Influence of Hypertension on Early Carotid Artery Remodeling

Gilles Chironi, Jerome Gariepy, Nicolas Denarie, Maria Balice, Jean-Louis Megnien, Jaime Levenson, Alain Simon

Objectives—We aimed to analyze the influence of hypertension on early large artery remodeling.

Methods and Results—Carotid intima-media thickness (IMT) and diameter were measured ultrasonographically in 394 normotensive subjects and 327 untreated and 528 treated hypertensive patients. IMT and diameter were increased in hypertensive groups, treated or untreated, compared with the normotensive group (P<0.001). Positive association existed between diameter and IMT in the overall study population (P<0.001), and this association interacted with the category of clinical groups (P<0.01). The slope of the diameter-IMT relationship was different between normotensive, untreated hypertensive, and treated hypertensive groups (P<0.01), with higher value in the treated hypertensive group than in untreated hypertensive and normotensive groups (P<0.05, P<0.01). Adjustment for blood pressure, lipid-lowering therapy, or multiple covariates (age, sex, systolic and diastolic blood pressures, body mass index, lipid-lowering therapy, smoking, and previous cardiovascular disease) did not abolish the diameter-IMT slope difference between clinical groups (P<0.01).

Conclusions—The sensitivity of carotid artery enlargement in response to increase in wall thickness was unchanged in untreated hypertension but altered by antihypertensive therapy compared with the normotensive condition. (Arterioscler Thromb Vasc Biol. 2003;23:1460-1464.)

Key Words: carotid arteries • remodeling • hypertension • ultrasonics • antihypertensive treatment

Arterial remodeling is potentially important in atherosclerosis, aiming at counteracting the development of lumen compromise of large artery by mutual adaptation of diameter to wall thickening.1 At the early stage of atherosclerosis characterized by slight intrusive or preintrusive wall thickening, the lumen size of the artery remains constant or even increases (compensatory enlargement).2 Advances in high-resolution B-mode ultrasonography offer the possibility of assessing concomitantly intima-media thickness (IMT) and diameter of carotid artery3 and obtaining in vivo information on the adaptation of IMT to diameter.4,5 Positive relationships were found between carotid diameter and IMT in populations of healthy subjects, independently of coexisting cardiovascular risk factors.6–8 However, these relations have not been examined specifically in patients with hypertension, even though the influence of blood pressure on large artery geometry and structure may change the ability of arteries to remodel their lumen as wall thickness increases. Therefore, the objective of the present study was to assess and compare the adaptation of lumen diameter to IMT in the common carotid artery of 3 groups of untreated and treated hypertensive patients and normotensive subjects.

Study Subjects
One thousand two hundred forty-nine consecutive subjects referred between April 2000 and May 2001 for cardiovascular risk assessment and having undergone appropriate ultrasonographic carotid examination were included in the study. They were divided into 2 groups according to the presence (hypertensive group, n=855) or absence (normotensive group, n=394) of hypertension defined as blood pressure ≥140 systolic or ≥90 mm Hg diastolic or the current use of antihypertensive treatment. Hypertensive patients were subdivided into 2 groups of untreated (n=327) and treated (n=528) subjects according to the absence or presence of current antihypertensive treatment for the past 3 months. Among treated hypertensive patients, 314 were treated with a class of drug given alone (monotherapy) or in association with a diuretic (diuretic bitherapy) and subdivided into the following 4 groups according to the class of drug: calcium antagonists, n=81; angiotensin converting enzyme inhibitors, n=82; β blockers, n=93; and angiotensin receptors antagonists, n=58.

Risk Factors Evaluation
Body mass index was calculated as the ratio between weight (kilogram) and square height (square meter).9 Brachial blood pressure was measured in the supine position after 10 minutes of rest and defined as the average of 3 consecutive measurements by sphygmomanometric procedure.9 Patients with secondary hypertension were excluded. Blood lipids and glucose were measured by enzymatic
smoking was defined as smoking each day of the previous 3 months.

Qualitative parameters were compared between groups by Student’s t test and compared between groups by ANOVA. All pairwise comparisons by Student’s t test were corrected with Bonferroni method.

Lumen diameter was defined as the average of the distances between the 2 leading edges of far- and near-wall lumen-intima interfaces along at least 0.5 cm of length using a computerized program validated in animals by comparison with a reference method of sonometric measurement (regression coefficient of 0.99). A study of repeatability in humans has shown that the percent change between 2 repeated carotid IMT measurements was 4.3%.6

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Statistical Analysis
Unadjusted quantitative parameters were expressed as mean (SE) and compared between groups by ANOVA. All pairwise comparisons by Student’s t test were corrected with Bonferroni method. Qualitative parameters were compared between groups by χ² test. Independent associations of IMT and diameter with clinical parameters were analyzed by multivariate linear regression analysis. Adjusted comparisons of quantitative parameters between groups (expressed as mean [SE]) were performed by multivariate analysis, entering the parameter to compare as dependent variable and the group category and adjustment covariates as independent variables. Univariate diameter-IMT relationships were assessed by least-square method, and the slopes of regression line were compared between groups by analysis of covariance. Adjusted slopes of diameter-IMT relationships were compared between groups by multivariate analysis, entering diameter as dependent variable and IMT, group category, [group category*IMT] product, and adjustment covariates as independent variables. Slopes were expressed as mean (SE). The statistical analysis was carried out on a computer (Apple McIntosh) with the use of JMP (SAS) and Excel (Microsoft) softwares. Statistical significance was considered to be \( P < 0.05 \).

Results
Normotensive, untreated hypertensive, and treated hypertensive groups had significant differences in all clinical parameters \(( P < 0.001 \), except for male sex, \( P = 0.01 \)). Pairwise comparisons of groups are given in Table 1, showing increased values of all parameters in the treated hypertensive group compared with all other groups, except for male sex, hypercholesterolemia and smoking more frequent in the normotensive group, and lipid-lowering therapy less frequent in untreated hypertensive group.

Table 1. Clinical Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normotensive Group (1)</th>
<th>Untreated Hypertensive Group (2)</th>
<th>Treated Hypertensive Group (3)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>394</td>
<td>327</td>
<td>528</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>50.1 ± 0.4</td>
<td>51.9 ± 0.5</td>
<td>56.5 ± 0.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>287 (73)</td>
<td>229 (70)</td>
<td>329 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5 ± 0.2</td>
<td>26.6 ± 0.2</td>
<td>27.5 ± 0.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>122.5 ± 0.8</td>
<td>150.9 ± 0.9</td>
<td>146.4 ± 0.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>77.1 ± 0.5</td>
<td>92.7 ± 0.5</td>
<td>87.6 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>245 (62)</td>
<td>140 (43)</td>
<td>249 (47)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lipid-lowering treatment, n (%)</td>
<td>115 (29)</td>
<td>61 (19)</td>
<td>181 (34)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>18 (5)</td>
<td>23 (7)</td>
<td>83 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>137 (35)</td>
<td>87 (27)</td>
<td>106 (20)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Previous CVD, n (%)</td>
<td>7 (2)</td>
<td>9 (3)</td>
<td>45 (9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SE or No. (n) with percentage in parentheses.

Statistical Analysis
Unadjusted quantitative parameters were expressed as mean (SE) and compared between groups by ANOVA. All pairwise comparisons by Student’s t test were corrected with Bonferroni method. Qualitative parameters were compared between groups by χ² test. Independent associations of IMT and diameter with clinical parameters were analyzed by multivariate linear regression analysis. Adjusted comparisons of quantitative parameters between groups (expressed as mean [SE]) were performed by multivariate analysis, entering the parameter to compare as dependent variable and the group category and adjustment covariates as independent variables. Univariate diameter-IMT relationships were assessed by least-square method, and the slopes of regression line were compared between groups by analysis of covariance. Adjusted slopes of diameter-IMT relationships were compared between groups by multivariate analysis, entering diameter as dependent variable and IMT, group category, [group category*IMT] product, and adjustment covariates as independent variables. Slopes were expressed as mean (SE). The statistical analysis was carried out on a computer (Apple McIntosh) with the use of JMP (SAS) and Excel (Microsoft) softwares. Statistical significance was considered to be \( P < 0.05 \).

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Normotensive, untreated hypertensive, and treated hypertensive groups had significant differences in all clinical parameters \(( P < 0.001 \), except for male sex, \( P = 0.01 \)). Pairwise comparisons of groups are given in Table 1, showing increased values of all parameters in the treated hypertensive group compared with all other groups, except for male sex, hypercholesterolemia and smoking more frequent in the normotensive group, and lipid-lowering therapy less frequent in untreated hypertensive group.

Carotid Dimensions
Multivariate analysis of carotid dimensions on clinical parameters showed that IMT was significantly associated (1) in the normotensive group with age \(( P < 0.001 \), body mass index \( P < 0.05 \), smoking \( P < 0.01 \), and previous CVD \( P < 0.001 \); (2) in the untreated hypertensive group with age \(( P < 0.001 \), systolic pressure \(( P < 0.05 \), and lipid-lowering therapy \( P < 0.05 \); and (3) in the treated hypertensive group with age \(( P < 0.001 \), male sex \(( P < 0.01 \), body mass index \(( P < 0.01 \), systolic pressure \(( P < 0.001 \), and smoking \(( P < 0.05 \). Diameter was associated (1) in the normotensive group with age \(( P < 0.05 \), male sex \(( P < 0.001 \), body mass index \(( P < 0.001 \), and previous CVD \( P < 0.05 \); (2) in the untreated hypertensive group with age \(( P < 0.001 \), male sex \(( P < 0.01 \), and systolic pressure \(( P < 0.01 \); and (3) in the treated hypertensive group with age \(( P < 0.001 \), male sex \(( P < 0.001 \), body mass index \(( P < 0.01 \), systolic pressure \(( P < 0.001 \), and smoking \(( P < 0.05 \). IMT differed between the 3 study groups \(( P < 0.001 \), with greater value in the treated hypertensive group than in
untreated hypertensive and normotensive groups \((P < 0.05, P < 0.001)\) and in the untreated hypertensive than in the normotensive group \((P < 0.001)\) (Figure 1). Diameter also differed between groups \((P < 0.001)\), with greater value in treated and untreated hypertensive groups than in the normotensive group \((P < 0.001)\) (Figure 1). After adjustment for blood pressure, IMT remained higher in treated and untreated hypertensive groups than in the normotensive group \((P < 0.001, P < 0.01)\), whereas the diameter difference was removed (Figure 1). Adjustment for lipid-lowering therapy did not change the groups’ difference of carotid dimensions, but adjustment for multiple covariates (age, sex, systolic and diastolic blood pressures, body mass index, lipid-lowering therapy, smoking, and previous cardiovascular disease) removed those differences between the study groups (Figure 1).

**Diameter-IMT Associations**

Multivariate analysis of carotid diameter in the overall study population (Table 2) showed that diameter was significantly associated with IMT \((P < 0.001)\) independently of other associations of diameter with the category of clinical groups \((P < 0.01, \text{models 1 and 3})\), with systolic pressure \((P < 0.001, \text{model 2})\), and with systolic pressure, age, male sex, and body mass index \((P < 0.001, \text{model 4})\). Table 2 shows also that significant interactions of IMT and clinical group category (IMT*group category) existed on diameter in all models \((P < 0.01)\). Such interaction allowed to analyze the diameter-IMT association separately in each normotensive, untreated hypertensive, and treated hypertensive group.

Diameter and IMT were positively correlated in the normotensive group \((r = 0.16, P < 0.01)\) and untreated hypertensive and treated hypertensive groups \((r = 0.25, r = 0.36, P < 0.001)\). Before adjustment, the diameter-IMT slope differed between study groups \((P < 0.01)\), with a greater slope in treated hypertensive group than in untreated hypertensive and normotensive groups \((P < 0.05, P < 0.01, \text{Figure 2})\). Adjustment for blood pressure, lipid-lowering therapy, or multiple covariates did not change the difference in diameter-IMT slope between groups \((P < 0.01, \text{Figure 2})\).

The distribution of wall tensile stress of the carotid artery by quartiles of diameter showed a significant difference in tensile stress \((P < 0.001)\) between the quartiles of diameter in each clinical group (Figure 3); moreover, tensile stress was increased in the 4th quartile compared with the 1st quartile similarly in the 3 clinical groups. The percent increase was 28% in the normotensive group, 26% in the untreated hypertensive group, and 31% in the treated hypertensive group.

**Discussion**

This population study shows a new finding and a substantial difference in the sensitivity of the mutual adaptation between carotid enlargement and wall thickening in 3 different groups of subjects, 2 groups with and without hypertension and 1 group undergoing antihypertensive treatment.

A positive association was found between lumen diameter and IMT in the overall study population independently of single or multiple confounding covariates. This association indicates that carotid artery enlargement and wall thickening adjust mutually.\(^5\)\(^7\) Moreover, the existence of significant
interaction of IMT and clinical group category on diameter before and after adjustment for various covariates allowed the analysis of the diameter-IMT association separately in each clinical group. The slope of the diameter-IMT relationship, which estimates the sensitivity of the carotid enlargement in response to wall thickening, differed substantially between groups. Such a difference was attributable to the diameter-IMT slope being higher in the treated hypertensive group compared with both other groups. It is unclear whether the altered sensitivity of carotid artery remodeling in treated hypertensive patients is actually detrimental or a beneficial change, because there is no literature data supporting a specific ideal threshold for the diameter-IMT slope. The fact that multiple clinical trials have shown benefit of antihypertensive treatment to reduce the risk of cardiovascular event suggests that the greater diameter-IMT slope in treated hypertensives may be a favorable phenomenon.

Potential confounding factors must be considered in the interpretation of the findings, mainly blood pressure and effects of therapy. Blood pressure per se is a known variable associated with large artery diameter and wall thickness. The present work confirms this fact by showing independent positive associations of diameter and IMT with systolic blood pressure in both hypertensive groups. Adjustments for blood pressure removed the difference in carotid diameter between hypertensive and normotensive groups but did not affect the difference in the diameter-IMT slope between the treated hypertensive group and both other groups. It is also suggested that the adaptation between carotid enlargement and wall thickening is independent of the direct effect of blood pressure. Among therapies, lipid-lowering drug is known to affect directly IMT progression, and its frequency was different between the 3 study groups. Adjustment for lipid-lowering drug treatment did not affect the differences in carotid dimensions and diameter-IMT slope between groups, therefore excluding a confounding influence of this medication. Lastly, adjustment for multiple covariates (age, sex, systolic and diastolic blood pressures, body mass index, lipid-lowering therapy, smoking, and previous CVD) that removed differences in IMT and diameter between groups did not change the difference in diameter-IMT slope between treated hypertensive group and the other 2 groups. It would have been interesting to analyze the separate influence of different types of antihypertensive drugs on these findings. However, such analysis is questionable, because many patients were treated with diuretics in association with the antihypertensive agent of interest, and there was unaccounted-for bias in assigning patients to different treatment regimens.

There are 2 main hypotheses for explaining the observed relationships between carotid diameter and IMT. The first one is in relation with the possible increase in shear stress resulting from IMT enhancement and leading to NO-dependent remodeling and carotid enlargement. It does not hold, because a theoretical calculation shows that IMT augmentation results in a very small increase in shear rate. An alternative possibility is that the mutual adaptation between diameter and IMT corresponds to a roughly conserved wall tensile stress in the carotid wall (pressure×radius/IMT). We have tested this hypothesis by calculating wall tensile stress in the 3 clinical groups. As diameter increased, the concomi-
itant carotid wall thickening was not sufficient to maintain constant the wall tensile stress. It increased approximately 30% between the 1st and the 4th quartiles of diameter, and such increase was similar in the 3 clinical groups (Figure 3). Therefore, the hypothesis of preservation of wall tensile stress does not seem to explain entirely the observed relationships between diameter and IMT, as well as the differences in the sensitivity of carotid remodeling between the treated hypertensive group and both other groups. Moreover, any proposed mechanistic explanation of our findings is difficult to test, because the cross-sectional design of our work does not allow us to determine the temporal sequence of the observed changes in diameter and IMT, which are important for the mechanistic discussion.

Finally, we have to emphasize that our measures were focused in the common carotid artery, which is the segment where the highest precision and reproducibility rates are obtained. Nevertheless, this does not allow us to extrapolate our findings to other carotid segments, because previous works, in particular the Atherosclerosis Risk in Communities study,5 have shown that the response of the common carotid geometry to the influence of risk factors was different from that of the internal carotid artery.

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References
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