Factors Underlying the Increase in Carotid Intima-Media Thickness in Borderline Hypertensives


Abstract—To define the role played by various risk and behavioral factors in the increase of carotid intima-media thickness (IMT) observed in borderline hypertensives. Using B-mode ultrasonography, we compared 97 borderline hypertensives enrolled in the HARVEST study to 27 normotensive controls. Intima-media thickness was measured in the right and left common carotid artery, bulb, and internal carotid artery. Mean IMT (m-IMT), maximum IMT (M-IMT), the mean of M-IMT (M-MAX), and the prevalence of raised lesions (IMT > 1 mm) were established. Compared to the controls, higher systolic BP, diastolic BP, mean arterial blood pressure levels and body mass index (BMI) were present in the borderline hypertensives, whereas age, smoking, physical activity, serum cholesterol, and triglycerides were similar. After adjusting for age, sex, heart rate, BMI, smoking, serum cholesterol, triglycerides, and physical activity, higher values of m-IMT and M-IMT were present in most carotid segments of borderline hypertensives compared with controls. After further adjustment for systolic BP and diastolic BP, differences were no longer significant. The adjusted M-MAX was 0.59 ± 0.12 in borderline hypertensives compared with 0.50 ± 0.10 in controls (P < 0.001). After adjustment for systolic BP and diastolic BP it was 0.58 ± 0.11 in borderline hypertensives compared with 0.50 ± 0.12 in controls (P < 0.005). In the various carotid segments, the prevalence of raised lesions was 1.2% in borderline hypertensives compared with 0.3% in controls (P < 0.001). In the multivariate analysis m-IMT, M-IMT, and M-MAX were related to ambulatory mean arterial pressure, systolic BP and diastolic BP, serum cholesterol and triglycerides, BMI, age, and physical activity. Higher IMT values were found in subjects who were physically active than in those who were sedentary. In borderline hypertensives, an increase in IMT takes place not only in the common carotid artery but also in the bulb and the internal carotid segment. Blood pressure levels are a main determinant of m-IMT while the interaction of BP with other risk factors such as age and plasma lipids is more relevant for advanced intima-media thickening such as M-MAX. (Arterioscler Thromb Vasc Biol. 1999;19:1231-1237.)

Key Words: intimal-medial thickness ■ carotid ■ borderline hypertension ■ risk factors

The carotid arteries are among the vessels that are prone to developing overt atherosclerotic lesions in the presence of risk factors such as cigarette smoking and hypertension.1,2 For this reason, several studies have been conducted with hypertensive subjects using ultrasound assessment of the intima-media thickness (IMT), which is taken as a reliable surrogate measurement of intimal thickening.3–5 Although there is evidence for an excess prevalence of intimal thickening and atherosclerotic lesions in patients suffering from definite hypertension compared with normotensive controls,3–5 medial hypertrophy can also occur in hypertensives,7–9 which cannot be distinguished from intimal thickening using ultrasound techniques. In addition to the increase in BP, hemodynamic factors such as cardiac output, heart rate, wall stress, shear stress, and pulse pressure may play an important role in the development of both intimal and medial hypertrophy.8,9,10 Whatever the nature of ultrasound IMT can be, previous studies support the view that it predicts coronary atherosclerosis8 and cerebrovascular events.3,7,11,12

Unfortunately, limited data on borderline hypertensives and carotid IMT are available, and there is some conflict in these findings. In the few studies reported in the literature thus far,13–15 values of common carotid IMT were higher in borderline hypertensives than in controls. While a relationship between BP levels and IMT of common carotid artery was found by univariate analysis of 20 borderline hypertensives in one study,13 none was found in the 73 borderline hypertensives studied by Lemne et al14 using multivariate analysis. In this latter study, the increase in carotid IMT was related to plasma lipids only, suggesting that in borderline hypertensives, a selective increase of the intimal component of IMT takes place. Moreover, data on IMT of carotid bulb and the internal carotid artery of borderline hypertensives are lacking in the literature.

The aim of the present study was to investigate the degree of IMT in the different carotid artery segments (common, bulb, internal) and the role of various risk and behavioral factors in borderline hypertensives enrolled in the HAR-
VESST. The HARVEST is a multicenter, perspective follow-up aimed at evaluating the prevalence and the progression of target organ damage in young borderline hypertensives. Our data show that in borderline hypertensives, an increase in IMT takes place in the different carotid artery segments. These findings seem to be related to BP, physical activity, serum cholesterol levels, BMI, and age.

Methods

Subjects

We studied 97 borderline hypertensives enrolled in the HARVEST and 27 normotensive control subjects. The HARVEST is a perspective, observational program which is being carried out in 18- to 45-year-old borderline hypertensives. The program was started in 1992. According to the HARVEST protocol, these borderline hypertensives are surveyed yearly. Anamnestic, clinical, and anthropometric data are collected. In particular, data on the onset of elevated BP, smoking habit, and physical or sports activity are collected. Physical activity is recorded. In particular, data on the onset of elevated BP, smoking habit, and physical or sports activity are collected. Physical activity is categorized as follows: fully sedentary, light physical activity, noncompetitive exerciser, competitive exerciser. Smokers are classified according to the number of cigarettes consumed per day.

BP levels and mean arterial pressure calculated as diastolic BP + (systolic BP - diastolic BP)/3, are defined by office measurements and 24-hour ambulatory BP monitoring using the A&D TM-2420 model 7 equipment. Office BP and heart rate are taken after 5 minutes rest in the supine position. Systolic BP and diastolic BP are defined according to Korotkoff sounds I and V, respectively. The mean of 6 different measurements performed at two different occasions is considered for inclusion in the HARVEST. Details about the ambulatory BP monitoring procedures have been published elsewhere. During the recordings, subjects are invited to follow their ordinary routine. In the exercisers, ambulatory BP monitoring is performed on a nonactive day. Subjects are asked to go to bed no later than 11 PM. BP and heart rate are measured every 10 minutes during waking hours (6 AM to 11 PM) and every 30 minutes during the nighttime.

Target organ involvement is investigated by assessment of proteinuria, staging of retinopathy according to Keith and Wegener, and echocardiography. The presence of secondary hypertension is ruled out on the basis of anamnestic criteria (family history, onset of hypertension, etc.), 24-hour urine collection for Na+, K+, catecholamine assessment, testing for plasma renin activity and aldosterone levels, and sequential nephroangiophotoscintigraphy.

Routine biochemical analyses including plasma lipids are also performed, as previously described. The protocol was approved by the local ethics committee and is being conducted in accordance with the Helsinki Declaration.

We invited the last 140 borderline hypertensives (systolic BP 140 to 159 mmHg and/or diastolic BP 90 to 94 mmHg) enrolled in the HARVEST to participate in the carotid ultrasound study. Of the 114 subjects who had the carotid ultrasound scans repeated twice, was 97 in the borderline hypertensive group, and 27 in the control group. None of the subjects participating in the carotid ultrasound study had evidence of cardiovascular disease or diabetes, and none were taking medications. All subjects gave their informed consent.

Carotid and Cardiac Ultrasonography

Ultrasonic examinations were performed using the Biosound 2000 II SA equipped with an 8 MHz annular array mechanical transducer. This system provides an axial resolution of about 0.10 mm. The pixel size of the B-mode at the reading station is 0.067 mm. Hence, measurements of any IMT greater than 0.10 mm are quantified during the measurement process in multiples of 0.067 mm. The right and left carotid arteries of each subject were examined by the same sonographer who was not aware of subjects’ BP levels. All subjects were examined in the same room in dim light, lying comfortably in the supine position. During the scans, the head was slightly turned from the sonographer. On average, the duration of the examination was 30 to 40 minutes. Once an optimal longitudinal image was obtained, it was stored on ½-inch super VHS videotape. Images were analyzed by two independent readers using a high-resolution videorecorder, coupled with a mouse-driven image analysis system. Intima-media thickness, defined as the distance between the lumen-intima and the media-adventitia interfaces, was measured at end-diastole in the far wall of the right and left sides of the common carotid artery, the bulb, and the internal carotid artery in lateral and posterior projection. The procedure described in the ARIC protocol was adopted. In summary, in 1 standard cm (right and left common carotid artery: proximal to the dilatation of the bulb, right and left carotid bulb: proximal to the flow divider, right and left internal carotid artery: distal to the flow divider) of the above 12 arterial segments, 10 measurements of IMT were taken at 1-mm increments. In each segment, mean IMT (m-IMT), and maximum IMT (M-IMT) were assessed. Moreover, according to previous observations, the mean of the M-IMT recorded in the 12 segments (M-IMT-MAX), and the prevalence of raised lesions (Raised lesions: IMT ≥ 1 mm, and a 100% increase in thickness compared to normal adjacent wall segments) was established in each subject. For raised lesions, the cutoff of 1 mm was taken in agreement with previous studies. To rule out potential interference of arterial diameter enlargement with IMT measurements, both intraluminal and interadventitial diameters of common carotid artery 1 cm proximal to the dilatation of the bulb were measured at end diastole in lateral projection. Both the radius/thickness and the lumen/wall ratios were established.

For each parameter, the mean value of measurements performed by the two readers was used. The interobserver variability was evaluated on the measurements obtained from all subjects participating in the study. In order to establish the intraobserver variability, a group of 20 randomly chosen subjects’ scans were repeated a few weeks later. Variability was measured as: 1). mean difference of repeated measurements according to the formula Σ (IMT1i−IMT2i)/n, that is, the sum of differences of two IMT measurements for n subjects divided by n², and 2). coefficient of variation according to the formula [Sx100/(S/2)], where S is the observer error (SD of the mean difference/√2) multiplied by 100 divided by the pooled mean values.

The staff involved in the ultrasonographic study have undergone the same training since 1993, with external survey periodically carried out by the Wake Forest University, Durham, NC. The intraobserver variability of IMT measurements was evaluated by comparing values obtained from the two sets of scans evaluated by each reader (97 borderline hypertensives+27 control subjects) was 0.05±0.10 mm (coefficient of variation 2.15%). By comparing the two sets of data obtained by the readers, a constant tendency to under- or overestimate, respectively, was found for each of them. The use of either set of measurements or of the mean value of the two sets yielded the same final outcome. The intraobserver variability, as assessed in the 20 subjects who had the carotid ultrasound scans repeated twice, was 0.05±0.02 mm (coefficient of variation 3.59%) and 0.06±0.01 mm (coefficient of variation 2.03%), respectively. For common carotid artery diameter measurements, the intraobserver variability was 0.15±0.24 mm (coefficient of variation 1.55%). The intraobserver variability was 0.08±0.23 mm (coefficient of variation 3.1%) and 0.03±0.24 mm (coefficient of variation 8.38%), respectively.

Subjects were also studied by M-mode and -dimensional echocardiography as previously described. Left ventricular internal diameter and wall thickness were measured at end diastole. Left ventricular mass was calculated according to the following equation: 0.81[IVS+LVID+PWT]−LVID³+0.6, where IVS is intraventricular septum in diastole, LVID is left ventricular end-diastolic diameter, and PWT is posterior wall thickness in diastole. Left ventricular mass index was established after correction for body surface area (LVMi, g/m²). Left ventricular stroke volume was calculated as end-diastolic volume minus end-systolic volume. Cardiac output (CO, L/min·m²) was indexed by body surface area.
TABLE 1. Demographic Data of the 2 Groups

<table>
<thead>
<tr>
<th></th>
<th>Borderline Hypertensives (N=97)</th>
<th>Control Normotensives (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males:females</td>
<td>76:21</td>
<td>15:12</td>
</tr>
<tr>
<td>Age, years</td>
<td>31 ± 7</td>
<td>30 ± 9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>145 ± 11</td>
<td>121 ± 9</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>92 ± 6</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>109 ± 5</td>
<td>90 ± 8</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>75 ± 9</td>
<td>72 ± 7</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>24 ± 3</td>
<td>22 ± 3</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.63 ± 0.64</td>
<td>4.99 ± 0.96</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.08 ± 0.12</td>
<td>1.19 ± 0.60</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.99 ± 0.59</td>
<td>5.05 ± 0.49</td>
</tr>
<tr>
<td>Fully sedentary/exercisers</td>
<td>50:47</td>
<td>13:14</td>
</tr>
<tr>
<td>Smokers/nonsmokers</td>
<td>18:79</td>
<td>7:20</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; BMI, body mass index; TC, plasma total cholesterol; and TG, plasma triglycerides.

Mean ± SD is reported.

Statistical Methods

Continuous variables were averaged and values expressed as mean ± SD. Normality of the two groups was previously ascertained with the Wilks and Shapiro test. Study and control groups were first compared with analysis of variance (ANOVA) and Bonferroni’s correction. The m-IMT, the M-IMT, and the M-MAX were analysed separately. As body mass index (BMI) was different in borderline hypertensives and in normotensive controls (Table 1), values of ultrasound measurements were corrected for BMI and all demographic variables using the 2V program of BMDP statistical package. Adjusted values were compared once more with analysis of covariance. A further adjustment for systolic and diastolic BP was then performed in order to elucidate the role of BP in determining arterial wall thickness. The null hypothesis was always rejected when P<0.05.

Differences in prevalence of categorical variables were evaluated with multilway frequency tables and compared with Pearson χ², a P<0.05 being considered as significant. Correlation between m-IMT, M-IMT, and M-MAX, respectively, and other continuous variables (age, 24-hour BP and heart rate, BMI, physical activity, serum cholesterol and triglycerides) was evaluated by double-precision multivariate analysis, indicating the multiple r and considering as significant a P<0.05.

Results

The demographic data are reported in Table 1. Compared to normotensive controls, BH showed significantly higher office systolic BP, diastolic BP, mean arterial pressure, and BMI, whereas age, serum cholesterol and triglycerides, glucose, smoking habit, and physical activity were similar. All women in the two groups were premenopausal. A comparable level of physical activity was present in the borderline hypertensives and in the controls: fully sedentary 50 (51.5%) compared with 13 (48.1%), light physical activity 23 (23.7%) compared with 7 (25.9%), noncompetitive exerciser 14 (14.4%) compared with 5 (18.5%), competitive exerciser 10 (10.3%) compared with 2 (7.4%). Among the 97 borderline hypertensives, 27 showed isolated systolic borderline hypertension (office systolic BP ≥140 and diastolic BP <90 mm Hg), another 29 showed isolated diastolic borderline hypertension (office systolic BP <140 and diastolic BP >90 mm Hg), and the remaining 41 showed an increase in both systolic and diastolic values. In the borderline hypertensives, the 24-hour ambulatory BP monitoring showed systolic BP values of 129.1±9.2 mm Hg (range 110.0 to 152.1 mm Hg), diastolic BP values of 80±7.3 mm Hg (range: 61.4 to 94.8 mm Hg), and mean arterial pressure values of 96.1±6.6 mm Hg (range 80.0 to 109.0 mm Hg). From the analysis of the anamnestic data, it turned out that in the borderline hypertensives, the presence of office BP values above the normal range was detected, on average, 38.1 months before the inclusion in the HARVEST.

Table 2 shows the values of m-IMT and M-IMT found in borderline hypertensives and in normotensive controls after adjusting for age, sex, heart rate, BMI, smoking, physical activity, plasma cholesterol and triglycerides. In borderline hypertensives, the m-IMT values were higher than in normotensive controls although the difference was statistically significant for the left carotid artery and the left internal carotid only. When considering the values of M-IMT, the difference between borderline hypertensives and controls was clearcut. In fact, significantly higher values of M-IMT were found at all sites but the right internal carotid.

Except for m-IMT of the right internal carotid compared with that of the left internal carotid of control subjects, values of m-IMT and M-IMT as measured at right and left side did not differ significantly in either of the groups.

After a further adjustment for office systolic BP and diastolic BP was accomplished on values of m-IMT and M-IMT reported in Table 2, the above differences were no longer significant.

TABLE 2. m-IMT (A) and M-IMT (B) Recorded in the Different Carotid Artery Segments

(A)

<table>
<thead>
<tr>
<th></th>
<th>m-IMT</th>
<th>RCA</th>
<th>LCA</th>
<th>RCA+LCA</th>
<th>RBU</th>
<th>LBU</th>
<th>RBU+LBU</th>
<th>LIC</th>
<th>RIC+LIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH (n=97)</td>
<td>0.44±0.11</td>
<td>0.49±0.09</td>
<td>0.48±0.09</td>
<td>0.48±0.12</td>
<td>0.47±0.10</td>
<td>0.49±0.12</td>
<td>0.40±0.11</td>
<td>0.39±0.09†</td>
<td>0.41±0.10</td>
</tr>
<tr>
<td>C (n=27)</td>
<td>0.41±0.12</td>
<td>0.41±0.11</td>
<td>0.44±0.10</td>
<td>0.42±0.12</td>
<td>0.42±0.12</td>
<td>0.44±0.10</td>
<td>0.40±0.12</td>
<td>0.30±0.10</td>
<td>0.37±0.11</td>
</tr>
</tbody>
</table>

(B)

<table>
<thead>
<tr>
<th></th>
<th>m-IMT</th>
<th>RCA</th>
<th>LCA</th>
<th>RCA+LCA</th>
<th>RBU</th>
<th>LBU</th>
<th>RBU+LBU</th>
<th>LIC</th>
<th>RIC+LIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH (n=97)</td>
<td>0.60±0.10</td>
<td>0.62±0.12</td>
<td>0.61±0.09</td>
<td>0.66±0.16</td>
<td>0.63±0.14</td>
<td>0.64±0.12</td>
<td>0.53±0.13</td>
<td>0.50±0.12†</td>
<td>0.53±0.11*</td>
</tr>
<tr>
<td>C (n=27)</td>
<td>0.50±0.11</td>
<td>0.49±0.13</td>
<td>0.49±0.10</td>
<td>0.53±0.17</td>
<td>0.49±0.16</td>
<td>0.51±0.14</td>
<td>0.49±0.15</td>
<td>0.38±0.13</td>
<td>0.45±0.12</td>
</tr>
</tbody>
</table>

m-IMT indicates mean intima-media thickness; M-IMT, maximum intima-media thickness; BH, borderline hypertensives; C, normotensives controls; RCA, right common carotid artery; LCA, left common carotid artery; RBU, right bulb; LBU, left bulb; RIC, right internal carotid artery; LIC, left internal carotid artery.

ANOVA. BH vs C. *P<0.05, †P<0.005, ‡P<0.001, §P<0.0001, ¶P<0.00001.

Mean values (mm) and SD are reported. Adjusted for sex, BMI, serum lipids, smoking, physical activity, heart rate, and age.
The M-MAX, adjusted for age, sex, heart rate, BMI, smoking, physical activity, and serum lipids, was 0.59 ± 0.12 in borderline hypertensives compared with 0.50 ± 0.10 in normotensive controls (P < 0.001). After further adjustment for office systolic BP and diastolic BP, it was 0.58 ± 0.11 in borderline hypertensives compared to 0.50 ± 0.12 in controls (P < 0.005, Figure 1).

The prevalence of raised lesions (>1 mm) was 9.7% (10/97) in borderline hypertensives compared with 2.7% (1/27) in controls. In the whole segments examined, the prevalence was 1.2% in borderline hypertensives compared to 0.3% (χ², P < 0.001) in the control group (Figure 1). Raised lesions were randomly distributed without evidence for a preferential site.

Differences in IMT values and the prevalence of raised lesions were not observed as a function of the pattern of BP elevation. In particular, isolated systolic borderline hypertensives did not differ from diastolic and systodiastolic borderline hypertensives.

Before and after adjustment for age, sex, heart rate, BMI, smoking, physical activity, and serum lipids, the right carotid artery and the left carotid artery intraluminal diameter was similar in the 2 groups (Figure 2). The assessment of interadventitial diameter gave a similar outcome (not shown). As shown in Figure 2, the radius/thickness ratio was lower in borderline hypertensives than in controls (7.03 ± 1.46 compared with 7.64 ± 1.43, P < 0.05). Moreover, a lower lumen/wall ratio was found in borderline hypertensives (12.1 ± 2.5 compared with 13.3 ± 2.6 in controls, P < 0.04). All the dimensional and functional echocardiographic indexes of borderline hypertensives did not differ from those of the control group. In particular, the left ventricular mass index (LVMI) was 88.9 ± 15.9 compared with 85.6 ± 13.1 g/m² in controls (P = NS) and cardiac output was 3.2 ± 0.8 compared with 3.0 ± 0.5 L/min · m² in controls (P = NS).

Using the univariate analysis, both office and 24-hour mean arterial pressure, systolic BP, and diastolic BP were related to m-IMT and M-IMT (not shown). In the multivariate analysis (Table 3), m-IMT, M-IMT, and M-MAX of borderline hypertensives were related to 24-hour mean arterial pressure, serum cholesterol, triglycerides, age, BMI, and physical activity, but not LVMI, cardiac output, heart rate, duration of borderline hypertension, smoking habit and sex. Mean arterial pressure was chosen for multivariate analysis because it is constant along the arterial tree and hence reflects the impact of pressure on the different carotid segments more reliably than brachial pressure. Interestingly, when either the 24-hour systolic BP and diastolic BP or the 24-hour pulse pressure were entered into the equation instead of 24-hour mean arterial pressure, it turned out that these parameters were related to all the various measurements of IMT as well. At the same time, a significant relationship was found with the other variables mentioned above, namely serum cholesterol and triglycerides, age, BMI, and physical activity. Other ambulatory BP monitoring parameters such as the trough to peak ratio or the separate evaluation of dippers and nondippers did not show any relationship to IMT values.
The role of physical activity was further investigated by comparing the IMT values recorded in subjects practicing any level of activity with those of fully sedentary subjects. As shown in Figure 3, the common carotid artery, the bulb, and the internal carotid artery of subjects belonging to the three “active” categories, (light physical activity, noncompetitive exerciser, competitive exerciser) from both the borderline hypertensives and the control group, displayed higher values of m-IMT and M-IMT compared with fully sedentary subjects of the two groups. The clinical and demographic data of sedentary subjects turned out to be comparable to that of exercisers (Table 4).

Discussion

Compared to the normotensive controls, young borderline hypertensives enrolled in the HARVEST showed increased carotid IMT, not only in the common carotid, but also in the bulb and the internal carotid artery. This is the first study demonstrating extensive structural change of the entire carotid artery wall in borderline hypertension. The reliability of our observation is endorsed by the outcome of the inter- and intraobserver survey which showed overall good reproducibility of ultrasound measurements in comparison with data from the literature.11,14,20,27,28 It is worth noting that most studies in this field provided data on the general variability of ultrasound techniques in the laboratory rather than the specific variability observed in the study itself.11,14,27 Moreover, the same differences between borderline hypertensives and normotensive controls were found using the two sets of ultrasound measurements obtained separately by each reader.

This study provides the first evidence for a definite role of BP levels in the determinism of carotid artery IMT in borderline hypertension. The increased IMT found in the bulb of the two groups. The clinical and demographic data of sedentary subjects turned out to be comparable to that of exercisers (Table 4).

![Figure 3. Mean media-intima thickness (m-IMT), maximum media-intima thickness (M-IMT) of common carotid artery (CA), carotid bulb (BU), and internal carotid artery (IC) in sedentary borderline hypertensives plus sedentary normotensive controls compared to exerciser borderline hypertensive plus exerciser normotensive controls (see text for details). ANOVA and Bonferroni’s correction. Mean±SD is reported.](image)

**TABLE 3. Multivariate Analysis of Factors Related to Intima-Media Thickness in Borderline Hypertensives**

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>m-IMT</th>
<th>24 Hour MAP</th>
<th>CT</th>
<th>TG</th>
<th>Age</th>
<th>BMI</th>
<th>Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>m-IMT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>0.507</td>
<td>0.499 (0.001)</td>
<td>0.506 (0.001)</td>
<td>0.486 (0.002)</td>
<td>0.501 (0.001)</td>
<td>0.410 (0.01)</td>
<td>0.372 (0.01)</td>
</tr>
<tr>
<td>BU</td>
<td>0.525</td>
<td>0.501 (0.001)</td>
<td>0.499 (0.001)</td>
<td>0.485 (0.002)</td>
<td>0.501 (0.001)</td>
<td>0.401 (0.02)</td>
<td>0.383 (0.01)</td>
</tr>
<tr>
<td>IC</td>
<td>0.556</td>
<td>0.520 (0.001)</td>
<td>0.497 (0.03)</td>
<td>0.461 (0.002)</td>
<td>0.530 (0.0001)</td>
<td>0.419 (0.002)</td>
<td>0.341 (0.02)</td>
</tr>
<tr>
<td><strong>M-IMT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>0.527</td>
<td>0.499 (0.001)</td>
<td>0.506 (0.001)</td>
<td>0.487 (0.001)</td>
<td>0.505 (0.0001)</td>
<td>0.410 (0.01)</td>
<td>0.373 (0.01)</td>
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<tr>
<td>BU</td>
<td>0.416</td>
<td>0.481 (0.002)</td>
<td>0.544 (0.001)</td>
<td>0.517 (0.003)</td>
<td>0.461 (0.0005)</td>
<td>0.445 (0.002)</td>
<td>0.436 (0.002)</td>
</tr>
<tr>
<td>IC</td>
<td>0.596</td>
<td>0.505 (0.001)</td>
<td>0.511 (0.001)</td>
<td>0.462 (0.001)</td>
<td>0.506 (0.0001)</td>
<td>0.422 (0.001)</td>
<td>0.367 (0.01)</td>
</tr>
<tr>
<td><strong>M-MAX</strong></td>
<td>0.603</td>
<td>0.488 (0.02)</td>
<td>0.556 (0.0001)</td>
<td>0.507 (0.001)</td>
<td>0.461 (0.0008)</td>
<td>0.403 (0.02)</td>
<td>0.441 (0.005)</td>
</tr>
</tbody>
</table>

m-IMT indicates mean intima-media thickness; M-IMT, maximum intima-media thickness; M-MAX, mean of maximum IMTs of each subject; 24 hour MAP, ambulatory mean arterial pressure; CT, serum cholesterol; TG, serum triglycerides; BMI, body mass index; CA, common carotid artery; BU, carotid bulb; IC, internal carotid artery. The r values along with the P values (in brackets) are reported.

**TABLE 4. Demographic Data of Sedentary Subjects and Exercisers**

<table>
<thead>
<tr>
<th></th>
<th>Sedentary (n=63)</th>
<th>Exercisers (n=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>30±8</td>
<td>31±8</td>
<td>0.488</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23±3</td>
<td>22±4</td>
<td>0.117</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>74±6</td>
<td>72±9</td>
<td>0.147</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132±9</td>
<td>134±9</td>
<td>0.218</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84±8</td>
<td>83±6</td>
<td>0.434</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.75±0.95</td>
<td>4.95±0.83</td>
<td>0.215</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.20±0.59</td>
<td>1.09±0.58</td>
<td>0.297</td>
</tr>
<tr>
<td>Smokers:nonsmokers</td>
<td>16:47</td>
<td>9:52</td>
<td>0.140</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HR, heart rate; TC, plasma total cholesterol; TG, plasma triglycerides. Mean±SD is reported.
and the internal carotid artery helps explain the decreased distensibility and compliance of the carotid artery bifurcation described by Van Merode et al.\textsuperscript{27} In a group of young borderline hypertensives. While the increase in m-IMT and M-IMT at the different carotid artery segments disappeared once adjustment for BP values was accomplished, differences in M-MAX were remarkable and did not disappear after adjusting for BP levels. Taking into account that a relationship between mean arterial pressure (which is similar at carotid and brachial sites) and values of IMT was also found by multivariate analysis, these data suggest that the impact of BP is more relevant for initial/middle, focal IMT rather than for more advanced and diffuse intimal remodeling such as that represented by M-MAX. However, a relationship between BP levels and IMT was not found using multivariate analysis in the 73 borderline hypertensives evaluated by Lemne et al.\textsuperscript{14} In this latter study, age and high-density cholesterol were consistently related to IMT of borderline hypertensives, while office BP levels were not. Age was the only determinant for “plaque” (defined as IMT >1 mm and a 100% increase in thickness compared with normal adjacent wall segments).\textsuperscript{14} In our study, both ambulatory and office BP were related to IMT parameters using univariate analysis. In the multivariate analysis however, a clearcut role was found for various parameters of ambulatory BP, (mean arterial pressure, systolic BP, diastolic BP, pulse pressure) but not for office BP. Therefore, one may speculate that in the Swedish subjects studied by Lemne et al\textsuperscript{14} the lack of impact of BP on intima remodeling can be due to lower “sensitivity” of office BP compared with 24-hour BP. Indeed, data of the literature\textsuperscript{10,31} strongly support the view that target organ damage, including carotid artery IMT,\textsuperscript{12} is predicted more reliably by 24-hour BP rather than by office BP. On the other hand, it may be that the higher levels of atherogenic lipoproteins found in the Swedish compared with the Italian borderline hypertensives overcome the potential influence of BP levels. In our borderline hypertensives, the multivariate analysis confirmed that, particularly at the level of internal carotid artery, mean arterial pressure is associated to m-IMT more strongly than cholesterol and triglyceride levels.

On the contrary, advanced structural change of the carotid artery wall, such as M-MAX, was more clearly influenced by plasma cholesterol and triglycerides. In this light, it is not surprising that the prevalence of “plaque” or raised intimal lesions above 1 mm was much lower in our borderline hypertensives than in the Swedish ones (1.2 compared with 26%).\textsuperscript{14} Population studies would obviously allow better evaluation of the relative impact of the various risk factors, but the relatively low prevalence of young borderline hypertensives in the general population would require a very large sample.

Age, BMI, and physical activity were other determinants of IMT in multivariate analysis. Although the age range was small, age seems to represent the most powerful factor for IMT in our borderline hypertensives and those studied by Lemne et al.\textsuperscript{14} as well. The lower mean age (31±7 compared with 49±6 years) and BMI (24±3 compared with 26±3) of our borderline hypertensives may represent an additional explanation for less advanced intima-media remodeling in our series.

While age and BMI are recognized factors related to the level of IMT,\textsuperscript{33} the relationship between physical activity and development of IMT in borderline hypertension seems quite puzzling. A role for physical activity independent from BP levels is clearly outlined when comparing the IMT values of sedentary compared with exerciser subjects shown in Figure 3. Except for the recent study by Cuspidi et al.\textsuperscript{15} in 14 borderline hypertensives and 14 athletes compared with 14 sedentary normotensives, no previous observations have been reported in the literature. These authors found that IMT values of common carotid artery are similar in borderline hypertensives and in normotensive athletes, and significantly higher than in normotensive controls. It was suggested that in athletes, vascular hypertrophy could represent a structural autoregulation process to reduce hemodynamic wall stress during exercise and that some contribution could also come from cyclic, exercise-induced activation of both the renin-angiotensin and the sympatho-adrenergic systems. On the other hand, significant changes in basic cardiac output or heart rate, which can induce neointima proliferation in response to change in cyclic arterial wall stress,\textsuperscript{8} were recorded neither in borderline hypertensives compared with controls nor in sedentary subjects compared with exercisers. As physical activity may result in increased left ventricular mass, one can speculate that it also induces increased carotid IMT through selective increase in the muscle component of the carotid wall, that is, the media layer. However, a significant increase in ventricular mass in relation to physical activity was not found in the echocardiographic study carried out in our borderline hypertensives. The role of physical activity and the interaction with increased blood pressure levels represent interesting aspects that deserve further specific studies.

A difference in carotid artery diameter was not found in borderline hypertensives compared with controls, so that changes in IMT are unlikely to be affected by adaptive change in carotid artery diameter. Moreover, values of R/T and L/W ratios were lower in borderline hypertensives compared with controls, suggesting that a sort of compensatory wall thickening occurred and that wall stress was not altered in borderline hypertensives. Altered flow-dilatation mechanisms may be relevant for development of IMT in young hypertensives with increased cardiac output and heart rate through changes in wall stress, shear stress or pulse pressure amplification. However, this does not seem to be the case of our borderline hypertensives as cardiac output and heart rate were not significantly increased compared with controls. Moreover, there was no relationship between level of IMT and cardiac output or heart rate in the multivariate analysis. If some sympathetic overactivity was expected in borderline hypertensives, it seems reasonable to assume that it was blunted by the high prevalence of subjects practicing physical activity. Other hemodynamic aspects including the problem of pulse pressure amplification could be specifically studied using different techniques such as noninvasive applanation tonometry.\textsuperscript{34}

As far as carotid artery diameter is concerned, it has been hypothesized that hypertensives\textsuperscript{5,15,36} may undergo some compensatory enlargement of the common carotid artery and this would result in some bias in the measurement of carotid IMT. This probably occurs in more extensive arterial wall remodeling such as that observed in severe atherosclerosis\textsuperscript{57} or in elderly people,\textsuperscript{38} but neither our borderline hypertensives nor did stable hypertensives studied by others\textsuperscript{39–41} did show any relevant increase in luminal diameter, even in the presence of increased cardiac output.\textsuperscript{40}
At the present time, the overall biological significance and the prognostic value of increased carotid IMT in borderline hypertension remain to be elucidated. Perspective studies, such as the HARVEST, are the appropriate approach to establish whether or not the increased carotid IMT found in borderline hypertensives carries a specific risk of cerebrovascular disease. This would disclose a new indication for undertaking antihypertensive therapy in borderline hypertension.

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References

Factors Underlying the Increase in Carotid Intima-Media Thickness in Borderline Hypertensives
P. Pauletto, P. Palatini, S. Da Ros, V. Pagliara, N. Santipolo, S. Baccillieri, E. Casiglia, P. Mormino and A. C. Pessina

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