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% confidence interval [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.8 Similar changes of the vessel wall are found in atherosclerosis. Furthermore, the presence of atherosclerosis has been associated with reduced arterial compliance.9 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.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, ophthalmo-
logic 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 participa-
tion 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 ques-
tionnaire, which included a Dutch version of the Rose
questionnaire for assessment of prevalent coronary
heart disease.14 A history of stroke and myocardial
infarction was obtained through direct questioning.
With respect to smoking behavior, subjects were cate-
gorized in groups of current smokers, former smokers,
and those who have never smoked. During two visits at
the research center, several cardiovascular risk indica-
tors 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 sphygmoma-
nometer. 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 ≥160 mm Hg and
diastolic blood pressure <90 mm Hg.15 Subjects with a
systolic blood pressure <160 mm Hg and a diastolic
blood pressure <90 mm Hg were considered normoten-
sive.

Ultrasonography of both carotid arteries was per-
formed with a 7.5-MHz linear-array transducer and a
duplex scanner (ATL UltraMark IV, Advanced Tech-
ology 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.16,17 The distances between the
interfaces represent the lumen diameter and the in-
tima–media wall thickness, respectively.16,17 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 le-
sions, 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 dis-
played on the screen of a personal computer by use of
additional dedicated software. This procedure has been
described in detail previously.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
(left + right)/2. With respect to focal lesions, the pres-
ence 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 (Bec-
ton Dickinson, Meylan, France) containing clotting ac-
tivator and separator for serum or 0.129 M sodium
citrate for plasma. Serum was separated by centrifuga-
tion 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 nitro-
gen and then stored at —80°C before assay. Serum total
cholesterol was determined by an automated enzymatic
procedure.20 High density lipoprotein (HDL) choles-
terol 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).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 antihyper-
tensive treatment and free of cardiovascular disease, 33
had isolated systolic hypertension. From the remaining
eligible population, 66 age- and sex-matched normoten-
sive 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 con-
founding 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.22
TABLE 1. Baseline Characteristics of Subjects With and Without Isolated Systolic Hypertension

<table>
<thead>
<tr>
<th>Characteristic</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>*</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>†</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.

*Matching variables.
†Difference 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 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 the two groups, as expected from the selection criteria. Diastolic blood pressure levels also were significantly different across the two groups. Compared with control 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 pressure 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>Characteristic</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.
cerebrovascular, cardiovascular, or peripheral arterial tension and intima-media vessel wall thickness. Hypertensive treatment and those with symptomatic served difference between the groups, provided that a may have occurred. This may have reduced the ob-

performed on one occasion. In particular, some misclas-

classified on the basis of a blood pressure reading however, reaching statistical significance.

those with elevated systolic blood pressure, without,
in age, sex, body mass index, serum lipids, fibrinogen,

Discussion

Our data indicate that the intima–media wall thick-

cness 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 pres-

sure. Moreover, the end-diastolic lumen diameter is significantly larger in those with isolated systolic hyper-

tension. 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 misclas-

sification of subjects with isolated systolic hypertension may have occurred. This may have reduced the ob-

served difference between the groups, provided that a true association exists between isolated systolic hyper-
tension and intima–media vessel wall thickness.

Second, to eliminate selection bias, subjects on anti-
hypertensive treatment and those with symptomatic cerebrovascular, cardiovascular, or peripheral arterial disease were excluded. Subjects using antihypertensive drugs may have artificially lowered blood pressure lev-

eels. Furthermore, in these subjects, a clustering of cardiovascular risk factors may be present, which is positively related to carotid atherosclerosis.10–12 In addition, subjects with prevalent coronary heart disease may have a relatively low blood pressure as a conse-
cquence of their disease or may receive additional drugs that may have an antihypertensive effect. If not ex-
cluded, 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.23 Ultrasound technique cannot dis-
criminate 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 athero-
sclerosis, since it has been associated with elevated levels of cardiovascular risk factors and with an in-
creased risk of myocardial infarction.10–12,24–25 Moreover, atherosclerotic carotid artery disease has been related to atherosclerosis in coronary arteries and per-

ipheral arteries.26–28

A decrease of the compliance of the aorta and the large arteries has been suggested to be the principal hallmark of isolated systolic hypertension.9 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 di-

minished 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,8,9,29 with studies that have reported a positive association between isolated systolic hyperten-
sion and atherosclerosis,30,31 and with a study in which ultrasonographically assessed carotid intima–media wall thickness was associated with systolic blood pressure elevation.32,33 The time-dependent relation between atherosclerosis, reduced arterial compliance, and iso-
lated 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.34 Apart from structural changes in the vessel wall, these differences may be attributed to differences in neural, humoral, and physical stimuli.6 A reduced arterial compliance has been associated with elevated blood pressure in young adults.35 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.36 Witteman,37 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

![Mean intima-media thickness common carotid artery](attachment://image.png)
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 accordance 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. Blood pressure may actually fall as a result of reduced arterial compliance of the aorta and large arteries.

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.

In conclusion, our observations among asymptomatic elderly subjects with isolated systolic hypertension indicate that atherosclerosis, as assessed by ultrasonographically determined intima-media 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.

Acknowledgments

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References

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