Arterial Wall Thickness in Familial Hypercholesterolemia
Ultrasound Measurement of Intima-Media Thickness
in the Common Carotid Artery

Inger Wendelhag, Olov Wiklund, and John Wikstrand

B-mode ultrasound was used to noninvasively determine wall thickness and lumen diameter in the common carotid artery in patients with familial hypercholesterolemia (n=53) and in a control group (n=53). The controls were matched for sex, age, height, and weight, and all had a serum cholesterol level below 6.5 mmol/l. The study was performed to evaluate whether the patients had a thicker arterial wall compared with that of the control group. Wall thickness was determined as the combined intima-media thickness of the far wall and is presented as the mean and maximum thickness of a 10-mm-long section of the common carotid artery. The difference between the groups was 0.13 mm in mean wall thickness (p<0.001; 95% confidence interval, 0.07-0.18 mm) and 0.20 mm in maximum wall thickness (p<0.001; 95% confidence interval, 0.09-0.23 mm). Fifty of the subjects were examined twice to estimate the interobserver variability. The coefficients of variation for mean and maximum wall thickness were 102% and 8.9%, respectively. The two study groups were well matched and differed only in lipid levels. Thus, there is reason to believe that the difference in wall thickness can be explained by the background of familial hypercholesterolemia and the increased cholesterol levels.

During recent years, noninvasive methods have been developed to study the extent of clinical atherosclerotic disease in the carotid arteries. B-mode (two-dimensional) medical ultrasound also seems to be a promising method for studies of the early, silent phases of atherosclerotic disease in the arterial wall. However, only large arteries like the carotid and femoral arteries are presently amenable to investigation. The arterial wall changes in these vessels are meant to be used as indicators for general atherosclerosis, including coronary atherosclerosis.

Familial hypercholesterolemia is a common inherited disease characterized by elevated low density lipoprotein (LDL) cholesterol levels and tendon xanthomas. These patients are at a high risk for coronary heart disease.

New drugs are available to lower plasma lipoprotein levels. With B-mode ultrasound, it is possible to perform repeated examinations and study the changes in vessel wall morphology over time. Hence, an important role of the method would be to evaluate the effect of cholesterol lowering on the atherosclerotic process. However, a prerequisite for the design of such studies is more information about the method's sensitivity and variability.

Earlier studies of in vitro experiments have shown that it is possible to measure lumen diameter and the combined intima-media thickness of the far wall in the common carotid artery. Several studies of selected patient material have also been published but none of the studies published so far has dealt exclusively with patients with familial hypercholesterolemia.

The aim of this study was to evaluate whether patients with familial hypercholesterolemia have a thicker arterial wall in the common carotid artery compared with that of a sex- and age-matched control group.

Methods

Study Groups

A group of patients (n=53) with heterozygous familial hypercholesterolemia was recruited from the lipid clinic of the Sahlgrenska Hospital, Gothenburg, Sweden, to participate in the present study of ultrasound examination of the carotid artery. This group will be referred to as the “hypercholesterolemic group.” The diagnosis of familial hypercholesterole-
smoking was defined as described in Table 1. Patients were 30 men and 23 women with a mean age of 52.8 years (range, 20–72 years) (Table 2). Premenopausal women were excluded, as were patients with diabetes, hepatic dysfunction, severe hypertension, or excessive obesity. The patients were examined after at least 8 weeks of a wash-out period from previous treatment with a lipid-lowering drug. During this period, the patients were given dietary advice.

A control group with serum cholesterol levels below 6.5 mmol/l was recruited from a representative population sample in Gothenburg. To each patient with hypercholesterolemia a subject was matched with regard to sex, age, height (±10 cm), and weight (±7 kg). Age matching was within ±5 years except in two cases (−6 and +7 years) (Table 2). For technical reasons, high-quality images from the common carotid artery were missing for two patient-control pairs. Therefore, all data are presented for 51 pairs.

In the hypercholesterolemic group, 14 patients had had a myocardial infarction and one had had a stroke. In the control group, two subjects had had a myocardial infarction and none had had a stroke. Eight patients with hypercholesterolemia and five control subjects were being treated for hypertension at the time of examination.

**Blood Pressure**

Resting blood pressure was measured phonographically in the right arm after about 30 minutes of supine rest, in connection with the ultrasound examination. A heart-sound microphone was placed over the brachial artery, and an automatically inflated and deflated standard cuff (Bouche-Brecht, FRG) was used. Cuff pressure, Korotkoff sounds, and an electrocardiographic signal (lead II) were simultaneously recorded on a Mingograph (Siemens-Elema, Sweden). Blood pressure was calculated to the nearest 1 mm Hg and was the mean of two recordings.

**Smoking**

Information on smoking habits was obtained by a self-administered questionnaire. The total number of years of smoking was multiplied by the average number of cigarettes smoked daily. The product was called “cigarette-years.”

**Biochemical Analysis**

Blood samples for total serum cholesterol, serum triglycerides, and lipoprotein fractions were drawn after a fasting period of 10–12 hours. Cholesterol and triglyceride levels were determined by fully enzymatic techniques by using a Gilford System 3500 Autoanalyzer (Gilford Instruments Inc., Oberlin, Ohio). High density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein (apo) B-containing lipoproteins with manganese chloride and heparin. LDL cholesterol was calculated as described by Friedewald et al.

Apo A-I, B, and E were analyzed by using frozen samples stored at −80°C. Apo A-I concentrations were measured by a rate-nephelometric method. Apo B and apo E levels were determined by electroimmunoassay. Levels of lipoprotein(a) were determined by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden).

**Carotid Ultrasonography**

Examination was performed with an ultrasound scanner (Acuson 128, Mountain View, Calif.) equipped with a linear 5- or 7-MHz transducer. The transducer aperture was 38 mm.

Subjects were examined in a supine position with the head turned to the left while resting on a specially designed firm cushion that was positioned at a 45° angle. The ultrasound transducer was placed over the right carotid artery at the level of the bifurcation. The electrocardiographic signal (lead II) was simultaneously recorded to synchronize the image capture to the top of the R wave (end diastole). The common carotid artery close to the bifurcation was scanned longitudinally, starting with the transducer placed anteriorly and medially of the artery and with the beam directed...
through the vessel. The artery was then scanned by moving the transducer in a lateral direction. At the position of best visibility of the wall structures, three images were captured from the common carotid artery just proximal to the carotid bulb (Figure 1). The image capture was performed by “freezing” the continuous registrations at end diastole by electrocardiographic triggering, with subsequent recording on videotape.

**Measurement of Wall Thickness and Lumen Diameter**

The ultrasound images from the videotape were analyzed by a computerized analyzing system. All analyses were performed in a blinded manner with regard to the group to which the images belonged. Wall thickness was defined as the distance from the leading edge of the lumen-intima interface of the far wall to the leading edge of the media-adventitia interface of the far wall. Lumen diameter was defined by the distance between the leading edges of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall. The measurements were made in the common carotid artery along a 10-mm-long section proximal to the carotid bulb. The computer program calculated the minimum, maximum, and mean values of intima-media thickness and lumen diameter. Three frozen images from the same section of the artery were measured, and the mean of these was calculated.

**Interobserver Variability**

To estimate the interobserver variability, a total of 50 subjects, 26 from the hypercholesterolemic group and 24 control subjects, underwent the ultrasound examination twice on the same day performed by two independent observers who were blinded with regard to the results of the other observer. Arterial wall thickness and lumen diameter from the two examinations were measured by each observer blinded with regard to the results of the other observer and also to the group from which the images came. For technical reasons, high-quality images were missing for three subjects.

The correlation coefficient between two independent observers was \( r = 0.83 \) for mean wall thickness and \( r = 0.89 \) for maximum wall thickness. Correlation coefficients were \( r = 0.96 \) for mean lumen diameter and \( r = 0.95 \) for minimum lumen diameter. The coefficient of variation for mean wall thickness was 10.2% and for maximum wall thickness, 8.9%. For mean and minimum lumen diameter, the coefficients of variation were 2.8% and 3.0%, respectively.

**Statistical Analysis**

MINITAB software in a PDP 11-34 computer was used in the statistics. Two-sided nonparametric tests were used. Because matching was performed and there was a significant relation among the 51 pairs in mean wall thickness of the common carotid artery.
TABLE 3. Serum Lipids and Lipoprotein Levels of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=51)</th>
<th>Familial hypercholesterolemia group (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD*</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.64±0.92</td>
<td>9.56±1.79</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>1.36±0.82</td>
<td>1.64±0.74</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.44±0.39</td>
<td>1.33±0.37</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.65±0.82</td>
<td>7.43±1.86</td>
</tr>
<tr>
<td>Apo A-I (g/l)</td>
<td>1.53±0.33</td>
<td>1.40±0.31</td>
</tr>
<tr>
<td>Apo E (g/l)</td>
<td>0.054±0.013</td>
<td>0.060±0.016</td>
</tr>
<tr>
<td>Apo B (g/l)</td>
<td>1.08±0.28</td>
<td>1.88±0.40</td>
</tr>
<tr>
<td>Lp(a) (mg/l)</td>
<td>59 (7-1,040)</td>
<td>230 (25-1,244)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; apo, apolipoprotein; Lp(a), lipoprotein(a).

*For Lp(a), values are median and range.

CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; apo, apolipoprotein; Lp(a), lipoprotein(a).

(r=0.48, n=51, p=0.001), the hypothesis of no difference in distributions between the groups was tested with Wilcoxon’s test for paired data. Furthermore, 95% confidence intervals for differences were calculated. Because the two groups, by definition, differed in serum lipids, these were not formally tested, but 95% confidence intervals for each of these variables in the two groups have been given.

The proportions of smokers (never, past, or current) in the two groups were compared by testing with Fisher’s test for paired comparisons. The other proportions (wall thickness) were tested with McNemar’s test. Limits for abnormality in the studied variables were arbitrarily set at the second highest value of the control group.

In the reproducibility study, means and standard deviations (SDs) for differences between the two observers were calculated. The SD of the interobserver error (s) was then calculated according to the formula

\[ s = \frac{SD}{\sqrt{2}} \]

The coefficient of variation (CV) describes the difference as a percentage of the pooled mean values (\( \bar{x} \)) and was calculated according to the formula

\[ CV = \frac{s \times 100\%}{\bar{x}} \]

Results

The two study groups were very similar in anthropometric data, blood pressure, and heart rate (Table 2). The proportion of current smokers was the same in the two groups, but there was a tendency (NS) for somewhat greater numbers of past smokers in the group with familial hypercholesterolemia. Smoking exposure calculated as total cigarette-years was very similar in the two groups (Table 2).

Serum Lipid and Lipoprotein Levels

Total and LDL cholesterol and apo B levels were higher in the hypercholesterolemic group compared

with the control group (see 95% confidence intervals, Table 3). For serum triglycerides, HDL cholesterol, and apo A-I, 95% confidence intervals in the two groups overlapped.

Lumen Diameter and Wall Thickness

The mean and maximum wall thicknesses (intima-media of the far wall) of a 10-mm-long section of the common carotid artery were significantly thicker in the hypercholesterolemic group than in the control group (\( p<0.001 \); Table 4 and Figures 2 and 3). The mean difference in thickness between the groups was 0.13 mm for mean wall thickness (95% confidence interval, 0.07–0.18 mm) and 0.20 mm for maximum wall thickness (95% confidence interval, 0.09–0.23 mm). Mean and minimum lumen diameters were significantly smaller in the hypercholesterolemic group than in the control group (\( p<0.05 \); Table 4). The mean difference between the groups was 0.21 mm for mean lumen diameter (95% confidence interval, 0.01–0.48 mm) and 0.24 mm for minimum lumen diameter (95% confidence interval, 0.05–0.48 mm).

The proportion of mean wall thickness >1.0 mm and the proportion of maximum wall thickness >1.3 mm were significantly higher in the hypercholesterolemic group compared with the control group (\( p<0.001 \); Figures 2 and 3).

The ratio between mean wall thickness and mean lumen diameter (relative wall thickness) was significantly higher in the hypercholesterololemic group compared with the control group (\( p<0.001 \); Table 4).

Wall Thickness and Serum Lipid and Lipoprotein Levels

The two study groups were analyzed together, and the correlation coefficients for the relations between arterial wall thickness and serum lipid and lipoprotein levels are presented in Table 5. Mean wall thickness was significantly correlated to total serum cholesterol (\( r=0.32, p<0.001 \)), to LDL cholesterol (\( r=0.30, p<0.01 \), and to apo B (\( r=0.32, p<0.01 \); Table 5 and Figure 4).
TABLE 4. Arterial Wall Thickness (Intima-Media of the Far Wall) and Lumen Diameter in the Common Carotid Artery of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=51)</th>
<th>Familial hypercholesterolemia group (n=51)</th>
<th>Mean difference between groups</th>
<th>95% CI for mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (mm)</td>
<td>Mean (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm)</td>
<td>0.72±0.13</td>
<td>0.85±0.22*</td>
<td>0.13</td>
<td>0.07—0.18</td>
</tr>
<tr>
<td>Maximum (mm)</td>
<td>0.90±0.17</td>
<td>1.10±0.36*</td>
<td>0.20</td>
<td>0.09—0.23</td>
</tr>
<tr>
<td>Lumen diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm)</td>
<td>6.09±0.71</td>
<td>5.88±0.66†</td>
<td>-0.21</td>
<td>-0.48—-0.01</td>
</tr>
<tr>
<td>Minimum (mm)</td>
<td>5.82±0.68</td>
<td>5.58±0.56†</td>
<td>-0.24</td>
<td>-0.48—-0.05</td>
</tr>
<tr>
<td>Wall thickness to lumen diameter ratio</td>
<td>0.12±0.02</td>
<td>0.14±0.03*</td>
<td>0.025</td>
<td>0.016—0.033</td>
</tr>
</tbody>
</table>

Values are mean±SD.
CI, confidence interval.
*p<0.001, †p<0.05.

**Wall Thickness and Age**

The relation between arterial wall thickness and age was statistically significant. The correlation coefficient was $r=0.48$ ($p<0.001$) in the hypercholesterolemic group and $r=0.49$ in the control group ($p<0.001$). If the two groups were combined in the analysis, the correlation coefficient was $r=0.43$ ($p<0.001$; Figure 5). The slope of the regression line relating age to wall thickness was 0.009 mm/yr in the hypercholesterolemic group and 0.005 mm/yr in the control group ($p=0.20$).

**Wall Thickness and Gender**

Table 6 shows that men and women differed with regard to both age and smoking habits. Therefore, a meaningful analysis of any gender differences could not be performed.
Wall Thickness and Smoking

Analysis of wall thickness in the different smoking habit groups (never, past, or current) was not performed because the gender distribution was different in these groups. However, in the control group a linear correlation analysis revealed no relation between cigarette-years and wall thickness (r=0.13), whereas in the hypercholesterolemic group the r value was 0.27 (p<0.05).

Discussion

This study was performed in part to evaluate whether the B-mode ultrasound method was capable of measuring in detail the wall thickness of the

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**TABLE 5. Correlation Coefficients for the Relation Between Arterial Wall Thickness (Intima-Media of the Far Wall) and Serum Lipid and Lipoprotein Levels**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypercholesteremic group+control (n=102) correlation vs.</th>
<th>Mean wall thickness (r)</th>
<th>Maximum wall thickness (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>0.32*</td>
<td>0.32*</td>
<td></td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>0.05</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.03</td>
<td>-0.01</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>0.30†</td>
<td>0.29†</td>
<td></td>
</tr>
<tr>
<td>Apo A-I (g/l)</td>
<td>0.01</td>
<td>-0.04</td>
<td></td>
</tr>
<tr>
<td>Apo E (g/l)</td>
<td>0.18</td>
<td>-0.15</td>
<td></td>
</tr>
<tr>
<td>Apo B (g/l)</td>
<td>0.32†</td>
<td>0.34*</td>
<td></td>
</tr>
<tr>
<td>Lp(a) (mg/l)</td>
<td>0.16</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; LDL, low density lipoprotein; apo, apolipoprotein; Lp(a), lipoprotein(a).

*p<0.001, †p<0.01.
The presence of intima–media thickening, however, is not necessarily atherosclerosis. Hemodynamic changes, for example, an increase in wall tension in the vessel, may lead to intimal thickening. This thickening of the intima may be diffuse in straight arteries, but in the carotid bifurcation where there are areas with low wall shear stress, there is often a focal intimal thickening. However, because blood pressure or heart rate did not differ between the groups, there is no reason to believe that wall tension or shear stress would differ. Hence, the difference in the intima–media between the groups is probably not explained by hemodynamic factors.

The two study groups were matched for sex, age, height, and weight. Exposure to smoking was similar. The only observed difference between the groups was in serum cholesterol, LDL, and apo B. A relation between extent of atherosclerosis and LDL or apo B has been shown in several studies. Consequently, the increased intima–media thickness may possibly be seen as an expression of early atherosclerotic disease.

The intima–media thickness increased with age in both groups, and the findings may indicate a higher increase in wall thickness in the hypercholesterolemic group. This observation is well in line with the early development of atherosclerosis in these patients. A relation was also found between wall thickness and cigarette-years in the hypercholesterolemic group but not in the control group. One may speculate that the higher the cholesterol level, the greater the importance of smoking as a risk factor.

No previous data are available on arterial wall thickness in a well-defined group of patients with familial hypercholesterolemia, although Poli et al have performed a similar study of hypercholesterolemic patients. They also found a significant increase in arterial wall thickness compared with that in a control group.

Further studies are ongoing to evaluate the progress of atherosclerotic disease with time in patients with familial hypercholesterolemia. The present study showed a highly statistically significant difference between the two study groups, and reproducibility was quite satisfactory. Hence, it should be possible to perform prospective studies in groups of patients like the present one. Data from prospective studies of patients with familial hypercholesterolemia are needed to calculate sample sizes for randomized

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**Table 6. Anthropometric Data, Blood Pressure, Heart Rate, and Smoking Habits in Men and Women**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Familial hypercholesterolemia group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=30)</td>
<td>Women (n=21)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.8±12.3</td>
<td>59.8±6.5</td>
</tr>
<tr>
<td>Body height (m)</td>
<td>178±5</td>
<td>166±6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.5±13.0</td>
<td>67.0±13.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3±3.3</td>
<td>24.1±3.9</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>122±13</td>
<td>129±21</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>71±9</td>
<td>78±9</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>65±11</td>
<td>62±8</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
<td>5.58±1.02</td>
<td>5.73±0.78</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>Past smoker (%)</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Total cigarette-years</td>
<td>8,750</td>
<td>2,240</td>
</tr>
</tbody>
</table>

Values are mean±SD.

BMI, body mass index; SBP/DBP, systolic/diastolic arterial blood pressure; HR, heart rate.
clinical trials whose aim is to prevent or postpone progression of the disease.

However, it should be borne in mind that the intima–media thickness of the carotid artery is used only as a surrogate variable for coronary atherosclerosis. The relation between this variable and coronary atherosclerosis or clinical disease has yet to be proven. Future long-term prospective studies, therefore, must also address the issue of how changes in the carotid and femoral arteries are correlated with coronary atherosclerosis and its sequelae, myocardial infarction and sudden death.

Acknowledgments

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References


KEY WORDS: atherosclerosis • B-mode ultrasound • reproducibility
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