Carotid Atherosclerosis In Familial Hypercholesterolemia

ALFREDO POSTIGLIONE, M.D., PAOLO RUBBA, M.D., BIAGIO DE SIMONE, M.D., LIDIA PATTI, UMBERTO CICERANO, M.D., AND MARIO MANCINI, M.D.

SUMMARY Common and internal carotids have been studied by noninvasive method (echo-Doppler) in 30 normolipemic patients with familial hypercholesterolemia (FH). Vascular lesions were detected in 14 patients (46%), who presented one or more lesions of different degree (between 1-15% and 16-49%). In one case, only one carotid had stenosis >50%. Severity and number of stenosis were related to age and levels of hypercholesterolemia. FH patients with carotid lesions showed a significantly higher LDL-cholesterol ($p < 0.01$) and plasma apolipoprotein B ($p < 0.001$) concentrations and a significantly lower HDL-cholesterol ($p < 0.05$) and plasma apolipoprotein A ($p < 0.001$) levels as compared to those with normal echo-Doppler findings. These data indicate that investigation of arterial districts other than coronaries are useful in quantitative evaluation of atherosclerotic involvement.

PATIENTS WITH FH are known to have increased risk of coronary heart disease as compared to normolipemic subjects, but few clinical data are available on extracoronary atherosclerosis. Affected patients have premature coronary heart disease, which causes angina pectoris, myocardial infarction and sudden death. This is commonly seen in homozygotes between age 5 and 30, and in heterozygotes in their 40's. Several studies confirm that the risk of coronary heart disease event in FH patients is 25 times higher than that in their unaffected relatives. Among unselected survivors of myocardial infarction, FH heterozygotes are between 3 and 6%. Using population genetic analysis of hyperlipidemia among survivors of myocardial infarction, Goldstein et al estimated a frequency of about 1 patient in 500 Caucasian individuals. This is a value not very far from that of Carter et al, who derived a frequency of about 1 homozygote in 200 persons.

Few data are available on the frequency of premature cerebrovascular and/or lower limb vascular disease in FH patients. It is important not to ignore extracardiac localization of atherosclerosis in FH patients and to study the prevalence of vascular lesions in arteries other than coronaries. Carotids can be actually well investigated by noninvasive methods, such as echo-Doppler, able of detecting irregularities of extracranial neck arteries.

Patients and Methods

Thirty patients (15 males, 15 females) with FH have been investigated. The FH diagnosis was based upon a) elevated plasma and LDL-cholesterol concentrations, which were in all cases above 300 mg/dl and 200 mg/dl respectively; b) the presence of tendon and cutaneous xanthomas and/or a pedigree with evidence of vertical transmission of hypercholesterolemia. None of the patients under study had relatives with lipoprotein abnormalities of multiple types. Four have been diagnosed as homozygotes by skin fibroblast culture (three receptor-defective and one receptor-negative).

Venous blood was collected in all patients after 12–14 hours fasting in a drug-free period from at least three weeks, but during an hypocholesterolemic diet (cholesterol < 300 mg/day and P/S ratio > 1.0). Plasma lipoproteins were separated by preparative ultracentrifugation very low density lipoprotein (VLDL) d < 1.006; low density lipoprotein (LDL): 1.006 < d < 1.063; high density lipoprotein (HDL) d > 1.063) and cholesterol and triglyceride determined by enzymatic authomated methods. Plasma apolipoprotein B and A concentrations have been measured by radial immunodiffusion.

Both common and internal carotids have been studied by a Duplex Scanner ATL Mark V, which combines B mode echography and pulsed Doppler ultrasound for detection of vascular lesions even mild or arterial wall irregularities. The study was performed...
of patients resting in supine position under standardized technique. This noninvasive method identifies different degrees of lesions: 1–15%, 16–49%, 50–99% and complete occlusion. Classification of the degree of lesions is based upon the recorded peak frequencies from the diseased area as well as the time of onset and degree of spectral broadening. Normal arterial wall is characterized by normal spectral broadening and normal window. Minimal vascular lesion (1–15%) was classified with mild spectral broadening in decelerating phase of systole with clear window; moderate lesion (16–49%) with spectral broadening throughout the systole with no detectable window and normal systolic peak frequency; severe stenosis (50–99%) was classified with marked spectral broadening and increased systolic peak frequency; occlusion when no signal was detectable. Four-vessel study was possible in all cases. By studying all four neck arteries in each patient, it was possible to investigate 120 neck arteries.

**Results**

Fourteen out of 30 FH patients (46%) presented carotid lesions, even if none, except one, was hemodynamically effective in reducing blood flow (> 50). Eight FH patients only out of 30 presented more than one lesion. Out of these six presented lesions of common and internal carotid on the same side. It was always possible to differentiate the two branches of the artery.

Table I divides all FH patients in three groups according to their plasma cholesterol level and table 2 shows the different degrees of severity of arterial lesions as a function of plasma cholesterol concentration. By considering the 14 patients with carotid lesions of different degrees of severity it was possible to divide them into nine with one or more lesions of mild grade (1–15%) and in five with at least one moderate lesion (16–49%). Table 3 shows the cholesterol content in LDL and HDL and plasma concentrations of apolipoprotein B and A in patients divided in groups as a function of absence or presence of lesions of different grades. The lowest values for LDL-cholesterol and apolipoprotein B were observed in those who had, at noninvasive investigation of neck arteries, no lesion. The levels were significantly increased in patients with carotid lesions of more severe grades. On the other hand HDL-cholesterol and plasma concentration of apolipoprotein A presented the highest values in the group of 16 patients with normal echo-Doppler examination, but decreased progressively in those with pathological findings. By comparing the patients with

| Table 1: FH Patients with Carotid Lesions as a Function of Plasma Cholesterol Level |
|---------------------------------|-----|-----|
| Cholesterol (mg/dl) | Patients (n) | Patients with lesions (n) | (%) |
| >500 | 8 | 8 | 100 |
| 350–499 | 16 | 5 | 31 |
| <350 | 6 | 1 | 16 |

out any sign of neck artery atherosclerosis with those 14 with different degree of lesions, the levels of atherogenic LDL-cholesterol and plasma apo B were found to be markedly elevated in patients with atherosclerotic lesions. On the other hand patients with abnormalities at vascular examination showed significantly lower levels of protective nonatherogenic HDL-cholesterol and plasma apo A values.

It can be presumed that arterial wall irregularities might be correlated to the period of time during which the risk factor (hyperlipidemia) has been acting and producing detectable atheroma. One might therefore expect to observe an arterial lesion at younger age in those patients with extremely severe hypercholesterolemia and at adult age in those with less pronounced genetic defect. Table 4 divides the FH patients according to their age and to plasma cholesterol level and shows in brackets the number of arteries observed with lesions of different severity. Homozygotes and severe heterozygotes are of course diagnosed at a younger age for the early appearance in all of them of tendon and cutaneous xanthomas. The marked hypercholesterolemia of 6 FH patients of age below 32 years was accompanied by the presence of stenosis in the 62% of neck arteries under study. This was reduced to two and one out of four arteries investigated (50% and 25% respectively) in other two older FH patients with extremely elevated plasma cholesterol concentration. In the group with less pronounced hypercholesterolemia (between 350 and 499 mg/dl) the percentage of neck arteries detected with different degree of stenosis increased with age, being nil in three youngest patients, and 7% and 25% respectively in those with age between 32 and 44 years and above 45. None of the FH patients with hypercholesterolemia below 350 mg/dl showed a carotid lesion under age of 45. It was possible to detect two lesions in one 49 year old FH patient, investigated by echo-Doppler.

**Discussion**

The noninvasive investigation of neck arteries has allowed detection of carotid lesions in many FH patients, thus confirming that premature atherosclerosis develops also in other arteries than coronary.

No data are available on the prevalence of FH among patients with transient cerebral ischemic attacks or survivors of stroke. On the other hand many reports are available on the frequency of premature and severe coronary event in these patients. The cumulative probability to develop fatal or nonfatal myocardial infarction is very high in FH patients: Stone et al found it 16% in heterozygote males at age 40 and 52%
at age 60. A frequency much higher than that of normolipemic unaffected subjects. Other studies reported that men with heterozygous form of FH present a 5% chance of having myocardial infarction by age 30, 51% by age 50 and 85% by age 60. Affected women at comparable age have a risk of 0.12 and 58%.

Even stronger is the probability for homozgyotes to have a coronary event. One homozgyote has been reported to have suffered myocardial infarction at 18 months of age, while very few survive past age 30. Furthermore homozgyote patients develop atheromatous involvement of the aortic valve and endocardium with clinically significant aortic stenosis. Less data available on probability of stroke in FH.

Our data show that carotid atherosclerosis in FH patients is mainly related to the severity of hypercholesterolemia and to the age of patients. Most elevated levels of plasma cholesterol concentration was followed by early development and precocious detection of vascular lesion: all homozgyotes and severe heterozgyotes had carotid lesions at young age. Two patients with plasma cholesterol level above 500 mg/dl and age above 32 years are heterozgyotes; very rarely homozgyotes can reach adult age. These two patients had very high values of plasma cholesterol, but not as extreme as homozgyotes (often above 900 mg/dl). This difference might explain the less frequent incidence of lesions in these two patients as compared to the other six of younger age. Others, with less pronounced genetic defect, develop arterial lesions at slower rate, detectable therefore at adult age. This phenomenon is further supported by the relationship with the levels of atherogenic LDL-cholesterol and apolipoprotein B. Their values are progressively increased in relation to the severity of carotid lesions. Development of arterial lesions might be also favoured by the concomitant decrease on nonatherogenic HDL-cholesterol and apolipoprotein A, which in our study were inversely related to the severity of atherosclerosis. It is possible that the symptomatic cerebrovascular disease in FH patients might occur later in life after the appearance of coronary heart disease (angina pectoris or myocardial infarction). Furthermore in our FH patients carotid lesions were not flow reducing (below 50% of internal lumen) at the time of investigation. It will be of great interest however to follow asymptomatic FH patients or survivors of myocardial infarction up to an older age in order to detect possible appearance of cerebrovascular disease, as transient ischemic attacks or stroke. The present study demonstrates the frequent occurrence of atherosclerotic lesions in neck arteries of FH patients. The noninvasive study offers the possibility of investigating the progression and the eventually regression of atherosclerosis in these patients under intensive and prolonged lipid lowering treatment, despite the fact that FH is certainly the most difficult and daunting hyperlipidemia to be treated.

TABLE 3

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Patients (n)</th>
<th>Cholesterol (mg/dl)</th>
<th>LDL</th>
<th>HDL</th>
<th>Apo B</th>
<th>Apo A</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>16</td>
<td>316 ±68</td>
<td>44 ±13</td>
<td>193 ±41</td>
<td>218 ±34</td>
<td></td>
</tr>
<tr>
<td>Mild (1-15%)</td>
<td>9</td>
<td>474 ±179†</td>
<td>35 ±11</td>
<td>277 ±63†</td>
<td>168 ±59*</td>
<td></td>
</tr>
<tr>
<td>Moderate (16-50%)</td>
<td>5</td>
<td>462 ±175*</td>
<td>31 ±14</td>
<td>295 ±60*</td>
<td>138 ±77*</td>
<td></td>
</tr>
<tr>
<td>All lesions</td>
<td>14</td>
<td>470 ±171†</td>
<td>33 ±12*</td>
<td>284 ±60*</td>
<td>157 ±17†</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; †p < 0.01; ‡p < 0.001 (significance versus 0 lesion).

TABLE 4

<table>
<thead>
<tr>
<th>Chol (mg/dl)</th>
<th>Age (yrs)</th>
<th>&lt;32</th>
<th>32-44</th>
<th>&gt;45</th>
</tr>
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<tbody>
<tr>
<td>&gt;500</td>
<td>6 (15)</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>350-499</td>
<td>3 (0)</td>
<td>7 (2)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>&lt;350</td>
<td>3 (0)</td>
<td>2 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

In parentheses number of carotid lesions in FH patients.

References
12. Mancini M, Carbonara A, Heremans J: Immunochemical quantita-
Cerebral Edema Associated With Cranectomy and Arterial Hypertension

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SUMMARY The present studies were performed to determine whether cerebral edema will develop as a consequence of arterial hypertension and/or cranectomy. Arterial hypertension was induced for 30 minutes by inflation of a balloon catheter situated in the descending aorta, and a cranectomy was performed. The cerebral edema noticed was evaluated by macroscopic and microscopic observations. BBB permeability of HRP and Evans blue and water content. In addition, ICP was measured in the cisterna magna and ICPP by a catheter-tip transducer. In arterial hypertension or cranectomy alone, some small areas of Evans blue extravasation with increased water content were seen in the cortex, which corresponded to the occipito-parietal parts of the arterial boundary zones. In contrast, when arterial hypertension was combined with cranectomy, these lesions extended further into underlying white matter with increased water content. Forty-eight hours later, extensive brain edema with a shift of midline structures developed on the side of cranectomy which differed from that in arterial hypertension or cranectomy alone. It is suggested that some hydrostatic pressure gradients, particularly between blood vessel and surrounding extracellular space and among different areas within the brain parenchyma, may play an important role in the development of brain edema.

CEREBRAL EDEMA still remains a formidable clinical problem despite many years of study. Detailed information on basic mechanisms involved in edema development are needed to provide new approaches to more rational therapeutic modalities.

Experimentally, the investigation of brain edema has been based on a large number of experimental models of brain edema. It is generally considered that many factors known to modify the edema process include cerebrovascular permeability, cerebrovascular hydraulic conductivity, brain metabolism, tissue hydraulic conductivity and compliance, tissue and cerebrovascular osmotic and hydrostatic pressure, cerebrospinal fluid production (CSF) rate and pressure, and pathway for CSF excretion through arachnoid villi. Recently, some workers have demonstrated that bulk flow is a major mechanism for edema formation and extension. Hydrostatic pressure gradients may be crucial in the formation of cerebral edema.

The experiment reported here was designed to study pathophysiologically whether changes in hydrostatic pressure gradients lead to cerebral edema in normal brain. Cranectomy and arterial hypertension were employed to control the changes in hydrostatic pressure.

Material and Methods

Surgical Protocol

The experiments were performed on adult cats weighing 2.1 to 4.0 kg. The animals were anesthetized with an intramuscular injection of Ketamine hydrochloride (10–15 mg/kg). A femoral vein was cannulated to infuse various drugs as necessary. Blood gasses and body temperature were maintained within physiological limits. The heads of the cats were placed in a stereotactic frame. Arterial hypertension was induced by inflation of a double lumen balloon situated in the descending aorta immediately distal to the left subclavian artery, which caused a blood shift as a result of total aortic obstruction as previously described by Me-sangeau et al. The blood pressure was measured by the balloon catheter, and systolic blood pressure above 250 mmHg was maintained for 30 minutes. A cranectomy, approximately 2.5 × 2.0 cm, was made on the right parietal bone dorsal to the coronal suture. Great care was taken to avoid damaging the brain during the procedure. The scalp wound was then closed. All surgical maneuvers were performed with aseptic technique. Animals were divided into the following 4 groups: Group 1, sham-operated controls (n = 13); Group 2, arterial hypertension alone for 30 minutes (n = 21); Group 3, cranectomy alone (n = 27);
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