Isolated Systolic Hypertension and Vessel Wall Thickness of the Carotid Artery

The Rotterdam Elderly Study

Michiel L. Bots, Albert Hofman, Anthony M. de Bruyn, Paulus T.V.M. de Jong, and Diederick E. Grobbee

We studied the association between isolated systolic hypertension (ISH) and generalized atherosclerosis as indicated by intima-media wall thickness (IMT) of the distal common carotid artery. The Rotterdam Elderly Study is a single-center study of a cohort of 11,854 elderly persons ≥55 years old. Baseline measurements included ultrasonic evaluation of plaques and vessel wall thickness of both carotid arteries and extensive measurements of cardiovascular risk factors. Mean IMT and lumen diameter of subjects with ISH (systolic pressure ≥160 mm Hg and diastolic pressure <90 mm Hg) among the first 1,000 participants (n=33) and 66 age- and sex-matched control subjects were compared. None of the subjects were using antihypertensive drug treatment, and all were free of cardiovascular disease. Mean IMT of the right common carotid artery was significantly higher in those with ISH than in normotensive subjects, with a mean difference of 0.07 mm (95% CI, 0.01, 0.14). Results for the left carotid artery were similar (mean difference, 0.06 mm; 95% CI, −0.01, 0.13). The end-diastolic mean lumen diameter was significantly larger in subjects with ISH than in control subjects for both right and left sides, with a mean difference of 0.70 mm (95% CI, 0.38, 1.01) and 0.48 mm (95% CI, 0.17, 0.80), respectively. Adjustment for differences in body mass index, serum lipids, smoking, and fibrinogen did not materially change the findings. Furthermore, atherosclerotic plaques were more frequently observed among those with ISH compared with control subjects, with a mean difference of 12% (95% CI, −1, 25). Our findings suggest that generalized atherosclerosis, ultrasonographically determined as increased carotid IMT, is associated with ISH in asymptomatic elderly subjects. (Arteriosclerosis and Thrombosis 1993;13:64–69)

KEY WORDS • carotid artery disease • carotid atherosclerosis • isolated systolic hypertension • elderly • intima-media wall thickness

Several studies have indicated that isolated systolic hypertension is a strong predictor of the future occurrence of atherosclerotic cardiovascular disease and total mortality in the elderly.1–3 Moreover, results from a double-blind, randomized, placebo-controlled trial of systolic hypertension in the elderly showed that antihypertensive treatment of isolated systolic hypertension, defined as a systolic blood pressure of ≥160 mm Hg and a diastolic blood pressure of <90 mm Hg, leads to a considerable reduction of cardiovascular morbidity and mortality in this age group.4

Isolated systolic hypertension is generally regarded as a consequence of a reduced compliance of the aorta and the large arteries.5,6 Stiffening of the arteries contributes to a disproportionate rise in systolic blood pressure.7 Age-related structural changes in the vessel wall, such as an increase in the ratio of collagen to elastin, have been recognized as major determinants of reduced arterial compliance.6 Similar changes of the vessel wall are found in atherosclerosis. Furthermore, the presence of atherosclerosis has been associated with reduced arterial compliance.8 The relative contribution of atherosclerosis to the pathogenesis of reduced arterial compliance and subsequent development of isolated systolic hypertension, however, is still debated.5,7 Recently, it has been shown that with high-resolution B-mode ultrasonography, the presence and extent of atherosclerosis of the carotid arteries can be noninvasively assessed in an effective and accurate way in populations at large.10–12

In this article, we present the findings among the first 1,000 participants of the Rotterdam Elderly Study on the association of isolated systolic hypertension in asymptomatic elderly subjects and vessel wall thickness of the distal common carotid artery.

Methods

Population

The Rotterdam Elderly Study is a single-center prospective follow-up study of a cohort of 11,854 elderly persons ≥55 years old. All residents of the suburb of Ommoord in Rotterdam, The Netherlands, are invited...
to participate in the study, which has been approved by the Medical Ethics Committee of Erasmus University, and written informed consent is obtained from all participants. The rationale and design of the Rotterdam Elderly Study have been described elsewhere.\textsuperscript{13} In short, the objective of the Rotterdam Elderly Study is to clarify the determinants of chronic disabling diseases in an aging population. Incidence and risk factors of neurogeriatric diseases, locomotor diseases, ophthalmologic diseases, and cardiovascular diseases are being studied. With respect to cardiovascular disease, the Rotterdam Elderly Study focuses on the contribution of thrombogenic factors to atherosclerotic disease and on the presence and progression of atherosclerosis of the vessel wall and its determinants. The study includes an extensive home interview followed by two visits at the research center for a clinical examination. The participation rate of the cohort at the time of the present analysis was 72%.

**Measurements and Definitions**

Information on current health status, medical and family history of chronic disease, drug use, and smoking behavior was obtained by use of a computerized questionnaire, which included a Dutch version of the Rose questionnaire for assessment of prevalent coronary heart disease.\textsuperscript{14} A history of stroke and myocardial infarction was obtained through direct questioning. With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers, and those who have never smoked. During two visits at the research center, several cardiovascular risk indicators were measured. Height and weight were measured, and body mass index (in kilograms per square meter) was calculated. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the analysis. Isolated systolic hypertension was defined as a systolic blood pressure \( \geq 160 \text{ mm Hg} \) and a diastolic blood pressure \( <90 \text{ mm Hg} \).\textsuperscript{15} Subjects with a systolic blood pressure \( <160 \text{ mm Hg} \) and a diastolic blood pressure \( <90 \text{ mm Hg} \) were considered normotensive.

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Wash.). According to the Rotterdam Elderly Study scanning protocol, a careful search was performed for the intima–lumen interface on the near wall and the lumen–intima interface and media–adventitia interface on the far wall of the distal common carotid artery.\textsuperscript{16,17} The distances between the interfaces represent the lumen diameter and the intima–media wall thickness, respectively.\textsuperscript{18,19} When an optimal longitudinal image was obtained, it was “frozen” on the R wave of the electrocardiogram and stored on videotape. This procedure was repeated three times for both sides. Subsequently, the common carotid artery was evaluated for the presence of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen. The entire ultrasound procedure was recorded on videotape. The actual measurements were performed off-line. From the videotape, the frozen images were digitized and displayed on the screen of a personal computer by use of additional dedicated software. This procedure has been described in detail previously.\textsuperscript{19} In short, with a cursor, the interfaces of the distal common carotid artery were marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. This method permits the determination of mean values as well as maximal values for intima–media wall thickness and lumen diameter. The average of the intima–media wall thickness and lumen diameter of each of the three frozen images was taken as the measure for current wall thickness of the distal common carotid artery and lumen diameter, respectively. In addition, for each subject, a total intima–media wall thickness was calculated \((l + r)/2\). With respect to focal lesions, the presence or absence of calcifications and acoustic shadowing was noted. For all criteria, alternative choices were present as “cannot tell” and “not recorded.”

A venipuncture was performed, applying minimal stasis, with a 21-gauge butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Blood samples were collected into siliconized Vacutainer tubes (Beckton Dickinson, Meylan, France) containing clotting activator and separator for serum or 0.129 M sodium citrate for plasma. Serum was separated by centrifugation at room temperature for 10 minutes at 1,600g. Plasma was separated by a two-stage centrifugation, first for 10 minutes at 1,600g at 4°C and subsequently for 10 minutes at 4°C at 10,000g, which yielded platelet-poor plasma. All samples were quickly frozen in liquid nitrogen and then stored at \(-80^\circ\text{C}\) before assay. Serum total cholesterol was determined by an automated enzymatic procedure.\textsuperscript{20} High density lipoprotein (HDL) cholesterol was measured similarly after precipitation of the non-HDL fraction with phosphotungstate-magnesium. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG).\textsuperscript{21}

Among the first 1,000 participants of the Rotterdam Elderly Study, subjects receiving antihypertensive drugs, those who reported a hospitalization because of a stroke or a myocardial infarction, and those who had a positive Rose questionnaire for angina pectoris or intermittent claudication were excluded from the analysis. Of the remaining subjects \((n=583)\) who were not on antihypertensive treatment and free of cardiovascular disease, 33 had isolated systolic hypertension. From the remaining eligible population, 66 age- and sex-matched normotensive control subjects were randomly selected.

**Data Analysis**

Mean levels and proportions of several cardiovascular risk indicators and mean vessel wall thickness and lumen diameter of subjects with and without isolated systolic hypertension were compared. The differences are presented with a 95% confidence interval (CI). Multiple linear regression analysis was used for analysis of differences across groups, adjusted for several confounding variables, notably body mass index, serum lipids, smoking, and fibrinogen. Analysis of covariance was used to estimate adjusted mean values of vessel wall thickness for tertiles of systolic and diastolic blood pressure. A linear regression model was used to test for trends.\textsuperscript{22}
TABLE 1. Baseline Characteristics of Subjects With and Without Isolated Systolic Hypertension

<table>
<thead>
<tr>
<th></th>
<th>No ISH</th>
<th>ISH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>66</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.7±7.8</td>
<td>72.0±8.3</td>
<td>p</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>39</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9±3.3</td>
<td>26.0±4.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>129.6±15.5</td>
<td>169.1±8.0</td>
<td>p</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>66.8±10.1</td>
<td>76.2±10.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smoking (% yes)</td>
<td>23</td>
<td>33</td>
<td>0.26</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.44±1.27</td>
<td>6.81±1.12</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.33±0.37</td>
<td>1.41±0.36</td>
<td>0.34</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.93±0.84</td>
<td>2.91±0.76</td>
<td>0.88</td>
</tr>
</tbody>
</table>

ISH, isolated systolic hypertension; HDL, high density lipoprotein. Values are percentages or mean±SD.

*pDifference results from selection of study group.

Results

In all subjects (n=99), the intima–media thickness of the far wall of the left common carotid artery could be assessed from the images stored on videotape. The intima–media wall thickness of the right common carotid artery could be measured in 98 subjects. The lumen diameter could be measured in 93 and 95 subjects, respectively.

Baseline characteristics of both groups are presented in Table 1. Mean systolic blood pressure was different across groups, as expected from the selection criteria. Diastolic blood pressure levels also were significantly different across the two groups. Compared with subjects, subjects with isolated systolic hypertension had higher mean serum total cholesterol and higher mean HDL cholesterol levels, and there were more current smokers among them. The differences, however, did not reach statistical significance.

Mean intima–media vessel wall thickness of the right common carotid artery was higher in those with isolated systolic hypertension than in normotensive subjects (Table 2). The mean difference was 0.07 mm (95% CI, 0.01, 0.14). Results for the left carotid artery were similar, with a mean difference of 0.06 mm (95% CI, -0.01, 0.13). No difference between the left and right carotid arteries was observed. Measurements at both sides were combined as total wall thickness (left+right)/2. After adjustment for differences in serum lipids, body mass index, smoking, and fibrinogen, total intima–media wall thickness remained significant across groups, with a mean difference of 0.08 mm (95% CI, 0.02, 0.14). Additional adjustment for differences in diastolic blood pressure between groups did not alter the results.

In subjects with isolated systolic hypertension, the end-diastolic lumen diameter was significantly wider than in control subjects for both right and left sides: mean difference, 0.70 mm (95% CI, 0.38, 1.01) and 0.49 mm (95% CI, 0.17, 0.80), respectively. Adjustments for differences in body mass index, serum lipids, smoking, fibrinogen, and diastolic blood pressure did not substantially alter the results (Table 2). Atherosclerotic lesions were more frequently observed in those with isolated systolic hypertension (adjusted difference, 12%). This finding, however, was of borderline statistical significance (95% CI, -1, 25).

Subjects were categorized in tertiles according to their level of diastolic blood pressure and in tertiles based on their systolic blood pressure. We compared mean total intima–media wall thickness within strata of diastolic and systolic blood pressure (Figure 1). Mean intima–media wall thickness gradually increased with rising levels of systolic blood pressure within all strata of diastolic blood pressure (test for trend, p<0.05 except for the lowest tertile, p=0.09). In addition, subjects in the lowest tertile of diastolic and systolic blood pressures appeared to have a higher mean intima–media wall thickness than those with relatively higher diastolic blood pressure levels and similar systolic blood pressure levels. This finding, however, did not reach the level of significance. With respect to subjects in the other ter-

TABLE 2. Dimensions of the Distal Common Carotid Artery in Subjects With and Without Isolated Systolic Hypertension

<table>
<thead>
<tr>
<th></th>
<th>No ISH</th>
<th>ISH</th>
<th>Mean difference (95% CI)</th>
<th>Adjusted mean difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>0.81±0.03</td>
<td>0.87±0.03</td>
<td>0.06 (-0.01, 0.13)</td>
<td>0.08 (0.02, 0.15)</td>
</tr>
<tr>
<td>Right side</td>
<td>0.79±0.02</td>
<td>0.86±0.03</td>
<td>0.07 (0.01, 0.14)</td>
<td>0.08 (0.01, 0.14)</td>
</tr>
<tr>
<td>Both sides†</td>
<td>0.80±0.02</td>
<td>0.86±0.03</td>
<td>0.06 (0.01, 0.12)</td>
<td>0.08 (0.02, 0.14)</td>
</tr>
<tr>
<td>Lumen diameter (mm‡)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>6.09±0.10</td>
<td>6.58±0.11</td>
<td>0.49 (0.17, 0.80)</td>
<td>0.60 (0.34, 0.86)</td>
</tr>
<tr>
<td>Right side</td>
<td>6.24±0.09</td>
<td>6.94±0.14</td>
<td>0.70 (0.38, 1.01)</td>
<td>0.74 (0.43, 1.03)</td>
</tr>
<tr>
<td>Both sides‡</td>
<td>6.18±0.09</td>
<td>6.77±0.12</td>
<td>0.59 (0.29, 0.89)</td>
<td>0.64 (0.38, 0.89)</td>
</tr>
<tr>
<td>Plaques (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>3</td>
<td>13</td>
<td>10 (-1, 21)</td>
<td>9 (-1, 20)</td>
</tr>
<tr>
<td>Right side</td>
<td>5</td>
<td>9</td>
<td>4 (-6, 14)</td>
<td>6 (-5, 15)</td>
</tr>
<tr>
<td>Both sides§</td>
<td>5</td>
<td>15</td>
<td>10 (-1, 21)</td>
<td>12 (-1, 25)</td>
</tr>
</tbody>
</table>

ISH, isolated systolic hypertension; CI, confidence interval. Values are percentages or mean±SEM.

*Adjusted for differences in body mass index, serum lipids, smoking, and fibrinogen.

†Both sides refers to (left+right)/2.

‡End-diastolic lumen diameter.

§Both sides refers to plaques present in either the left or the right common carotid arteries or both.
Mean intima-media thickness
carotid artery

**FIGURE 1.** Bar graph showing mean total wall thickness (in millimeters) by levels of systolic and diastolic blood pressure, adjusted for differences in age, sex, body mass index, serum lipids, smoking, and fibrinogen.

Diastolic blood pressure (mmHg)

FIGURE 1: Bar graph showing mean total wall thickness (in millimeters) by levels of systolic and diastolic blood pressure, adjusted for differences in age, sex, body mass index, serum lipids, smoking, and fibrinogen.

**Discussion**

Our data indicate that the intima-media wall thickness of the common carotid artery, assessed with high-resolution B-mode ultrasonography, is significantly higher in asymptomatic elderly subjects with isolated hypertension than in those without elevated blood pressure. Moreover, the end-diastolic lumen diameter is significantly larger in those with isolated systolic hypertension. These findings are independent of differences in age, sex, body mass index, serum lipids, fibrinogen, and smoking. In addition, atherosclerotic thickening of the intima-media vessel wall increased gradually with rising levels of systolic blood pressure. Furthermore, atherosclerotic plaques appeared to be more common in those with elevated systolic blood pressure, without, however, reaching statistical significance.

Before the findings can be accepted, some aspects of the study need to be considered. First, subjects were classified on the basis of a blood pressure reading performed on one occasion. In particular, some misclassification of subjects with isolated systolic hypertension may have occurred. This may have reduced the observed difference between the groups, provided that a true association exists between isolated systolic hypertension and intima-media vessel wall thickness.

Second, to eliminate selection bias, subjects on antihypertensive treatment and those with symptomatic cerebrovascular, cardiovascular, or peripheral arterial disease were excluded. Subjects using antihypertensive drugs may have artificially lowered blood pressure levels. Furthermore, in these subjects, a clustering of cardiovascular risk factors may be present, which is positively related to carotid atherosclerosis. In addition, subjects with prevalent coronary heart disease may have a relatively low blood pressure as a consequence of their disease or may receive additional drugs that may have an antihypertensive effect. If not excluded, these subjects are more likely to be part of the control group, and this may artificially reduce the magnitude of the difference between the groups.

Finally, it may be argued that the method used to assess carotid atherosclerosis may not truly reflect the atherosclerotic process. Atherosclerosis is viewed as a disorder that is restricted to the intima layer of the arterial vessel wall. Ultrasound technique cannot discriminate between the intima layer and the media layer of the vessel wall. However, an ultrasonographically determined increase in intima-media wall thickness may be regarded as an indicator of generalized atherosclerosis, since it has been associated with elevated levels of cardiovascular risk factors and with an increased risk of myocardial infarction. Moreover, atherosclerotic carotid artery disease has been related to atherosclerosis in coronary arteries and peripheral arteries.

A decrease of the compliance of the aorta and the large arteries has been suggested to be the principal hallmark of isolated systolic hypertension. The finding of an increased intima-media wall thickness and a larger lumen diameter among elderly subjects with isolated systolic hypertension is compatible with a diminished arterial compliance. Our observations of an increased intima-media wall thickness and a higher prevalence of atherosclerotic plaques in the carotid arteries, however, indicate that atherosclerosis may be associated with isolated systolic hypertension. These findings are compatible with results from studies that have shown a reduced aortic compliance in subjects with atherosclerosis, with studies that have reported a positive association between isolated systolic hypertension and atherosclerosis, and with a study in which ultrasonographically assessed carotid intima-media wall thickness was associated with systolic blood pressure elevation.

The time-dependent relation between atherosclerosis, reduced arterial compliance, and isolated systolic hypertension cannot be determined with our data because of the cross-sectional design of this study.

Evidence from other studies may be used to address this issue. Early in life, interindividual differences exist in arterial stiffness. Apart from structural changes in the vessel wall, these differences may be attributed to differences in neural, humoral, and physical stimuli. A reduced arterial compliance has been associated with elevated blood pressure in young adults. Data from the Framingham Heart Study have indicated that in middle-aged subjects, elevated systolic blood pressure and pulse pressure are major determinants of isolated systolic hypertension in the future.

Witteeman, in a 9-year follow-up study among 614 women 45–64 years old, observed a gradual progression of radiographically diagnosed atherosclerosis of the abdominal aorta with increasing levels of systolic blood pressure, suggesting
that systolic blood pressure is causally related to the atherosclerotic process. Our observation indicating a gradual increase in intima-media wall thickness with rising levels of systolic blood pressure is in accordace with those findings. These data may indicate that a reduced arterial compliance may lead to a mild elevation of systolic blood pressure (or pulse pressure). Blood pressure elevation sets a pathophysiological process in progress, possibly atherosclerosis, that may lead to a further reduction of the compliance of the large arteries and a subsequent rise in systolic blood pressure. This process may enhance arterial stiffness and atherosclerosis, leading to a further increase in systolic blood pressure and to development of isolated systolic hypertension. Additionally, isolated systolic hypertension in itself may further enhance the development of atherosclerosis.

Some early reports have suggested that in the elderly, in addition to a rise in systolic blood pressure, diastolic blood pressure may actually fall as a result of reduced arterial compliance of the aorta and large arteries. With age, the lowering effect of arterial stiffening on the diastolic blood pressure may outweigh the elevating effect of increased peripheral resistance on diastolic pressure. This hypothesis implies that in the elderly, a low diastolic blood pressure might be regarded as an indicator of prevalent vascular damage (atherosclerosis). Data to support this may be found in results from recent studies in the very old, suggesting a lower mortality rate in those with diastolic blood pressure levels ranging from 85 to 95 mm Hg than in those with low diastolic blood pressure levels. Furthermore, a low diastolic blood pressure (<75 mm Hg) has been associated with an increased risk of progression of atherosclerosis of the abdominal aorta compared with diastolic blood pressure values ranging from 75 to 84 mm Hg. Our data, however, did not demonstrate an increased vessel wall thickening for all levels of systolic blood pressure in subjects with low diastolic blood pressures compared with subjects with relatively higher diastolic blood pressures. These relations need further attention.

In conclusion, our observations among asymptomatic elderly subjects with isolated systolic hypertension indicate that atherosclerosis, as assessed by ultrasonographically determined intima-media vessel wall thickness and plaques, is probably involved in isolated systolic hypertension. Whether increased vessel wall thickness is the result of isolated systolic hypertension or whether it may also contribute to blood pressure elevation remains to be established.

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We are grateful to the participants of the Rotterdam Elderly Study. We thank all field workers, ultrasound technicians, computer assistants, and laboratory technicians in the Ommoord Research Center for their enthusiasm and skillful contributions to the data collection.

References


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