Premature Development of Iliac Artery Stenosis in Asymptomatic Type II Hyperlipoproteinemia

Paolo Rubba, Alfredo Postiglione, Biagio De Simone, Fulvio Faccenda, Gabriele Riccardi, and Mario Mancini

There is conflicting evidence on the relationship between increased low density lipoprotein (LDL) concentration in Type II hyperlipoproteinemia and premature development of peripheral atherosclerosis of the lower limbs. We evaluated the early signs of iliac artery involvement in patients with asymptomatic Type II hyperlipoproteinemia. Of these, 23 were Type IIA, 12 were Type IIB. Thirty-five consecutive patients, ages 40 to 60 years, with asymptomatic Type II hyperlipoproteinemia (LDL cholesterol ≥3.80 mmol/liter, 147 mg/dl) and 54 normocholesterolemic controls (plasma cholesterol <5.70 mmol/liter, 220.6 mg/dl) from a random sample of clinically healthy, 50-year-old men had a noninvasive examination to detect common and external iliac artery stenosis. Both Type II patients and the controls were examined by the echo-Doppler technique (Duplex Scanner III-ATL Mark V) with spectral analysis of the Doppler signals. This method is sensitive not only to severe stenosis or occlusion but also to non-flow-reducing stenosis (<50% narrowing of the lumen diameter) and to minor wall irregularities (1%-15% stenosis). In Type II patients, 19 of 70 limbs (27%) were abnormal as compared to 6 of 108 limbs (6%) in the controls (p < 0.001). The premature development of an obliterating disease of the iliac arteries was demonstrated in persons asymptomatic for Type II hyperlipoproteinemia.

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Type II hyperlipoproteinemia (HLP) is an abnormal plasma lipoprotein pattern characterized by high levels of low density lipoprotein (LDL). The underlying genetic abnormality might be familial hypercholesterolemia (FH), combined hyperlipidemia (CH), or polygenic hypercholesterolemia.1 The plasma pattern of Type II HLP has been consistently associated with the premature development of coronary heart disease,2 but evidence relating increased plasma LDL concentration to premature atherosclerosis of the lower limbs is conflicting.

Many retrospective studies3,4 have suggested that increased plasma LDL plays a minor role in peripheral atherosclerosis. Some researchers also have reported3-8 an increase of very low density lipoprotein (VLDL), hypertriglyceridemia, or a reduced concentration of high density lipoprotein. In a prospective study performed in Switzerland9 it was not possible to determine whether premature development of lower limb atherosclerosis was related to hypercholesterolemia, to hypertriglyceridemia, or to both. Two angiographic studies10,11 have attempted to relate the site of vascular occlusion to specific lipoprotein abnormalities. Both suggest that Type II hyperlipoproteinemia is closely related to the development of aortoiliac atherosclerosis.

Very recently a new procedure, duplex scanning, has been devised for the noninvasive evaluation of stenoses in the iliac arteries. We validated this interesting method in our laboratory versus angiography and found good correlation with contrast studies.12,13 Using this procedure, we were able to evaluate possible iliac artery stenoses in patients with asymptomatic Type II hyperlipoproteinemia and in normocholesterolemic controls.
Methods

Patients

The study group consisted of 35 consecutive male patients at our lipid clinic who were seen for primary Type II HLP. Their age range was 40 to 60 years. Typing of HLP was done with preparative ultracentrifugation, and cholesterol and triglyceride were determined in the separated lipoprotein fractions. There were 23 patients with LDL cholesterol concentrations higher than 3.80 mmol/liter (147 mg/dl) and VLDL triglyceride lower than 1.38 (121.4 mg/dl) who were typed as IIA. We found 12 patients with LDL cholesterol higher than 3.80 mmol/liter (147 mg/dl) and VLDL triglyceride higher than 1.38 (121.4 mg/dl) who were defined as Type IIB. Secondary forms of HLP were not included in this study.

The controls were a random sample of 54 clinically healthy 50-year-old men living in Naples. Hypercholesterolemic individuals with total plasma cholesterol levels higher than 5.70 mmol/liter (220.6 mg/dl) were excluded.

All the patients and controls answered questions about angina, stroke, myocardial infarction, and intermittent claudication; all were given an ECG; information on smoking habits was collected by a questionnaire. Blood pressure was determined with a zero-random sphygmomanometer (Gelman, United Kingdom). Diastolic pressure was measured at the V phase of Korotkoff sounds and the mean of two consecutive measurements was calculated. Criteria for exclusion in both patients and controls were the presence of neoplasia or other chronic serious illnesses, previous myocardial infarction or stroke, intermittent claudication, treated diabetes, and treated hypertension.

Duplex Scanning

Evaluation of iliac artery stenosis was performed by an echo-Doppler ATL Mark V (Duplex Scanner III). This system incorporates two different modalities of examination in one instrument. A real-time B-mode image is generated by three 3MHz pulsed echo transducers mounted on a rotating wheel. Each transducer is activated sequentially as it passes over the acoustic window of a water-filled silastic boot. The second component of the system consists of a 3 MHz single-gated pulsed Doppler transducer mounted on the side of the scanhead. During the examination of the patient a B-mode image is displayed on an oscilloscope screen and the position of the Doppler beam is indicated by a white line with a small dot indicating the exact site being examined.

The pulsed Doppler allows sampling of blood flow at discrete points from within the lumen of the vessel. Checks of the sample volume position in the middle stream of the lumen are currently performed in all patients by repeat shifts from B-mode image to Doppler before a permanent record of the spectrum is obtained. Recordings are routinely taken from the origin of the common femoral artery at the inguinal ligament; this site corresponds to the distal end of the external iliac artery. Flow abnormalities due to common or external iliac artery stenosis are detectable by this procedure.

In addition to the audible signal, real-time spectrum analysis of the Doppler signal is performed. Spectrum analysis is displayed on an oscilloscope screen from which a permanent record is obtained with a Polaroid oscilloscope camera. Time is reported on the abscissa and frequency (in KHz), on the ordinate. On tracings of this type we determine: 1) the height of the systolic frequency peak measured from baseline at midsystole, 2) the spectrum width at midsystole, 3) the height of the reverse flow component at mid-diastole. The interpretation of the Doppler velocity spectra is primarily based on the evaluation of these three parameters (Figures 1-5).

The diagnostic criteria adopted for the noninvasive evaluation of stenoses of the iliac arteries are as follows:

- Stenosis more than 85% or complete occlusion = no signal or low systolic peak, reverse flow component nondetectable.
- Stenosis 51% to 85% = spectrum broadening, reverse flow component nondetectable.
- Stenosis 16% to 50% = spectrum broadening, reverse flow component detectable.
- Arterial wall irregularities (stenosis < 16%) = late systolic and diastolic spectrum broadening.

A validation study performed by reference to angiography has demonstrated a highly significant correlation between the findings of echo-Doppler examination and those obtained by angiography. The results of an extension of this study will be briefly summarized.

Femoral artery catheterization and contrast arteriography were performed in 77 patients with occlusive disease of the lower limbs at different levels.

![Figure 1. Spectrum analysis in a patient with normal iliac arteries.](http://atvb.ahajournals.org/)
The arteriograms were interpreted by a trained radiologist. All vessels were graded according to the percent reduction in luminal diameter and were placed into one of five categories: 1) occlusion or stenosis >85%, 2) 51% to 85% stenosis, 3) 16% to 50% stenosis; 4) wall irregularities or 1% to 15% stenosis, 5) no abnormality.

All patients were then asked to undergo an echo-Doppler examination; the spectrum analysis results were obtained by a visual interpretation of the hard-copy spectrum analyzer output, without knowledge of the arteriography findings. Each vessel was assigned to one of the arteriographic categories according to the principles outlined in the previous section.

Table 1 summarizes the comparison between the angiography findings and those obtained by the echo-Doppler examination. Two of the 17 arteriographically normal vessels had minor spectrum changes. Three of the 12 vessels with minor wall irregularities had normal spectrums. On the other hand, all patients with more than 15% stenosis showed spectrum abnormalities. Table 2 reports data on the sensitivity, specificity, and predictive value of this methodology.

<table>
<thead>
<tr>
<th>Doppler (%)</th>
<th>0</th>
<th>1-15</th>
<th>16-50</th>
<th>51-85</th>
<th>86-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>1-15</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>16-50</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>51-85</td>
<td>1</td>
<td>7</td>
<td>9</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>86-100</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Cutoff Point Between Normality and Disease at Two Different Levels of Increasing Severity

<table>
<thead>
<tr>
<th></th>
<th>Wall abnormality or stenosis (any degree)</th>
<th>Stenosis &gt; 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Specificity</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>Predictive value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive test</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>Negative test</td>
<td>83%</td>
<td>93%</td>
</tr>
</tbody>
</table>

The sensitivity, specificity, and predictive value corresponding to the two different cutoff points are calculated according to reference 18.

Results

Table 3 shows the main features of Type II cases and normocholesterolemic controls. These two groups were comparable in all respects; they were markedly different only in plasma cholesterol concentration and slightly different in total plasma triglyceride and HDL cholesterol (explained by the mild hypertriglyceridemia in Type IIB patients). Figure 6 shows that 27% of the limbs of HLP patients examined by the Duplex Scanner had arterial wall abnormalities. In six cases there was a stenosis in the range of 16% to 50%, in 13 cases there were minor wall abnormalities (stenosis less than 16%). Arterial lesions were far less common in normocholesterolemic men (6 of 108 limbs were abnormal on echo-Doppler examination), with only two with stenosis of 16% to 50% and four with less than 16%. The difference was statistically significant (chi square = 16.39, p < 0.001).

If we consider separately those with stenosis of 1% to 15% and those with 16% to 50% stenosis, we find significantly more abnormalities in Type II patients than in normocholesterolemic controls (p < 0.01 and p < 0.05 respectively; exact Fisher test, 2a). In both groups no flow-reducing stenosis (≥50%) was detectable. This agrees with the fact that all study participants were asymptomatic. There was no significant difference in the severity of vascular involvement between Type IIA and Type IIB patients (26% of limbs in Type IIA and 29% in Type IIB patients were abnormal.)

Discussion

The present study demonstrates more frequent wall abnormalities and stenoses in the iliac arteries of Type IIA and IIB patients than in normocholesterolemic controls of the same gender and age. This suggests that increased LDL concentration, the dis-

Table 3. Main Risk Factors for Atherosclerotic Cardiovascular Disease in 54 Clinically Healthy 50-Year-Old Men and in 35 Asymptomatic Patients with Type II Hyperlipidemia (23 Type IIA and 12 Type IIB)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>BMI</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>Cig/day</th>
<th>Chol (mmol/liter)</th>
<th>TG (mmol/liter)</th>
<th>HDL chol (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>50</td>
<td>27</td>
<td>132</td>
<td>83</td>
<td>14</td>
<td>5.01</td>
<td>1.35</td>
<td>1.28</td>
</tr>
<tr>
<td>(n = 54)</td>
<td>±1</td>
<td>±1</td>
<td>±2</td>
<td>±2</td>
<td>±2</td>
<td>±0.10</td>
<td>±0.10</td>
<td>±0.04</td>
</tr>
<tr>
<td>Type II</td>
<td>49</td>
<td>27</td>
<td>134</td>
<td>83</td>
<td>14</td>
<td>8.55†</td>
<td>2.06*</td>
<td>1.11†</td>
</tr>
<tr>
<td>(n = 35)</td>
<td>±1</td>
<td>±1</td>
<td>±3</td>
<td>±2</td>
<td>±2</td>
<td>±0.49</td>
<td>±0.19</td>
<td>±0.06</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* p < 0.05, significant vs control.
† p < 0.01, significant vs control.

The equivalent values for 1 mmol/liter for cholesterol and triglycerides are 38.7 mg/dl and 88.0 mg/dl, respectively. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; Cig = cigarette; Chol = cholesterol; TG = triglyceride; HDL = high density lipoprotein.
tinctive feature of Type II HLP, is associated with premature development of arteriosclerosis oblit-
erans in the iliac arteries.

The increased VLDL concentration and reduced HDL of Type IIIB HLP do not seem to add any further harmful effect to that of high plasma LDL. However, the number of Type IIIB patients examined was too small to draw any definite conclusion on the roles of VLDL and HDL on atherogenesis in the iliac arteries.

Our findings of premature iliac artery atherosclerosis in Type II HPL are in agreement with previous angiographic studies which did not provide adequate control material. One of the advantages with noninvasive methodologies for vascular diagnosis is that they allow more accurate case-control studies, because the vascular examination is completely noninvasive and easily accepted by clinically healthy controls. Another advantage of the Duplex scanning technique is the low error due to interindivi-
dual variation in repeat examination on different days.

The information available on atherosclerosis of the iliac arteries in living men comes almost entirely from angiographic data. In fact, this arterial area is not easily accessible with conventional noninvasive diagnostic techniques. Duplex scanner and spectrum analysis, therefore, may give useful information on this frequent site of atherosclerotic occlusion. Duplex scanning might be the methodologic basis for studies on the natural history of the atherosclerotic process. In this type of investigation, echo-Doppler is a useful technique for the detection of moderate steno-
sis. Angiography is sensitive to early lesions such as fatty streaks, and the questionnaire for intermittent claudication reveals advanced flow-reducing stenoses or occlusions. Our methodologic approach could be very useful in evaluating the long-term ef-
fectiveness of different lipid-lowering treatments. In these studies, patients with Type II HLP are good subjects because of the frequency of detectable arterial abnormalities, which can be initially traced and then followed up during long-term lipid-lowering treatment.

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