Original Article

Vascular Remodeling of the Carotid Artery in Patients with Untreated Essential Hypertension Increases with Age

Rie SASAKI, Shigeru YAMANO, Yuta YAMAMOTO, Shigetoshi MINAMI, Junko YAMAMOTO, Takao NAKASHIMA, Minoru TAKAOKA, and Toshio HASHIMOTO

We examined whether hypertrophy of the carotid artery in patients with untreated essential hypertension is associated with compensatory carotid artery enlargement as these patients age. Carotid ultrasonography was evaluated in 163 patients with untreated essential hypertension (74 males and 89 females) and in 76 normotensive subjects. Intima-media end-diastolic thickness (IMT) and outer vessel diameter (VD) were measured, and relative wall thickness (IMT/R, R = VD/2) and vascular mass (VM) were calculated. Determinants of vascular hypertrophy in patients with untreated essential hypertension were also investigated. VD, VM, and IMT were significantly correlated with age in both the normotensive and hypertensive groups. Additionally, IMT was significantly correlated with VD in both groups. There was no correlation between increasing age and IMT/R in either group. IMT, VD and VM were significantly higher in the hypertensive group > 50 years than in age-matched normotensive controls. However, IMT/R was significantly higher in the 50–59 years hypertensive group than in normotensive controls of the same age group. In addition to age, VM was related to systolic blood pressure, pulse pressure, fasting blood sugar, IMT, VD, and IMT/R in the hypertensive group. Multivariate regression analysis in the hypertensive group indicated that IMT/R was the strongest predictor of carotid vascular mass. Age and pulse pressure were also independently related to vascular mass. These results indicate that, as patients with untreated hypertension age, carotid arteries undergo remodeling. This should add further impetus to the implementation of appropriate hypertension treatment for such patients. (Hypertens Res 2002; 25: 373–379)

Key Words: aging, carotid artery, hypertension, vascular remodeling

Introduction

Vascular remodeling is an active process of structural alteration and is dependent on the dynamic interaction between locally generated growth factors, vasoactive substances, and hemodynamic stimuli. Remodeling is usually an adaptive process that occurs in response to long-term changes in hemodynamic conditions, but it may subsequently contribute to the pathophysiology of vascular diseases and circulatory disorders (1). The atherosclerotic vessel undergoes a remodeling process of compensatory enlargement that preserves the luminal diameter despite the increase in the size of the plaque (2, 3). Glagov et al. (2) and Zarins et al. (3) found a highly significant association of artery size and plaque area in left human coronary arteries, which delayed the decrease in the vascular lumen until the lesion occupied about 40% of the internal elastic lamina. Similar investigations have been made in pathoanatomic studies of postmortem specimens (4), epicardial ultrasound imaging (5), and intravascular ultrasound of the coronary arteries (6). These studies examined arterial sites with moderate and large atherosclerotic plaques.
In addition, Steinke et al. (7) and Labropoulos et al. (8), used duplex scanning to examine carotid arteries at an early stage of atherosclerosis, and demonstrated that increasing plaque volume was significantly associated with enlargement of carotid artery segments, which compensated for arterial narrowing.

However, there have been no studies of vascular remodeling of the carotid artery prior to the development of plaques. In this paper, we sought to determine whether carotid arterial hypertrophy in hypertensive patients was associated with compensatory carotid artery enlargement as these patients age. The determinants of vascular hypertrophy in patients with untreated essential hypertension were also investigated.

### Subjects and Methods

#### Subjects

Between January 1998 and December 2000, carotid ultrasonography was evaluated in 163 individuals with untreated essential hypertension who were outpatients at Nara Medical University Hospital. Subjects enrolled in the study included 74 males and 89 females with an age range of 24 to 82 years and a mean age of 56 years. Nineteen patients (13 males and 6 females) were 20–39 years, 26 patients (10 males and 16 females) were 40–49 years, 55 patients (22 males and 33 females) were 50–59 years, 42 patients (25 males and 17 females) were 60–69 years, and 23 patients (6 males and 17 females) were 70–82 years.

Hypertension was defined according to the criteria for arterial hypertension established in 1997 by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), i.e., a systolic pressure of at least 140 mmHg and/or a diastolic pressure of at least 90 mmHg (9). Blood pressure was measured by a physician in the hospital outpatient clinic with a mercury sphygmomanometer after the subject had been seated for 5 min or longer. For purpose of analysis, the blood pressure was taken as the average of three or more measurements over two or more sessions for each patient. Patients with secondary hypertension, diabetes mellitus, hyperlipidemia, a history of clinical cerebrovascular disease or coronary heart disease were excluded. Patients with carotid plaques observed by B-mode ultrasonography were also excluded from the study.

The normotensive group consisted of 76 subjects who had no risk factors for stroke or coronary heart disease, such as hypertension, diabetes mellitus, hyperlipidemia, or arrhythmia. These patients were chosen to match in age and gender with the hypertensive subjects. Their ages ranged from 27–85 years (mean, 59 years). Normotensive subjects were either healthy volunteers, outpatients being treated for unrelated conditions, or patients undergoing routine clinical checkups at the same hospital during the time interval specified above.

Oral informed consent was obtained from all subjects. The institutional ethics committee at our hospital approved this study protocol.

#### Carotid Ultrasonography

Carotid ultrasonographic studies were performed with a high-resolution linear-array 7.5 MHz probe (LOGIQ 700; Yokogawa, Tokyo, Japan). The subject was comfortably seated during bilateral imaging of the extracranial carotid artery in the neck. The intima-media end-diastolic thickness (IMT) of the posterior (far) wall of both common carotid arteries was measured. In addition, the end-diastolic outer vessel diameter (VD) was measured at 5, 10, and 20 mm caudal to the bulb, and these measurements were averaged. The IMT was calculated on two-dimensional longitudinal sections of the carotid artery as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line according to the methods validated by Pignoli et al. (10) and Salonen et al. (11). In addition, we chose to use the estimation of vascular mass (VM) as an index of vascular hypertrophy (12) because it incorporates changes in both arterial wall thickness and lumen diameter. IMT can be affected by a simultaneous change in lumen diameter induced by blood pressure, or compensatory widening in the presence of atherosclerotic wall changes. Relative wall thickness (IMT/VD; R = VD/2) and VM were calculated. VM was calculated, as previously reported according to the following formula as previous reported (12):

\[
VM = \frac{pL(\pi R^2 - \pi r^2)}{R}
\]

where \(\rho\) is the arterial wall density (\(\rho = 1.06\)), \(L\) is the length of the arterial segment, and \(R\) and \(r\) are the values of diastolic internal and external radii, respectively. A carotid atherosclerotic plaque was defined as the presence of a discrete thickening that was at least 50% greater than the surrounding wall within any segment of either carotid artery (13). IMT was never measured at the level of a discrete plaque.

#### Statistical Analysis

Data are reported as the mean \(\pm\) SD. The \(\chi^2\) test was used to compare subject characteristics. The unpaired Student’s \(t\)-test was used both to compare subject characteristics and to compare measurements between the hypertensive and normotensive groups. Pearson’s correlation coefficient was used to evaluate the relationship between age and VD or VM. The relation between continuous variables was evaluated by linear regression. Independence of association was assessed by stepwise regression analysis. Statistical analysis was performed using the statistical software package Stat View (Abacus Concepts, Berkeley, USA). Differences were considered to be statistically significant when \(p\) was < 0.05.
Results

Characteristics of the Subjects

Table 1 shows the clinical characteristics of the normotensive and hypertensive groups. There were no significant differences in age, gender, heart rate, high density lipoprotein cholesterol level, or incidence of smoking. Total cholesterol level, fasting blood glucose level, and body mass index were significantly higher in hypertensive patients than in normotensive subjects. The systolic blood pressure and diastolic pressure were significantly higher in hypertensive patients than in normotensive subjects.

Age Related Carotid Structural Changes and Remodeling

VD and VM were significantly correlated with age in both the normotensive and hypertensive groups (Figs. 1, 2). IMT was also significantly correlated with age in the hypertensive group ($r = 0.40, p < 0.001$) and in the normotensive group ($r = 0.44, p < 0.001$). Additionally, IMT was significantly correlated with VD in the hypertensive group ($r = 0.35, p < 0.001$) and in the normotensive group ($r = 0.42, p < 0.001$). However, relative wall thickness (IMT/R) showed a slight but not significant positive correlation with age in both the hypertensive group ($r = 0.21, p < 0.1$) and normotensive group ($r = 0.19, p < 0.1$). IMT, VD, and VM were significantly higher in the hypertensive group > 70 years than in normotensive controls of the same age group, and IMT/R was significantly higher in the hypertensive 50–59 years than in normotensive controls of the same age group (Table 2).

Determinants of Carotid Vascular Mass

In addition to age, VM was significantly related to the sys-
tolic blood pressure, pulse pressure, fasting blood sugar, IMT, VD, and IMT/R in the hypertensive group. In the normotensive group, VM was significantly related to age, IMT, VD, and IMT/R (Table 3). We performed multivariate regression analysis to determine which factors were independently related to carotid vascular mass. IMT/R was the strongest predictor of carotid vascular mass in the hypertensive group. Age and pulse pressure were also independently related to vascular mass in this group. In the normotensive group, age and IMT/R were independently related to vascular mass (Table 4).

**Discussion**

Several pathoanatomic or clinical studies (1–7) have suggested that during the early stages of the atherosclerotic process, adaptive and compensatory mechanisms may prevent the reduction of the lumen of coronary arteries by increasing the size of the artery. Carotid artery enlargement also occurs with increases in IMT (14). The artery appears to compensate for the presence of thickened walls by dilatation, thereby stabilizing the shear stress experienced at the interface between blood and the endothelium (15). However, the relationship between increasing age and vascular remodeling, including vascular hypertrophy and enlargement, in both hypertensive patients and normotensive subjects has remained unclear. Accordingly, we here used carotid ultrasound to investigate the common carotid arteries of 20- to 85-year-old subjects with untreated hypertension or normotension.

Geometric vascular remodeling of the common carotid artery in hypertension involves enlargement of the vessel with thickening of its wall (16). Several clinical studies have reported that the carotid internal diameter enlarges with age in both normotensive (17, 18) and hypertensive (19) subjects. In the present study, VD, VM, and IMT measurements were significantly and positively correlated with increasing age in both hypertensive and normotensive subjects. Our results are in agreement with previous reports (17–19), and suggest that age is one of the most important factors in vascular remodeling and hypertrophy.

We confirmed that an increase in VD is associated with an increase in IMT. This result supports the hypothesis that the artery is able to dilate in order to compensate for an increase in IMT (2). Our study is different from previous reports (1–7) in that we examined this phenomenon in the common
carotid artery in the absence of plaques. Thus, this compensation must start at a very early stage, before a focal increase in the IMT is detectable by sonography. Furthermore, our results suggest that plaque formation is not required for the mutual adaptation of lumen diameter and IMT to occur. They may also suggest that the mechanism underlying the association between luminal enlargement and increased IMT in the common carotid artery may be at least partially different from those underlying its association with atherosclerosis (14). The mechanism of compensatory dilatation is unknown. It has been suggested that a local increase in the wall shear stress may promote endothelium-dependent arterial dilatation or that atheroma formation may lead to degradation of the underlying media and adventitia, with outward bulging of the plaque (3). Others have suggested that arterial wall remodeling may occur due to the migration of medial smooth muscle cells and the ischemic atrophy of the medial layer (7). On the other hand, IMT/R measurement was not related to an increase in age in either of the groups in this study. Our results suggest that the vascular remodeling and hypertrophy that occurs with aging develop despite a constant IMT/R value. This is in contrast to the findings of Riley et al. (18), who reported that the IMT/R ratio increased slightly but significantly with increasing age. The reason for this discrepancy between our results and those of Riley et al. is unclear. Their mean values of IMT/R varied from 0.16 to 0.18, whereas ours varied from 0.12 to 0.15. Thus the discrepancy between the two results may be due to racial differences. Furthermore, arterial disease may occur earlier in our population than in that studied by Riley et al. In ultrasound studies that analyzed carotid diastolic dimensions using B-mode images, the dimensions were found to be significantly greater in untreated hypertensive patients than in age-matched controls (16, 19). Common carotid artery IMT has also been shown to increase in a linear manner throughout life (20). And other studies have reported that carotid arterial IMT was greater in hypertensive than in normotensive subjects who were matched for age and cardiovascular risk factors (16, 21). In the present study, VM and IMT were significantly greater in hypertensive >50 years than in normotensive subjects of the same age group. An increased IMT has been directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular diseases (22). VM, which is

Table 3. The Correlation Coefficients between the Vascular Mass of the Carotid Artery and Cardiovascular Risk Factors and Carotid Arterial Structural Parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertensive Coefficients</th>
<th>Hypertensive p value</th>
<th>Normotensive Coefficients</th>
<th>Normotensive p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.48</td>
<td>&lt;0.001</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.15</td>
<td>NS</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.36</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.01</td>
<td>NS</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting blood sugar</td>
<td>0.26</td>
<td>&lt;0.01</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.02</td>
<td>NS</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.21</td>
<td>NS</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.11</td>
<td>NS</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Intima-media thickness</td>
<td>0.58</td>
<td>&lt;0.001</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vessel diameter</td>
<td>0.59</td>
<td>&lt;0.001</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.72</td>
<td>&lt;0.001</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS, not significant; HDL, high density lipoprotein

Table 4. Multivariate Regression Analysis of Vascular Mass of the Carotid Artery in Hypertensive and Normotensive Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Independent variables</th>
<th>Coefficient (B)</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>Age</td>
<td>0.134</td>
<td>0.039</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>0.004</td>
<td>0.052</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Pulse pressure</td>
<td>0.141</td>
<td>0.063</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Fasting blood sugar</td>
<td>0.003</td>
<td>0.032</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Relative wall thickness</td>
<td>56.529</td>
<td>7.267</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Age</td>
<td>0.137</td>
<td>0.033</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Relative wall thickness</td>
<td>50.432</td>
<td>7.688</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS, not significant; SE, standard error.
closely associated with IMT, may be a more appropriate parameter than IMT for describing vessel wall size, since this arterial parameter takes into account both IMT and lumen diameter (23). And the carotid cross-sectional area (VM/PL) may better discriminate between patients with and those without hypertensive or atherosclerotic disease (24). Hence, the suppression of any increase in VM appear to be an important aim in the prevention of cardiovascular diseases. To prevent such an increase in VM in hypertensive patients, and induction of a compensatory enlargement of the artery, any increase in thickening of IMT in these patients should be held to the approximate level observed in normal aging.

In univariate analysis of relationships between cardiovascular risk factors or carotid artery parameters and VM, each of age, systolic blood pressure, pulse pressure, fasting blood sugar, IMT, VD, and IMT/R were significantly correlated with VM in the hypertensive group. In multivariate regression analysis, age, pulse pressure, and IMT/R were independent predictors of VM in the hypertensive group. On the other hand, age and IMT/R were independent predictors of VM, but blood pressure (systolic blood pressure and pulse pressure) did not show a correlation with VM in the normoten sive group. These results indicate that the increase in VM would constitute a type of remodeling via high blood pressure or pulse pressure in patients with essential hypertension.

In our study, IMT/R was one of the strongest predictors of carotid vascular mass. An increase in IMT/R in the presence of vascular mass implies concentric vascular hypertrophy. The left ventricular geometric pattern has been shown to predict cardiovascular events in hypertension. In a study by Koren et al., patients with concentric hypertrophy (increased relative wall thickness and mass) had the highest likelihood of dying or having a cardiovascular event (25). In addition, relative wall thickness is an independent predictor of left ventricular systolic and diastolic dysfunctions in essential hypertension (26). It is unclear whether vascular hypertrophy evaluated by geometric pattern has a clinical significance similar to left ventricular hypertrophy. However, concentric vascular hypertrophy might predict the cardiovascular risk, since increased IMT has been recognized as a risk factor of cardiovascular diseases.

The present study has some limitations. First, as reported in a previous study (27), brachial artery blood pressure measurements may not always accurately reflect blood pressure in the common carotid artery. Although comparisons of intraarterial pressure in the large vessels with brachial artery pressures determined by noninvasive oscillometric methods are in generally good agreement (28), pulse pressure measured by pressure waveforms in the carotid artery is greater than that observed in the brachial artery (29). Second, in addition to mechanical factors, neurohumoral and genetic factors should be considered in any analysis of carotid artery remodeling, because they can directly influence the remodeling not only of conduit arteries but also of arterioles.

In conclusion, the carotid artery in patients with untreated hypertension reveals various types of remodeling that increase with age. These findings add further impetus to the implementation of appropriate treatment for such patients.

References

15. Zarins CK, Zatina MA, Giddens DP, Ku DN, Glagov S:


25. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114: 345–352.


