

Increase in Carotid Intima-Media Thickness in Grade I Hypertensive Subjects White-Coat Versus Sustained Hypertension

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Abstract—We studied 74 never-treated grade I hypertensive subjects aged 18 to 45 years and 20 normotensive control subjects to define the rate of increase in carotid intima-media thickness (IMT) and the potential role played by the various risk factors. IMT was assessed as mean IMT and as maximum IMT in the right and left common carotid artery, carotid bulb, and internal carotid artery at baseline and at the 5-year follow-up. In grade I hypertensive subjects, both mean IMT and mean of maximum IMT were significantly higher compared with baseline values. Compared with normotensive subjects, both mean IMT and maximum IMT increased significantly (at least $P<0.01$) in each carotid artery segment. The increase in cumulative IMT was 3.4-fold for mean IMT and 3.2-fold for mean of maximum IMT. Levels of mean arterial pressure at 24-hour monitoring and total serum cholesterol were factors potentially linked to the increment in mean IMT and mean of maximum IMT. Age was also relevant for the increment in mean of maximum IMT, whereas body mass index played some role in the increment of mean IMT. During the follow-up, mean IMT and mean of maximum IMT increased to a greater degree in white-coat hypertensive subjects ($n=35$) and sustained hypertensive subjects ($n=39$) than in normotensive control subjects. No differences were found between white-coat hypertensive subjects and sustained hypertensive subjects for both mean IMT and maximum IMT. Levels of mean arterial pressure at 24-hour monitoring affected the increment in IMT in both white-coat hypertensive subjects and sustained hypertensive subjects. In conclusion, our findings indicate that carotid IMT is greater and grows faster in white-coat hypertensive subjects than in normotensive subjects without significant differences with sustained hypertensive patients. (*Hypertension*. 2008;51:1300-1305.)

Key Words: hypertension ■ carotid artery disease ■ ultrasound ■ carotid atherosclerosis

Epidemiological studies¹ and intervention trials² have established that carotid intima-media thickness (IMT), as measured by ultrasound, is a good marker of atherosclerotic disease. Moreover, ultrasound measurement of carotid IMT has repeatedly been shown to predict the occurrence of both stroke and myocardial infarction in the general population.³ For these reasons, an increased carotid IMT has been considered by some authors as a marker of subclinical atherosclerosis,⁴ although in hypertensive subjects, especially in young subjects, it seems more likely to represent target organ damage.⁵ IMT has also been taken as a surrogate end point for clinical events in several intervention trials using antihypertensive medications.⁶ Blood pressure (BP) plays a role in the increase in carotid IMT in many⁷ but not all studies,⁸ and prospective data on the time course of IMT growth and the relative impact of the various risk factors are not defined in untreated hypertensive subjects.

In a previous cross-sectional study, we have evaluated a cohort of never-treated, young subjects with grade I hyper-

tension, enrolled at the University of Padova within the frame of the Hypertension and Ambulatory Recording VEnetia STudy (HARVEST).⁹ It turned out that, compared with normotensive control subjects, a greater IMT was present in the common carotid artery, in the bulb, and in the internal carotid artery and that BP levels and plasma lipids were among the main determinants of carotid IMT.⁹

We, therefore, sought to establish in the same cohort the time course of carotid artery remodeling along with the role played by the various risk factors in a 5-year follow-up study. One main aim of the present study was to evaluate the characteristics of carotid artery IMT in white-coat hypertension subjects (WCHs) in comparison with sustained hypertensive subjects (SHs).

Methods

Subjects

We studied 74 grade I hypertensive subjects (60 men and 14 women) aged at enrollment 18 to 48 years (30.5 ± 8.7 years), never treated for

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hypertension, taking part in the HARVEST in the center of Padova. The HARVEST is a prospective study aimed at evaluating the prevalence and the progression of markers of each target organ damage in young subjects at low cardiovascular risk screened for stage I hypertension. Subjects having a systolic BP in the 140 to 159 mm Hg range or a diastolic BP in the 90 to 99 mm Hg range at screening were considered for inclusion in the HARVEST.⁹ All of the hypertensive subjects underwent 24-hour ambulatory BP monitoring (ABPM) during a routine working day. Subjects with daytime ambulatory BP <135/85 mm Hg were defined as WCHs.¹⁰ Twenty normotensive volunteers (10 men and 10 women) aged 32.8 ± 7.4 years (P not significant versus grade I hypertensive subjects) at enrollment underwent routine biochemical analyses and the same ultrasound procedures as the grade I hypertensive subjects. None of the subjects were taking medications. The study was conducted in accordance with the Helsinki Declaration and institutional procedures. All of the subjects gave their informed consent.

Carotid and Cardiac Ultrasound Studies

Carotid ultrasound examinations of the common carotid artery, bulb, and internal carotid artery were performed bilaterally using the Bio-sound 2000 II SA equipped with an 8-MHz annular array mechanical transducer (Esaote) according to our previous study.⁹ In each carotid artery segment, measurements of mean (mean IMT) and maximum IMT were taken. Moreover, the common carotid diameter, the mean of the maximum IMT recorded in 12 segments, and the prevalence of raised lesions (raised lesions: IMT >1 mm and a 100% increase in thickness compared to normal adjacent wall segments) were established in each subject (please see <http://hyper.ahajournals.org>).

The mean difference for repeat measurements of mean IMT was 0.012 ± 0.052 mm (coefficient of variation: 4.44%; coefficient of correlation: $r=0.878$; $P<0.0005$). The mean difference for repeat measurements of maximum IMT was 0.003 ± 0.031 mm (coefficient of variation: 9.65%; coefficient of correlation: $r=0.979$; $P<0.0005$). Finally, the Bland-Altman statistics confirmed the good reproducibility of measurements. Subjects were also studied for albuminuria excretion rate and by M-mode and bidimensional echocardiography according to previously described procedures.⁹

Statistical Methods

Hypertensive subjects and normotensive control subjects were compared by ANOVA and the 2-sided Tukey's posthoc test. The mean IMT and the mean of maximum IMT were analyzed separately with ANCOVA after correction for age, sex, plasma lipids, smoking habits, and body mass index (BMI). Correlation between mean IMT and mean of maximum IMT, respectively, and other continuous variables was evaluated by double-precision multivariate analysis, indicating the multiple r and considering a $P<0.05$ as significant. The SYSTAT 10.0 package was used.

Results

At baseline, 97 grade I hypertensive subjects and 27 normotensive subjects were enrolled in the carotid ultrasound study. At the 5-year follow-up, 74 grade I hypertensive subjects still untreated and 20 normotensive subjects completed the study.

Data related to main risk factors of grade I hypertensive subjects are reported in Table 1. Compared with values at enrollment, at follow-up, grade I hypertensive subjects showed higher BMI and plasma total cholesterol. Values of office systolic BP, diastolic BP, and mean arterial pressure (MAP) did not change with time, whereas ambulatory 24-hour systolic BP, diastolic BP, and MAP increased significantly. Compared with the 20 normotensive control subjects, at enrollment, grade I hypertensive subjects showed higher office systolic BP (144 ± 11 mm Hg versus 121 ± 10 mm Hg in control subjects; $P<0.0005$), diastolic BP (92 ± 6 mm Hg versus 76 ± 8 mm Hg in control subjects; $P<0.0005$), MAP

Table 1. Data From Grade I Hypertensive Subjects

Variable	Baseline (N=74)	Follow-Up (N=74)	P
BMI, kg/m ²	24.4 ± 2.9	25.2 ± 3.0	<0.0005
Total cholesterol, mg/dL	195.9 ± 38.0	213.1 ± 37.2	0.005
No.	71	54	
HDL-C, mg/dL	57.3 ± 18.1	57.5 ± 14.0	NS (0.844)
No.	46	24	
Triglycerides, mg/dL	114.9 ± 53.2	120.0 ± 59.0	NS (0.870)
No.	71	54	
Glucose, mmol/L	89.7 ± 11.7	94.7 ± 11.3	NS (0.222)
No.	70	25	
Systolic BP, mm Hg	144.1 ± 11.4	142.8 ± 16.2	NS (0.522)
Diastolic BP, mm Hg	91.6 ± 6.3	92.8 ± 10.4	NS (0.256)
MAP, mm Hg	109.1 ± 5.5	109.5 ± 11.1	NS (0.771)
Heart rate (bpm)	75.2 ± 8.5	73.0 ± 11.1	0.042
ABPM systolic BP, mm Hg	128.3 ± 9.3	132.6 ± 11.3	<0.0005
No.		64	
ABPM diastolic BP, mm Hg	79.5 ± 6.7	83.7 ± 7.9	<0.0005
No.		64	
ABPM MAP, mm Hg	95.8 ± 6.3	100.0 ± 8.4	<0.0005
No.		64	
ABPM heart rate (bpm)	71.7 ± 7.4	72.7 ± 7.4	NS (0.189)
No.		64	

HDL-C indicates high-density lipoprotein cholesterol; NS, not significant. MAP is defined as diastolic BP + (systolic BP – diastolic BP)/3. Mean $\pm$ SD is reported unless otherwise specified. Continuous variables were analyzed by paired t test.

(109 ± 5 mm Hg versus 91 ± 8 mm Hg in control subjects; $P<0.0005$), and BMI (24.4 ± 2.9 versus 22.1 ± 2.3 in control subjects; $P=0.002$). Age, plasma lipids, heart rate, smoking habits, and physical activity habits were comparable in the 2 groups (data not shown).

At enrollment, values of cumulative mean IMT and mean of maximum IMT were significantly higher in grade I hypertensive subjects compared with control subjects (Table 2). At the 5-year follow-up, values of the above IMT parameters increased significantly in grade I hypertensive subjects (Table 2). A less-remarkable, although statistically significant, increment was also observed in control subjects (Table 2). As far as mean IMT and maximum IMT in the various carotid artery segments is concerned, higher follow-up values were observed in grade I hypertensive subjects compared with control subjects (Table S1, available at <http://hyper.ahajournals.org>). The average increment in mean IMT in the 5-year time span was much more pronounced in all of the carotid artery segments of grade I hypertensive subjects compared with normotensive control subjects (Figure 1A). The same trend was observed for maximum IMT and its mean cumulative value (Figure 1B). Accordingly, the prevalence of raised lesions was significantly higher in hypertensive subjects than in control subjects at baseline, as well as at follow-up: 10.3% in hypertensive subjects versus 3.7% in control subjects ($P<0.001$) and

Table 2. Values of Mean IMT (mm) and Mean of Maximum IMT (mm) Recorded at Baseline and Follow-Up in the 2 Groups

Variable	Grade I Hypertensive Subjects (n=74)	Control Normotensive Subjects (n=20)	P
Mean IMT T1	0.46±0.08	0.41±0.08	0.033
P	<0.0005	0.003	
Mean IMT T2	0.57±0.09	0.46±0.10	<0.0005
Mean of maximum IMT T1	0.59±0.09	0.51±0.10	0.002
P	<0.0005	0.007	
Mean of maximum IMT T2	0.70±0.12	0.54±0.13	<0.0005

T1 indicates baseline; T2, 5-year follow-up. Mean±SD is reported unless otherwise shown. Differences of continuous variables between groups were analyzed by ANCOVA adjusted for sex, BMI, serum lipids, smoking, heart rate, and age. Differences between baseline and follow-up values were analyzed by paired *t* test.

16.2% in hypertensive subjects versus 5.0% in control subjects ($P<0.001$), respectively. It should be noted that, after adjusting for MAP at enrollment, almost all of the differences in the IMT parameters reported in both Table 2 and Figure 1 were no longer significant.

As far as the role played by the various risk factors is concerned, the multivariate regression analysis (Table 3)

Increment in carotid artery IMT in the two groups

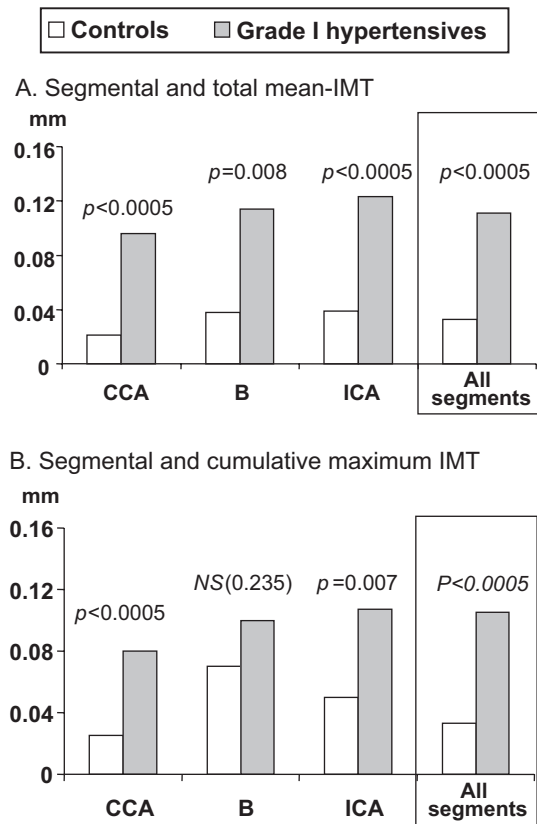


Figure 1. Time-related increment in carotid artery IMT in the 2 groups. A, Difference in segmental and cumulative mean IMT (boxed). B, Difference in maximum IMT recorded bilaterally at each carotid artery segment and in mean of maximum IMT (boxed). CCA indicates common carotid artery; B, bulb; ICA, internal carotid artery.

Table 3. Multivariate Regression Analysis for Factors Potentially Linked to Increased IMT in Grade I Hypertensive Subjects (n=74; Best Models)

Individual Variables	Coefficient	SEs	P
Increment of mean IMT			
Intercept	-0.467		
MAP at ABPM T1	0.436	0.001	<0.0005
Total cholesterol T1	0.231	0.0005	0.025
BMI T1	0.187	0.002	0.075 (NS)
Increment of mean of maximum IMT			
Intercept	-0.471		
MAP at ABPM T1	0.338	0.001	<0.0005
Age	0.280	0.001	0.013
Total cholesterol T1	0.224	0.0005	0.040

For increment of mean IMT, multiple $r^2=0.317$ ($P<0.0005$); for increment of mean of maximum IMT, multiple $r^2=0.336$ ($P<0.0005$). T1 indicates value at baseline.

showed that levels of MAP at ABPM and total serum cholesterol at enrollment were factors linked to the increment in cumulative mean IMT and mean of maximum IMT. Age was also relevant for the increment in mean maximum IMT, whereas BMI played some role in the increment of mean IMT. Before and after adjustment for age, sex, heart rate, BMI, smoking, and serum lipids, both left and right carotid artery diameters were similar in the 2 groups at baseline, as well as at follow-up.

According to the present criteria,¹⁰ we stratified the 74 untreated stage 1 hypertensive subjects according to whether they were WCH (n=35) or SH (n=39) at baseline assessment. At baseline, WCHs were younger (27.9 ± 8.3 versus 32.7 ± 8.6 years; $P=0.017$) than SHs. No between-group difference was found as far as sex, BMI, total cholesterol, or triglycerides were concerned. In all of the carotid segments, the baseline mean IMT did not differ between the 2 hypertensive groups and was similar to that in the normotensive control subjects (data not shown). Segmental and cumulative means of maximum IMT were similar in WCHs and SHs, and values of both parameters were slightly higher compared with normotensive subjects (WCHs versus normotensive subjects: $P=0.004$; SHs versus normotensive subjects: $P=0.049$; data not shown). During the 5-year follow-up, cumulative mean IMT and mean of maximum IMT increased to a greater degree in the WCHs and SHs than in the normotensive control subjects (Figure 2). No significant differences were found between WCHs and SHs for both mean IMT ($P=0.27$) and mean of maximum IMT ($P=0.18$). At multivariate analysis (Table 4), the value of MAP at baseline ABPM was a common factor affecting the increment of IMT in both WCHs and SHs.

At follow-up, in grade I hypertensive subjects, a mild increase in the left ventricular mass index was observed (96.0 ± 14.7 versus 90.8 ± 16.1 g/m² at baseline; $P=0.028$). However, neither absolute values of ventricular mass nor its increment were related to any IMT parameters or their changes over time. Albuminuria level did not change significantly over time (18.2 ± 60.5 versus 12.1 ± 32.8 mg/24 hours

Increment in cumulative carotid artery IMT in normotensive controls and Grade I hypertensives

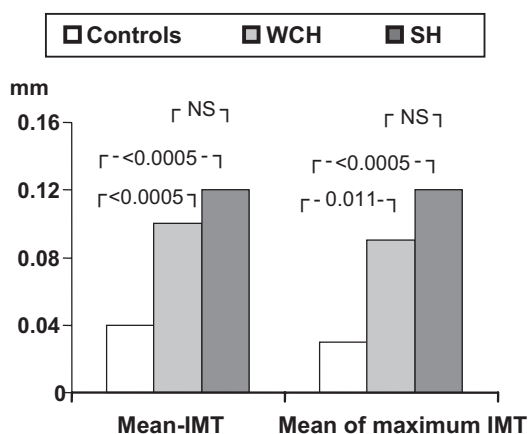


Figure 2. Time-related increment in cumulative carotid artery IMT in WCHs or SHs and control subjects.

at baseline; *P* value not significant), and its changes did not correlate with changes in IMT measurements.

Discussion

Among the various factors affecting the degree of carotid IMT, high BP ranks as a major determinant not only in elderly subjects¹¹ but also in adolescents and children.¹² The impact of various parameters of BP, such as systolic and diastolic values, mean BP, pulse pressure, and values from 24-hour continuous monitoring on carotid IMT, has been extensively evaluated in population studies, as well as in intervention trials. From these studies, the annual rate of change in mean and in the mean maximum IMT of common carotid artery of control groups has been estimated,⁶ and various intervention trials have yielded the amount of IMT progression or regression observed in groups of treated hypertensive subjects.² However, studies specifically designed to assess the progression of IMT in the various carotid

artery segments in the early stage of hypertension were not conducted. Although the biological meaning of IMT remains debated,¹³ this issue is of importance, as one may infer the expected rate of progression of cardiovascular risk from the rate of growth of IMT.^{1,6}

Data from the present study showed that, at the end of follow-up, in grade I hypertensive subjects who did not require antihypertensive treatment, an increase in cumulative carotid IMT took place that was 3.4-fold greater for mean IMT and 3.2-fold for mean of maximum IMT compared with normotensive control subjects, despite the significant time-related increase, which was also observed in the latter (Figure 1 and Table 2). A higher degree of IMT was observed in each carotid artery segment (common, bulb, and internal) of grade I hypertensive subjects in comparison with normotensive subjects (Figure 1 and Table 2). This was true for both mean IMT and mean maximum IMT, although the increase in mean maximum IMT was less remarkable than the one observed for mean IMT. A similar behavior of mean IMT versus mean of maximum IMT was also observed in the ELSA study¹⁴ and may indicate that initial carotid artery lesions (ie, thickening of intima layer) do not progress in the same way as advanced lesions. This is in agreement with data from the PathoBiological Determinants of Atherosclerosis in Youth (PBDAY) Study¹⁵ showing that some initial intima lesions (type IIa) are not prone to further progression, whereas others (type IIb) are. Although the possibility exists for detecting these lesions by qualitative ultrasound image analysis,¹⁶ this was not feasible at the time that the HARVEST was started. At variance with previous studies,^{17,18} there was no relationship between the observed increase in left ventricular mass index and the various parameters of carotid artery IMT, but this was not surprising, because our study was not powered to investigate this aspect. As far as the prevalence of raised lesions is concerned, both at baseline and follow-up, it was significantly higher in grade I hypertensive subjects compared with normotensive control subjects. A difference in the prevalence

Table 4. Multivariate Regression Analysis for Factors Potentially Linked to Increased IMT in White-Coat or Sustained Grade I Hypertension Subjects (Best Models)

Individual Variables	White-Coat Hypertension (n=35)			Sustained Hypertension (n=39)		
	Coefficient	SE	P	Coefficient	SE	P
Increment of mean IMT						
Intercept	-0.483			-0.728		
MAP at ABPM T1	0.417	0.002	0.010	0.470	0.002	0.001
Age	0.372	0.001	0.019	0.294	0.003	0.038
Triglycerides	0.317	0.0005	0.039			
Increment of mean of maximum IMT						
Intercept	-0.540			-0.624		
MAP at ABPM T1	0.353	0.003	0.019	0.390	0.002	0.013
Age	0.533	0.001	0.001	0.261	0.0005	NS (0.087)
BMI	-0.275	0.004	NS (0.058)			
Triglycerides	0.262	0.0005	NS (0.074)			

Increment of mean IMT for WCHs was multiple $r^2=0.393$ ($P=0.002$) and for SHs was multiple $r^2=0.340$ ($P=0.001$). Increment of mean of maximum IMT for WCHs was multiple $r^2=0.477$ ($P=0.001$) and for SHs was multiple $r^2=0.239$ ($P=0.008$). T1 indicates value at baseline; NS, not significant.

of raised lesions was also found in previous intervention trials,^{14,19} but a direct comparison is not appropriate because of discrepancies in design among studies. It should be noted that the remodelling of carotid arteries occurred in the absence of any changes in carotid artery diameter, which may affect IMT measurements,²⁰ and was endorsed by the good reproducibility of measurements of IMT.

It is worth noting that data from the Finnish Study involving 1257 healthy men >42 years of age²¹ showed that each increase in IMT of 0.1 mm resulted in an 11% increase in the risk of myocardial infarction. Therefore, it seems reasonable to infer that a similar increase in risk took place in our cohort of young subjects, because we found a cumulative increase of 0.111 mm/5 years and 0.105 mm/5 years in mean IMT and in mean maximum IMT (Figure 1), respectively.

The multivariate regression analysis for factors potentially underlying the increase in carotid artery IMT (Table 3) showed that baseline values of MAP at ABPM, plasma total cholesterol, and BMI were factors linked to the increment in mean IMT. Baseline values of MAP at ABPM, age, and BMI were factors related to the increment in maximum IMT. The importance of baseline MAP was further evidenced by the fact that, after adjusting for this parameter, most of the difference in IMT observed between the normotensive and the hypertensive subjects was lost.

The clinical importance of WCH remains a controversial issue. WCH has been considered a benign clinical condition for long, but recent studies performed in large samples followed for long periods of time indicated that WCHs may be at increased risk of events.^{22,23} In our series we found that, compared with SHs, WCHs were slightly younger and had lower BP at ABPM. In spite of these differences, the increment in cumulative carotid artery IMT (both mean and maximum IMT) was similar in WCHs and SHs and significantly higher in both groups compared with normotensive control subjects (Figure 2). Such an increment in IMT of WCHs was not observed in the cross-sectional series from the Ohasama Study,²⁴ but this can be related to the fact that 34% of the WCHs enrolled in the Ohasama Study were on antihypertensive medication. Moreover, differences in study design, method of out-of-office BP measurement (home versus ambulatory), age, and risk factor profiles of the 2 cohorts make it difficult to compare the 2 studies. Our observation emphasizes the relevance of white-coat hypertension in promoting carotid artery remodelling. Moreover, given the fact that the degree of carotid IMT predicts the occurrence of overt carotid atherosclerosis and stroke,³ our finding can help explain the increased rate of stroke described in WCH patients in a previous report, which included the Ohasama cohort.²⁴ In the multivariate analysis (Table 4), age, and metabolic factors such as the baseline BMI and triglycerides were factors particularly involved in the remodelling of carotid arteries of WCHs. This observation is in line with recent clinical studies in which prehypertension was associated with higher prevalence of metabolic syndrome compared with normotensive status.²⁵ Psychological stress is another factor potentially involved in the progression of carotid IMT,²⁶ and hyperactivity to stressful stimuli has been described in WCHs.²⁷

Perspectives

Our study indicates that, in young grade I hypertensive subjects whose BP remained below the criteria for treatment, carotid IMT is greater and grows faster than in normotensive subjects. This potentially implies an increased risk of cardiovascular events and prompts for a more tight clinical control along with target organ surveillance. The unfavorable remodeling of carotid arteries observed in our WCHs, similar to SHs, represents a novel and partly unexpected observation. Thus, WCHs should not be regarded as having a benign condition, because it may increase susceptibility to vascular complications early in life. Future studies should be aimed at better defining the pathophysiological mechanisms underlying the increase in carotid artery IMT in WCHs, as well as the incidence of hard events, such as stroke and myocardial infarction in this category of hypertensive subjects. These observations indirectly support the policy for early and tight BP control strengthened by the recent European Society of Cardiology/European Society of Hypertension guidelines¹⁰ even in young subjects at low cardiovascular risk.

Disclosures

None.

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