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Impact of prehypertension on carotid artery intima–media thickening: Actual or masked?

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ABSTRACT

Background: Recent studies have reported that prehypertension is associated with increased values of common carotid artery intima–media thickness (CCA-IMT). The aim of this study was to assess the impact of daytime ambulatory blood pressure (BP) levels on the association of prehypertension with CCA intima–media thickening in prehypertensive subjects.

Methods: A total of 807 subjects with office systolic BP < 140 and diastolic BP < 90 mmHg, underwent 24 h ambulatory BP (ABP) monitoring and carotid artery ultrasonographic measurements. The study population was divided into 3 groups according to office and daytime ABP levels: (1) normotensives: subjects with office BP < 120/80 mmHg and daytime ambulatory BP values within the normal range, (2) actual prehypertensives: individuals with office SBP (120–139 mmHg) and/or DBP (80–89 mmHg) and daytime ambulatory BP values within the normal range and (3) prehypertensives with masked hypertension (MH): patients with office SBP (120–139 mmHg) and/or DBP (80–89 mmHg) and elevated daytime ambulatory BP values.

Results: Prehypertensive patients with MH had higher ($p < 0.01$) CCA-IMT values (0.712 mm; 95%CI: 0.698–0.725) than actual prehypertensives (0.649 mm; 95%CI: 0.641–0.656) and normotensives (0.655 mm; 95%CI: 0.641–0.670) even after adjustment for baseline characteristics. Normotensives and actual prehypertensives did not differ significantly regarding CCA-IMT values ($p > 0.05$). After adjusting for potential confounders, (including demographic characteristics, vascular risk factors, and office BP) prehypertension with MH was independently ($p < 0.01$) associated with a 0.06 mm increment in CCA-IMT (95%CI: 0.03–0.09).

Conclusions: Patients with office BP levels in the prehypertensive range, who also have elevated daytime ABP levels, had higher CCA-IMT values than patients with prehypertension with normal daytime ABP values and normotensive individuals.

1. Introduction

The widespread use of ambulatory blood pressure (ABP) monitoring in clinical practice has allowed the identification of different blood pressure types such as sustained normotension, sustained hypertension, white-coat hypertension and masked hypertension (MH). Masked hypertension, which is present when normal office blood pressure (BP) is recorded in parallel with ambulatory or self measurements in the hypertensive range [1], is a relatively new entity of great interest under investigation. Recent evidence supports that individuals in this condition are more likely to have increased left ventricular mass and common carotid artery intima–media thickness (CCA-IMT), than normotensive subjects [2].

Furthermore, the Seventh Joint National Committee on the Prevention, Evaluation and Treatment of Hypertension (JNC-7) in 2003 introduced the term ‘prehypertension’ to designate individuals whose systolic BP levels are in the range of 120–139 mmHg and/or diastolic BP between 80 and 89 mmHg [3]. The concept behind this new term derives from the fact that the Prospective Studies Collaboration paper has shown a continuous straight line relationship between BP and cardiovascular risk right across the distribution of BP values in Western countries [4]. Wang and Wang estimated that 31% of the population in the United States is prehypertensives [5]. Additionally, several studies have demonstrated that prehypertesive individuals present higher left

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ventricular mass and CCA-IMT than their normotensive counterparts [6].

The definition of prehypertension is based on office BP values. However, the application of 24-h ABP monitoring in prehypertensive patients revealed that prehypertension is not a homogeneous BP type. More specifically, this is a mixed condition composed by prehypertensive subjects with normal ABP values (actual prehypertensives) and prehypertensives with elevated ABP values (masked hypertensives) [7]. However, according to JNC-7 guidelines, patients can be either prehypertensives or masked hypertensives, not both. Therefore, prehypertensives with elevated daytime ABP levels, whose behavior regarding target-organ damage resembles that of masked hypertensives, should be conventionally regarded as prehypertensives with MH.

In view of the former considerations, it would be of great interest to clarify whether the association of prehypertension with increased CCA-IMT is due to actual prehypertension or masked hypertension. We aimed to assess which component of prehypertension is mainly associated with CCA intima–media thickening in prehypertensive patients.

2. Methods

2.1. Study population

From January 1999 to January 2009, a consecutive series of 7568 subjects were referred for evaluation to the Outpatient Hypertension Unit of our department. Among them 807 individuals fulfilled the following inclusion criteria: (1) office systolic BP (SBP) <140 and diastolic BP (DBP) <90 mmHg; (2) no previous antihypertensive treatment; (3) absence of clinical evidence of hypertension related complications (coronary artery disease, heart failure, cerebrovascular disease, renal insufficiency or peripheral artery disease); (4) no clinical signs or laboratory evidence of secondary causes of arterial hypertension; (5) at least three valid BP measurements per hour over 24-h ABP monitoring (75% successful measurements), and (6) carotid artery ultrasonographic measurements.

The above group of patients was evaluated by means of 24-h ABP monitoring. Subjects were referred to our laboratory by their primary physician for conventional clinical indications, including suspected nocturnal hypertension, evaluation of hypotension, or symptoms suggesting possible abnormal BP variations such as headache, tinnitus, dizziness, fainting and epistaxis. History of diabetes mellitus, hypercholesterolaimia, cigarette smoking and body mass index were recorded. The study was approved by the local scientific committee and all participants gave informed consent.

Participants were divided into 3 subgroups according to office and daytime BP levels: (1) normotensives: office SBP < 120 mmHg and DBP < 80 mmHg and daytime SBP < 135 mmHg and DBP < 85 mmHg, (2) actual prehypertensives: office SBP (120–139 mmHg) and/or office DBP (80–89 mmHg) and daytime SBP < 135 mmHg and DBP < 85 mmHg, (3) prehypertensives with masked hypertension: office SBP (120–139 mmHg) and/or office DBP (80–89 mmHg) and daytime SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg (Appendix A).

2.2. Office BP measurements

Office BP was measured by a physician three times in each arm using a mercury sphygmomanometer during a single office visit. Individuals with BP differences between the arms greater than 20 mmHg for systolic and 10 mmHg for diastolic BP were excluded from the study (6 subjects). A standard cuff was then applied around the nondominant arm and systolic and diastolic BP values were identified from the first and fifth phase of Korotkoff sounds. During the measurements, the participants remained seated with the arm supported and placed at heart level. The first measurement was taken at the beginning of the medical visit, 5 min after the subject assumed the sitting posture. The second measurement was taken after 5 min and the third immediately before application of the ABP monitoring equipment. In each subject, the three initial BP values provided by the sphygmomanometer were averaged to obtain a single systolic and diastolic office BP value.

2.3. Ambulatory BP monitoring

All subjects underwent 24-h ABP monitoring on a usual working day. They were instructed to act and work as usual and to keep their nondominant arm still and relaxed at the side during measurements. ABP values were recorded using oscillometric Spacelabs 90207 equipment (Spacelabs, Redmond, WA). The office and the ambulatory BP readings were recorded on the same day. Recordings were obtained automatically at 15-min intervals throughout the 24-h study period. Daytime was defined as the interval between 09:00 h and 21:00 h and night-time was the interval between 01:00 h and 06:00 h [8]. For each patient we computed mean daytime and night-time SBP and DBP. All subjects were instructed to rest and sleep during the night-time and to maintain their usual activities during the day. None of the study participants were bedridden or hospitalized during ABP monitoring. Individuals who stated that they had not rested during the night interval were excluded from further evaluation. The accuracy of the ABP monitoring devices was checked monthly by obtaining 10 automatic and 10 ausculatory BP readings simultaneously from the same arm via a Y-tube. In all instances the values did not differ by more than 5 mmHg for each reading.

2.4. Carotid artery ultrasonographic measurements

The left and right CCA were examined in the anterolateral, posterolateral, and mediolateral directions with a high-resolution ultrasound Doppler system (Acuson 128XP), equipped with a 7-MHz linear-array transducer. Subjects were examined in the supine position, with the head turned 45° from the site being scanned. Both carotid arteries were scanned longitudinally to visualize the IMT in the far wall of the artery. The best images of the far wall that could be obtained were used to determine the CCA. Measurements were made on frozen images, magnified to standard size online. The CCA-IMT value was defined as the mean of the right and left IMT of the CCA, calculated from 10 measurements on each side, taken 10 mm proximal to the carotid bifurcation. The lumen/intima leading edge (I-line) to media/adventitia leading edge (M-line) method, which has been previously validated anatomically, was used [9]. Longitudinal B-scan frames were obtained by one experienced operator (CP) [10–12] and subsequently were analyzed offline, manually by two investigators blinded to the BP recordings. The intra observer coefficient of variation of this method in our laboratory was 7.5% as previously described [13].

2.5. Statistical analyses

Statistical comparisons were performed between the 3 subgroups in terms of baseline characteristics, office BP values, ABPM parameters, and CCA-IMT values. Dichotomous variables were compared using the chi-square test and continuous variables were compared using one-way analysis of variance. Bonferroni's correction for multiple comparisons was applied as appropriate. The CCA-IMT (after adjustment for baseline characteristics) was also compared among the three subgroups by means of ANCOVA. The covariate adjusted mean values were computed and are presented with their corresponding 95% CI.