Premature Carotid Atherosclerosis: Does It Occur in Both Familial Hypercholesterolemia and Homocystinuria?

Ultrasound Assessment of Arterial Intima-Media Thickness and Blood Flow Velocity

Paolo Rubba, MD; Michele Mercuri, MD; Fulvio Faccenda, MD; Arcangelo Iannuzzi, MD; Concetta Irace, MD; Pietro Strisciuglio, MD; Agostino Gnasso, MD; Rong Tang, MD; Generoso Andria, MD; M. Gene Bond, PhD; Mario Mancini, MD

Background and Purpose  Homocystinuria due to cystathionine β-synthase deficiency and familial hypercholesterolemia are inherited disorders of metabolism that are associated with premature development of cardiovascular disease. This study addresses the possibility that different patterns of carotid wall damage and cerebral blood flow hemodynamics are present in these two metabolic diseases.

Methods  Twelve patients with homocystinuria due to cystathionine β-synthase deficiency (mean age, 24 years), 10 patients with homozygous familial hypercholesterolemia (mean age, 26 years), and 11 healthy control subjects (mean age, 26 years) underwent a vascular examination by noninvasive methods. B-mode ultrasound imaging was used to obtain measurements of intima-media thickness of common carotid, bifurcation, and internal carotid arteries as an index of atherosclerosis. Cerebral blood flow velocity was estimated from vascular examination of the middle cerebral artery by transtemporal Doppler. Systolic, diastolic, and mean velocities were measured. Pulsatility index, a possible indicator of vascular resistance in the cerebral circulation, was also calculated.

Results  Mean maximum intima-media thickness was 1.4 mm in patients with familial hypercholesterolemia, 0.6 mm in patients with homocystinuria, and 0.6 mm in control subjects. The difference between hypercholesterolemic and homocystinuric patients or control subjects was statistically significant (P<.001). Diastolic blood flow velocities were significantly reduced in the middle cerebral arteries of hypercholesterolemic patients compared with homocystinuric patients or control subjects (P<.05), whereas systolic or mean velocities did not differ. The pulsatility index, a possible indicator of vascular resistance in the cerebral circulation, was significantly higher in hypercholesterolemic patients compared with homocystinuric patients or healthy control subjects (P<.01). A direct relation was demonstrated between pulsatility index of the middle cerebral artery and mean maximum intima-media thickness of carotid arteries on the same side (P<.001).

Conclusions  Familial hypercholesterolemia is responsible for diffuse and focal thickening of carotid arteries and possibly also for hyperlipidemic endothelial dysfunction extending to small resistance arteries and leading to a disturbed cerebral blood flow. Patients with homocystinuria due to homocystinuria for cystathionine β-synthase deficiency seldom have plaques in their carotid arteries. They are similar to healthy control subjects with regard to both intima-media thickness and blood flow velocity in the middle cerebral artery. Therefore, it is unlikely that typical atherosclerotic lesions precede thrombotic events in homocystinuria. However, it is possible that arterial dilatations caused by medial damage lead to thrombosis in homocystinuric patients.

Key Words  • carotid arteries  • hypercholesterolemia  • metabolism  • ultrasonics
arterial lesions. This quantitative method has been validated when compared with anatomic pathology and allows measurements of intima-media thicknesses. Ultrasound can also be used to differentiate diffuse from localized thickening. Transcranial Doppler ultrasound is reliable for monitoring cerebral flow velocity in the middle cerebral artery, which channels approximately 80% of internal carotid flow to the cerebral circulation. By combining B-mode ultrasound with transcranial Doppler it is possible to evaluate noninvasively the relations between the extent and severity of carotid atherosclerosis and hemodynamic consequences within the cerebral circulation.

No information is available thus far that compares in vivo examination of young patients with homocystinuria or familial hypercholesterolemia using B-mode and transcranial Doppler ultrasonography.

Subjects and Methods

Patients

Quantitative B-mode ultrasound imaging and flow velocity evaluation with transcranial Doppler ultrasound were performed in 12 homocystinuric patients who were homozygotes for cystathionine \( \beta \)-synthase deficiency (age range, 8 to 42 years; 6 males, 6 females), in 10 patients with homozygous familial hypercholesterolemia (age range, 4 to 49 years; 5 males, 5 females), and in 11 control subjects (age range, 21 to 35 years; 5 males, 6 females). The vascular examination was performed in the outpatient clinic of the Institute of Internal Medicine and Diseases of Metabolism of the Medical School in Naples.

In our patients the diagnosis of homocystinuria\(^1\) due to homozygosis for cystathionine \( \beta \)-synthase deficiency was based on the following criteria: (1) presence of homocysteine in the urine and (2) abnormally low cystathionine \( \beta \)-synthase activity in cultured skin fibroblasts and/or hypermethioninemia and hyperhomocystinemia with low or undetectable levels of cysteine. Index cases were referred by local ophthalmologists after diagnosis of lens dislocation; the other affected patients were identified by screening the families of index cases. All homocystinuric patients but one were responsive to pyridoxine. They had received pyridoxine since the time of diagnosis for 3 to 15 years. Ankle pressure estimated by the continuous-wave Doppler method was abnormally low and indicative of obliterating arterial disease of the lower limbs\(^6\) in 3 of 12 homocystinuric patients. Four cases of 12 had wall irregularities in the iliac arteries based on Duplex evaluation.\(^5\) None reported previous myocardial infarction, stroke, angina pectoris, or intermittent claudication.

Homozygous familial hypercholesterolemia\(^6\) was diagnosed in our 10 patients when all the following criteria were met: (1) plasma cholesterol above 600 mg/dL (15.5 mmol/L) before treatment in a nonjaundiced child; (2) occurrence of tendon xanthoma before age 20; and (3) both parents with severe hypercholesterolemia. In 4 homozygotes the clinical diagnosis was supported by skin fibroblast cultures that demonstrated defective receptor activity. None of the hypercholesterolemic patients reported previous myocardial infarction, stroke, or intermittent claudication, but angina was present in 5 patients. In these patients there was also angiographic evidence of coronary heart disease. In all homozygotes, noninvasive measurement of transvalvular aortic gradients was performed using Doppler ultrasound.\(^4\) In 2 patients a clinically significant pressure gradient (>30 mm Hg) was detected. Ankle pressure determined by continuous-wave Doppler\(^10\) was abnormally low in 11 of the 12 patients. Hypercholesterolemic homozygotes of 10 had wall irregularities in the iliac arteries determined by duplex scanning.\(^10\) At the time of the study all the patients had been without drug therapy or low-density lipoprotein apheresis for at least 2 months and had consumed a low-saturated fat diet since the time of diagnosis.

Eleven apparently healthy medical students (5 men, 6 women) with a mean age similar to that of familial hypercholesterolemic homozygotes and homocystinuric patients were invited to undergo vascular examination and blood sampling, using the same protocols adopted for the patients. No vascular abnormality was detected by noninvasive ultrasound methods in any of the control subjects.

Methods

B-Mode Ultrasound Imaging of Carotid Arteries

The ultrasound imaging examinations were performed by two experienced and certified sonographers (F.F. and A.I.) following a standardized protocol developed by the Division of Vascular Ultrasound Research at the Bowman Gray School of Medicine.\(^17\) Aims of the protocol are to define intra-arterial carotid artery anatomic references (ie, crest at the origin of the bifurcation and the arch of the flow divider) and specific ultrasonic interfaces on both near and far walls to provide valid and reliable measurements of intima-media thickness. As defined previously,\(^11\) intima-media thickness measurements are determined from three specific and standardized segments for each side (Fig 1), ie, the distal common carotid artery, carotid bifurcation, and proximal internal carotid artery.\(^13\) Therefore, 12 wall measurements are determined in each patient.

The Biosound 2000 II s.a. (Biosound Inc) was used to examine the extracranial carotid arteries. This system is equipped with an 8-MHz transducer that features pulsed-wave Doppler and spectrum analysis capabilities and provides high-resolution ultrasonic images with 0.3-mm axial resolution and 256 degrees of gray level. Images were videorecorded on SVHS videotapes for independent quantification of wall thickness and atherosclerosis extent and severity. At the Ultrasound Reading Center in Winston-Salem, NC, a certified ultrasound reader reviewed the videotaped examinations to determine, using a computer-assisted system,\(^12,17\) quantitative wall thickness measurements. For each individual wall in each segment and on both sides (ie, near and far walls of left and right common carotid, bifurcation, and internal carotid arteries), the reader selected the frame that contained the thickest wall. Up to 12 measurements were taken for each patient.
examination, and a composite score of the extent and severity of atherosclerosis, ie, mean maximum intima-media thickness (Mean-Max), was calculated for each subject. Mean-Max is an estimate of the extent and severity of carotid intima-media thickness largely used in clinical trials.13-15,18 The Mean-Max is the mean of the 12 maximum thicknesses at each of the 12 standard carotid walls, ie, right and left, near and far distal common, bifurcation, and internal carotid artery walls. Because of anatomic characteristics and/or lack of appropriate imaging, some of the walls cannot be measured in some cases. While this problem might create a potential reduction of the statistical power, there is no agreement among the investigators on how to handle it. Currently, there are two different approaches: to disregard the problem or to impute thickness estimates based on large samples. Because of the small sample size, our decision was to accept a reduction in the statistical power. Additional extent scores were calculated by side (left and right sides) and by wall (near and far walls). The severity of atherosclerosis, estimated by the single individual maximum intima-media thickness from the 12 walls (TMax), was another morphological end point of the study.

Quality control data derived from several ongoing multicenter trials at the Division of Vascular Ultrasound Research show that the reproducibility for measuring Mean-Max, expressed as the 95th percentile of the absolute differences for blinded repeated measurements, approx 0.3 mm. This figure represents the overall combined error of method and includes instrument, subject, sonographer, and reader variabilities.19

Although the scanning protocol was specifically designed to measure arterial wall thicknesses rather than lumen diameters, internal and external diameters of common carotid arteries could also be measured in 10 homocystinuric patients, 8 hypercholesterolemic patients, and 11 healthy control subjects. The internal and external lumen diameters of the common carotid arteries were measured only where the four critical interfaces were available. The internal lumen diameter was measured as the linear distance between the near and far lumen-intima interfaces; the external lumen diameter was the distance between the near and far adventitia-media interfaces. In four cases the lumen diameters were not measurable. In a preliminary laboratory investigation Mercuri et al (unpublished data; presented at the 15th Scientific Meeting of the International Society of Hypertension; March 20-24, 1994; Melbourne, Australia) found that the internal lumen diameter was missing in 25% of the cases and the external lumen diameter in 15%. When the lumen was measurable, the coefficient of variation in replicate blind determination was 4.5% for the internal lumen diameter and 2.2% for the external lumen diameter.

**Determination of Cerebral Blood Flow Velocity by Transcranial Doppler**

A 2-MHz pulsed-wave transcranial Doppler velocimeter (SD 100) was used for the determination of middle cerebral artery blood flow velocity.14-18 Bidirectional signals were recorded, and real-time spectral analysis was accomplished with fast Fourier transformation.

The probe was placed against the side of the skull, above the zygomatic arch. To check that the original signal was from the middle cerebral artery, the depth of focus was progressively increased until bidirectional flow appeared from the terminal bifurcation of the internal carotid artery. The position of the probe was adjusted for maximal reflected signal at a standardized depth of 45 mm and then maintained in this position throughout the recording period. An adjustable cursor was used for identifying peak systolic and end-diastolic velocities for each recording. The coefficients of variation for repeat measurements of peak systolic and end-diastolic velocities on the same patient by the same sonographer, were 5% and 2.8%, respectively. Pulsatility index, a possible indicator of cerebral vascular resistance, was calculated according to the following formula: (systolic velocity–diastolic velocity)/mean velocity.19

**Other Methods**

Blood pressure was measured in the right and left arms by the auscultatory method using a sphygmomanometer and an 8- to 12-cm-wide cuff. Serum cholesterol and triglyceride concentrations were determined by enzymatic methods.20-21 Descriptive and inferential statistical analyses were performed following Snedecor and Cochran22 by using STATGRAPHICS.23 Intergroup differences were evaluated by using one-way ANOVA and Tukey's test.24 Homogeneity of the variance was assessed using Cochran's, Bartlett's, and Hartley's tests and multiple range analyses. Linear regression analyses were used to test the association between B-mode and Doppler ultrasound end points. To evaluate diastolic cerebral blood flow velocity among the three groups (independently of differences in systolic velocity), ANCOVA was performed.25-26 Based on the regression line of diastolic over systolic velocity, diastolic velocity values were adjusted to a standard value of systolic velocity (ie, 100 cm/s). The adjusted values for diastolic velocity were then compared by ANOVA or used in regression analysis.

**Results**

The mean ages of homocystinuric patients, homozygotes for familial hypercholesterolemia, and healthy control subjects were 23.6, 25.9, and 26.1 years, respectively. Serum cholesterol (mean, 691 mg/dL) was approximately fourfold higher (P<.001) in familial hypercholesterolemic patients compared with homocystinuric patients (mean serum cholesterol, 153 mg/dL) or control subjects (mean, 153 mg/dL). Triglyceride concentration (mean, 174 mg/dL) was also somewhat higher (P<.01) in hypercholesterolemic patients compared with homocystinuric patients and control subjects (mean, 69 and 65 mg/dL, respectively).

Systolic and diastolic blood pressures were normal in all subjects, and the mean values did not differ among the three groups. There were two smokers in each of the three groups. Fig 2 presents the individual estimates of the extent (Mean-Max) of carotid wall thickness determined from B-mode ultrasound imaging in homocystinuric patients, homozygous familial hypercholesterolemic patients, and control subjects. This figure also includes the individual ages of patients and control subjects. No significant correlation was found between age and intima-media thickness.

The two hypercholesterolemic patients with exceedingly high values of intima-media thickness were the two smokers of the group. Only one plaque (focal thickening exceeding 1.3 mm) was detected in the carotid arteries of homocystinuric patients. The proportions of arterial segments with plaque in hypercholesterolemic patients were as follows: 13 of 20 (65%) in common carotid, 15 of 20 (75%) in carotid bifurcation, and 14 of 20 (70%) in the internal carotid artery.

Table 1 provides further detail on carotid thicknesses among the three groups and includes the extent score by side (left versus right mean maximum intima-media thickness [Mean-Max]) and the severity of the disease expressed as the individual maximum intima-media thickness (TMax). Statistical analyses showed that the extent (Mean-Max) and severity (TMax) of atherosclerosis in hypercholesterolemic patients were significantly higher than in either homocystinuric patients or healthy

**Figure 2**

Results for mean intima-media thickness (Mean-Max) and mean maximum intima-media thickness (TMax).

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean-Max (mm)</th>
<th>TMax (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocystinuric</td>
<td>0.93</td>
<td>0.85</td>
</tr>
<tr>
<td>Homozygous familial HCH</td>
<td>1.25</td>
<td>1.15</td>
</tr>
<tr>
<td>Control</td>
<td>1.10</td>
<td>0.95</td>
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</table>
control subjects ($P<.001$, ANOVA, Tukey's test). Table 1 also presents group comparisons of systolic, end-diastolic, and mean flow velocities together with pulsatility index evaluated by transcranial Doppler over the middle cerebral artery. On both sides diastolic velocity was lower and pulsatility index higher in the hypercholesterolemic group compared with homocystinuric patients or healthy control subjects. Systolic or mean flow velocities were not different among the three groups. If individual values for diastolic flow velocities were adjusted for variability in systolic flow velocity, the differences were even more pronounced (data not shown).

An inverse relation ($P<.05$) was found between age and diastolic flow velocities in our series of case and control subjects. If individual values of diastolic velocity were adjusted for age variability, the differences between the three groups were confirmed (right diastolic velocity, $F=3.56$, $P<.05$; left diastolic velocity, $F=6.38$, $P<.01$).

An inverse relation between carotid artery thickness and adjusted diastolic flow velocity in the middle cerebral arteries was demonstrated in patients with familial hypercholesterolemia ($r=-.399$, $P<.001$). In these hypercholesterolemic patients no relation was found between severity of the aortic gradient and diastolic flow velocity. Pulsatility index (Fig 3) measured on the middle cerebral artery was directly related to carotid artery thickness ($r=4.56$; $P<.001$).

Fig 4 illustrates external and internal diameters of common carotid arteries as determined by B-mode ultrasound imaging in homocystinuric and hypercholesterolemic patients and healthy control subjects. Mean values in the three groups did not differ; however, there were two homocystinuric and four hypercholesterolemic patients whose external diameter exceeded the mean+3SD of control subjects; in the same two homocystinuric patients (aged 26 and 42 years) the internal diameter was more than the mean+3SD of control subjects. The mean age of hypercholesterolemic patients with increased external diameter did not differ from that of the case patients with normal external diameter (24 and 27 years, respectively). No significant relation between age and common carotid artery diameter was demonstrated in this series of relatively young case and control subjects. In two hypercholesterolemic patients (aged 4 and 45 years) with normal external diameter, the internal diameter was less than the mean—3SD of the control subjects.

Discussion

This is the first study that compares the extent, severity, and hemodynamic impact of carotid atherosclerosis in homozygotic familial hypercholesterolemic patients with homocystinuric patients using quantitative ultrasound imaging and transcranial Doppler. A completely different pattern is demonstrated in the two conditions.

Carotid arteries of the hypercholesterolemic group had higher values for intima-media thickness than either homocystinuric or control groups. Focal thickenings suggesting atherosclerotic lesions were found in all hypercholesterolemic subjects. Increased intima-media thickness is therefore a constant feature in conditions of severe hypercholesterolemia and involves the common carotid arteries, which, in a general population, are relatively spared from vascular lesions compared with the carotid bifurcation or internal carotid arteries. In our hypercholesterolemic patients, severe thickening often led to increase in the external diameter of common carotid arteries (Fig 4). This finding can be explained by the compensatory enlargement that occurs in human atherosclerotic arteries. 25

In nonhuman primate hypercholesterolemic models, intimal thickening of carotid arteries estimated from pathology specimens was associated with enhanced vasoconstriction of large intracranial cerebral arteries after infusion of serotonin. 26 A mechanism possibly explaining this augmented vasoconstrictive response is an alteration in endothelium-dependent modulation of vascular reactivity. 27, 28 In hypercholesterolemic monkeys, increased vascular tone was associated with lower cerebral flow in response to infusion of collagen-activated platelets. 29 Our patients with familial hypercholesterolemia had disturbed cerebral blood flow even in the presence of non-flow-reducing arterial lesions in the carotid arteries. It is unlikely that the hemodynamic abnormality we have found was due to the aortic gradient that had been demonstrated in hypercholesterolemic patients. 3 In fact, in our patients there was no relation between the severity of the aortic gradient and the degree of impairment in the diastolic flow velocity.

The hemodynamic disturbance was confined to diastolic flow, while systolic and mean flow velocities were normal. An inverse relation was demonstrated...
TABLE 1. Wall Thicknesses of Carotid Arteries and Flow Velocities in Middle Cerebral Arteries of Homocystinuric and Hypercholesterolemic Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Wall thicknesses, mm</th>
<th>HC (n=12)</th>
<th>FH (n=10)</th>
<th>C (n=11)</th>
<th>F ratio</th>
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<tbody>
<tr>
<td>Right mean maximum</td>
<td>0.632*</td>
<td>1.452**</td>
<td>0.550*</td>
<td>13.1†</td>
</tr>
<tr>
<td></td>
<td>(0.408-0.855)</td>
<td>(1.207-1.697)</td>
<td>(0.317-0.784)</td>
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<tr>
<td>Left mean maximum</td>
<td>0.587*</td>
<td>1.374**</td>
<td>0.573*</td>
<td>32.4†</td>
</tr>
<tr>
<td></td>
<td>(0.456-0.718)</td>
<td>(1.230-1.517)</td>
<td>(0.436-0.709)</td>
<td></td>
</tr>
<tr>
<td>Overall mean maximum</td>
<td>0.620*</td>
<td>1.422**</td>
<td>0.564*</td>
<td>20.8†</td>
</tr>
<tr>
<td></td>
<td>(0.449-0.790)</td>
<td>(1.235-1.609)</td>
<td>(0.386-0.743)</td>
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</tr>
<tr>
<td>Maximum thickness</td>
<td>0.908*</td>
<td>2.602**</td>
<td>0.807*</td>
<td>28.7†</td>
</tr>
<tr>
<td></td>
<td>(0.601-1.214)</td>
<td>(2.267-2.937)</td>
<td>(0.488-1.127)</td>
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</table>

Blood flow velocities, cm/s

<table>
<thead>
<tr>
<th></th>
<th>HC (n=12)</th>
<th>FH (n=10)</th>
<th>C (n=11)</th>
<th>F ratio</th>
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<tr>
<td>Right systolic</td>
<td>100.0</td>
<td>94.4</td>
<td>93.8</td>
<td>0.393</td>
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<tr>
<td></td>
<td>(90.7-109.3)</td>
<td>(84.2-104.6)</td>
<td>(84.1-103.5)</td>
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<tr>
<td>Left systolic</td>
<td>99.7</td>
<td>92.6</td>
<td>97.2</td>
<td>0.552</td>
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<tr>
<td></td>
<td>(91.7-107.8)</td>
<td>(83.8-101.4)</td>
<td>(88.8-105.6)</td>
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<tr>
<td>Right diastolic</td>
<td>47.1*</td>
<td>37.3*</td>
<td>44.7</td>
<td>3.43*</td>
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<tr>
<td></td>
<td>(42.6-51.6)</td>
<td>(32.3-42.3)</td>
<td>(40.0-49.4)</td>
<td></td>
</tr>
<tr>
<td>Left diastolic</td>
<td>48.3*</td>
<td>36.7*</td>
<td>46.7*</td>
<td>5.57†</td>
</tr>
<tr>
<td></td>
<td>(44.0-52.7)</td>
<td>(31.9-41.5)</td>
<td>(42.2-51.3)</td>
<td></td>
</tr>
<tr>
<td>Right mean</td>
<td>64.7</td>
<td>56.2</td>
<td>61.2</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>(56.6-72.7)</td>
<td>(47.9-64.5)</td>
<td>(54.5-67.9)</td>
<td></td>
</tr>
<tr>
<td>Left mean</td>
<td>65.4</td>
<td>54.9</td>
<td>63.6</td>
<td>3.12</td>
</tr>
<tr>
<td></td>
<td>(57.9-72.9)</td>
<td>(47.9-61.9)</td>
<td>(57.6-69.7)</td>
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<tr>
<td>Heart rate, bpm</td>
<td>73.3</td>
<td>74.6</td>
<td>70.0</td>
<td>0.71</td>
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<tr>
<td></td>
<td>(64.5-82.1)</td>
<td>(63.9-85.3)</td>
<td>(62.6-77.4)</td>
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<tr>
<td>Right pulsatility index</td>
<td>0.83*</td>
<td>1.02**</td>
<td>0.80*</td>
<td>6.01†</td>
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<tr>
<td></td>
<td>(0.74-0.91)</td>
<td>(0.87-1.16)</td>
<td>(0.72-0.89)</td>
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<tr>
<td>Left pulsatility index</td>
<td>0.80*</td>
<td>1.02**</td>
<td>0.80*</td>
<td>6.91†</td>
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<td></td>
<td>(0.71-0.88)</td>
<td>(0.88-1.16)</td>
<td>(0.70-0.88)</td>
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</table>

HC indicates homocystinuric patients; FH, familial hypercholesterolemic patients; C, healthy control subjects; and bpm, beats per minute. Values are mean with 95% confidence interval in parentheses. *P<.05, †P<.01, ANOVA (F ratio).

Multiple comparison (Tukey's test); statistically significant where same superscript.

between diastolic flow velocity in the middle cerebral artery and intima-media thickness in the carotid arteries. At the same time (Table 1) pulsatility index, a possible indicator of vascular resistance in the cerebral circulation, was abnormally elevated in familial hypercholesterolemia patients and positively related to the degree of carotid wall thickening (Fig 3). In the coronary circulation of hypercholesterolemic animals, vascular tone increase was also demonstrated in small arteries30 and arterioles.31 Abnormally high vascular tone of cerebral resistance vessels might explain the reduction in diastolic flow velocity and the increase in pulsatility index that we have demonstrated in hypercholesterolemic patients.

Hypercholesterolemia is thought to lead to endothelial dysfunction,3233 even in the absence of typical

Fig 3. Plot shows direct relation (linear regression) between carotid wall thickness (log Mean-Max [mean maximum intima-media thickness], estimate of the extent of atherosclerosis) determined with B-mode ultrasound imaging and pulsatility index in homozygotes for familial hypercholesterolemia (both sides).
atherosclerotic lesions, through subendothelial accumulation of oxidized low-density lipoproteins. Oxidatively modified lipoproteins, which are formed by interaction of circulating low-density lipoproteins with different cell types in the arterial wall, are powerful inhibitors of endothelium-dependent relaxation. Therefore, familial hypercholesterolemia is responsible for diffuse and focal thickening of large conduit arteries and possibly also for hyperlipidemic endothelial dysfunction extending to small resistance arteries and leading to abnormal cerebral blood flow. This extensive involvement of cerebral circulation seldom results in stroke or transient ischemic attack. This has been related to the presence or absence of responsiveness to pyridoxine treatment, with pyridoxine-responsive patients having a more benign clinical course. All patients in our series, with a single exception, were pyridoxine responsive, and most had been on treatment for several years. No symptoms of ischemia were reported, but there was evidence of flow-reducing stenoses in lower-extremity arterial circulation in three cases. The single homocystinuric patient who was nonresponsive to pyridoxine had relatively low velocity in his middle cerebral artery and bilateral arterial obstruction in the lower extremities but no evidence of carotid plaque.

The mechanism underlying the thrombotic events that occur even in early-treated, pyridoxine-responsive patients is unknown. On the basis of our observations it is unlikely that typical atherosclerotic lesions precede thrombus formation in homocystinuric patients within this age range. It is possible that the vascular lesions in more severe cases of homocystinuria, in which patients have not been treated for several years, are to some extent different from those seen in our early-detected and well-treated cases. However, pathology studies in untreated patients who prematurely died of severe thromboembolic disease rarely show typical atherosclerotic lesions (Table 2). A more consistent autopsy finding in these patients is arterial dilatation, which has been suggested to precede the thrombotic event. In our study two homocystinuric patients showed an increase in circulation from the systolic rise in blood pressure, thereby reducing the probability of stroke.

Patients with homocystinuria for cystathionine β-synthase deficiency and healthy control subjects had similar intima-media thicknesses. Blood flow velocity in the middle cerebral artery of homocystinuric patients did not differ from that found in healthy control subjects and was higher than in the hypercholesterolemic group.

Homocystinuric patients show considerable heterogeneity in their clinical picture. This has been related to the presence or absence of responsiveness to pyridoxine treatment, with pyridoxine-responsive patients having a more benign clinical course. All patients in our series, with a single exception, were pyridoxine responsive, and most had been on treatment for several years. No symptoms of ischemia were reported, but there was evidence of flow-reducing stenoses in lower-extremity arterial circulation in three cases. The single homocystinuric patient who was nonresponsive to pyridoxine had relatively low velocity in his middle cerebral artery and bilateral arterial obstruction in the lower extremities but no evidence of carotid plaque.

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**TABLE 2. Gross Pathology and Histological Findings In 12 Homocystinuric Patients Who Prematurely Died of Cardiovascular Diseases**

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Author (Year)</th>
<th>Reference</th>
<th>Gross Pathology</th>
<th>Histology</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombi</td>
<td>Intimal Thickening</td>
</tr>
<tr>
<td>1</td>
<td>Gibson et al (1964)</td>
<td>38</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
<tr>
<td>2</td>
<td>Carson et al (1965)</td>
<td>3</td>
<td>+ + +</td>
<td>+ + +</td>
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Pt indicates patient.
both the external and internal diameters of their common carotid arteries (Fig 4). This finding is consistent with that of arterial dilatations demonstrated at autopsy by other authors. In the future, scanning procedures specifically aimed at diameter measurement in the carotid arteries should be performed in larger series of homocystinuric patients.

In homocystinuric patients arterial histology often shows medial alterations, fragmentation of internal elastic lamina, and endothelial thickening (Table 2). Medial thinning is often observed in association with thick intimas and may help explain why the overall intima-media thickness in the homocystinuric group does not differ from that of the control subjects. At present, B-mode ultrasound cannot reliably detect the ultrasonic interface between intima and media, ie, internal elastic lamina; therefore, subtle abnormalities in the structure of intima and media are not demonstrated. The relatively frequent detection of high blood pressure in patients with severe cases of untreated homocystinuria, in association with the microscopic evidence of alterations in internal elastic lamina and media, leaves open the possibility that thrombosis is a consequence of focal intimal damage in the absence of adequate medial support. The frequent occurrence of aneurysmal lesions in homocystinuric patients is consistent with the view of a major role of medial damage in this form of premature vascular disease.

Direct toxicity of homocysteine on endothelial cells might increase the susceptibility to intimal damage and thrombosis. However, recent data indicate that the arterial wall of homocystinuric patients might be protected, to some extent, by a mechanism that modulates the adverse vascular effects of homocysteine. Furthermore, plasma concentrations of homocysteine in homocystinuric patients (0.1 to 0.2 mmol/L) are generally lower than those associated with severe endothelial damage in vitro.

Conclusions

The different ultrasound data demonstrated in homozygous familial hypercholesterolemia and homocystinuria are likely to reflect two different mechanisms of arterial damage. Hypercholesterolemia or hyperhomocysteinemia, of milder degree are frequent in the population and have both been associated with premature development of cardiovascular disease. In most instances the inherited defect is likely to interact with environmental influences (diet, smoking habits) or with coexisting diseases (diabetes mellitus, hypertension), giving rise to a mixed pattern of stenotic and aneurysmal lesions, with intima-media thickening and/or thrombosis.

Whereas detection and treatment of hypercholesterolemia have already achieved widespread acceptance, early detection and treatment of homocysteinemia are at their beginning. B-mode ultrasound imaging and transcranial Doppler offer adequate means for detection and follow-up of hypercholesterolemia-related vascular damage. It is still to be determined which method is most helpful for the early diagnosis of vascular disease in hyperhomocysteinemia. A better definition of the type of vascular damage and of the pattern of evolution of the arterial lesions will improve our understanding of basic mechanisms leading to premature vascular disease in humans.

Acknowledgments

The authors are grateful to Rosanna Scala and Tammy Nail for devoted assistance in the preparation and revision of the manuscript.

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8. Faccenda F, Rubba P, Gnasso A, Pauciullo P, Postiglione A, Cortese C, Mancini M. Noninvasive ultrasound evaluation of the pathologic examination of the arterial wall in patients with severe cases of untreated homocystinuria, in association with the microscopic evidence of alterations in internal elastic lamina and media, leaves open the possibility that thrombosis is a consequence of focal intimal damage in the absence of adequate medial support. The frequent occurrence of aneurysmal lesions in homocystinuric patients is consistent with the view of a major role of medial damage in this form of premature vascular disease. Direct toxicity of homocysteine on endothelial cells might increase the susceptibility to intimal damage and thrombosis. However, recent data indicate that the arterial wall of homocystinuric patients might be protected, to some extent, by a mechanism that modulates the adverse vascular effects of homocysteine. Furthermore, plasma concentrations of homocysteine in homocystinuric patients (0.1 to 0.2 mmol/L) are generally lower than those associated with severe endothelial damage in vitro.

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Premature carotid atherosclerosis: does it occur in both familial hypercholesterolemia and homocystinuria? Ultrasound assessment of arterial intima-media thickness and blood flow velocity.
P Rubba, M Mercuri, F Faccenda, A Iannuzzi, C Irace, P Strisciuglio, A Gnasso, R Tang, G Andria and M G Bond

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