever carotid atherosclerotic plaque is detected in healthy individuals with high normal BP, it may be considered as a risk predicting factor for subclinical organ damage. None of the studied groups in this study showed carotid atherosclerosis, namely, an IMT greater than 1.2 mm as mentioned by Lee et al.[17] Carotid wall shear stress, demonstrated in this study by the evidence of significant high resistive index, is implicated in the atherogenesis process, and this finding is in agreement with Lee et al's study.[18] The results of Uthoff et al's[19] study suggested that IMT is suitable for cardiovascular risk prediction as well as for progression measurements, while resistive index cannot be recommended for progression measurements. Therefore, both IMT and resistive index of carotid can predict subclinical atherosclerosis in hypertensive (systolic and diastolic) patients.

The results of high BMI in group III and IV compared with group II are in agreement with Chirinos et al,[20] who found that isolated diastolic hypertension and systolic-diastolic hypertension account for most cases of obesity-related hypertension. Evidence of subclinical atherosclerosis among patients with isolated diastolic hypertension is more obvious and significant compared with isolated systolic hypertensive patients. This finding

is opposite to the Ohasama study conducted by Inoue et al,[21] which reported that isolated systolic hypertension was associated with a high risk of stroke similar to that found in systolic-diastolic hypertension. This is due to the exclusion of isolated diastolic hypertension from the analysis because the prevalence was low.

Although the sample size of this study is small, it highlights the significant evidence of subclinical atherosclerosis in isolated diastolic compared with isolated systolic hypertension. One of the study limitations is to look for the mortality and co-morbidity by following-up the patients for a certain period of time.

In conclusion, lipid profile and high resolution B-mode ultrasonography of the carotid arteries are good predictive measures of subclinical atherosclerosis. Isolated diastolic hypertension and combined systolic-diastolic hypertension account for early subclinical atherosclerosis compared with isolated systolic hypertension. Further study is recommended to estimate the relative risk ratio of stroke among patients with each subtype of hypertension.

References

1. Widimský J. [Target values in hypertension treatment. Will they apply in older patients with hypertension, diabetics and in patients with IHD?] ***Vnitr Lek*** 2009; 55: 833-840. Czech.
2. Scholze J. [Isolated systolic hypertension.] ***MMW Fortschr Med*** 2009; 15: 40-41. German.
3. Dorjgochoo T, Shu XO, Zhang X, Li H, Yang G, Gao L, et al. Relation of blood pressure components and all-cause, stroke and coronary heart disease mortality in urban Chinese women: a population-based perspective study. ***J Hypertens*** 2009; 27: 468-475.
4. Ekundayo OJ, Allman RM, Sanders P, Aban I, Love TE, Arnett D, et al. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. ***Hypertension*** 2009; 53: 458-465.
5. Pickering TG. Isolated diastolic hypertension. ***J Clin Hypertens (Greenwich)*** 2003; 5: 411-413.
6. Strandberg TE, Salomaa VV, Vanhanen HT, Pitkälä K, Miettinen TA. Isolated diastolic hypertension, pulse pressure, and mean arterial pressure as predictors of mortality during a follow-up of up to 32 years. ***J Hypertens*** 2002; 20: 399-404.
7. Saladini F, Dorigatti F, Santonastaso M, Mos L, Ragazzo F, Mattarei M, et al. Natural history of hypertension subtypes in young and middle-age adults. ***Am J Hypertens*** 2009; 22: 531-537.
8. Palm-Meinders IH, Box FM, de Craen AJ, Blauw GJ, van Buchem MA, van der Ground J, et al. Diastolic wall shear stress in the internal carotid artery is associated with different cardiovascular risk factors than systolic wall shear stress. ***Cerebrovasc Dis*** 2009; 28: 185-190.
9. Kelly TN, Gu D, Chen J, Huang JF, Chen JC, Duan X, et al. Hypertension subtype and risk of cardiovascular disease in Chinese adults. ***Circulation*** 2008; 118: 1558-1566.
10. Kazmierski R, Watala C, Podsiadly E, Dorszewska J, Kozubski W. Association of atherosclerotic risk factors with carotid adventitial thickness assessed by ultrasonography. ***J Clin Ultrasound*** 2009; 37: 333-341.
11. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. ***Circulation*** 2007; 115: 459-467.
12. Morito N, Inoue Y, Urata M, Yahiro E, Kodama S, Fukuda N, et al. Increased carotid artery plaque score is an independent predictor of the presence and severity of coronary artery disease. ***J Cardiol*** 2008; 51: 25-32.
13. Cordero A, Andrés E, Ordoñez B, Leon M, Laclaustra M, Grima A, et al. Usefulness of triglycerides-to-high-density lipoprotein cholesterol ratio for predicting the first coronary event in men. ***Am J Cardiol*** 2009; 104: 1393-1397.
14. Dobiásová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). ***Clin Biochem*** 2001; 34: 583-588.
15. Pourcelot L. Application cliniques de l'examen Doppler transcutan. In: Peronneau P, editor. Velocimetrie Ultrasonore Doppler. Paris (FR): Inserm; 1975. p. 213-240.
16. Sehestedt T, Jeppesen J, Hansen TW, Rasmussen S, Wachtell K, Ibsen H, et al. Which markers of subclinical organ damage to measure in individuals with high normal blood pressure? ***J Hypertens*** 2009; 27: 1165-1171.
17. Lee CD, Jae SY, Iribarren C, Pettee KK, Choi YH. Physical fitness and carotid atherosclerosis in men. ***Int J Sports Med*** 2009; 30: 672-676.
18. Lee MY, Wu CM, Yu KH, Chu CS, Lee KT, Sheu SH, et al. Association between wall shear stress and carotid atherosclerosis in patients with never treated essential hypertension. ***Am J Hypertens*** 2009; 22: 705-710.
19. Uthoff H, Staub D, Meyerhans A, Hochuli M, Bundi B, Schmid HP, et al. Intima-media thickness and carotid resistive index: progression over 6 years and predictive value for cardiovascular events. ***Ultraschall Med*** 2008; 29: 604-610.
20. Chirinos JA, Franklin SS, Townsend RR, Raij L. Body mass index and hypertension hemodynamic subtypes in the adult US population. ***Arch Intern Med*** 2009; 169: 580-586.
21. Inoue R, Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, et al. Stroke risk in systolic and combined systolic and diastolic hypertension determined using ambulatory blood pressure. The Ohasama study. ***Am J Hypertens*** 2007; 20: 1125-1131.