Study of Nailfold Capillaries in Hypertriglyceridemia (Types III and IV Hyperlipoproteinemia)

By Peter T. Kuo, M.D., Louise Y. Feng, Ph.D., and José Pamintaun, M.D.

SUMMARY
Reflected light nailfold capillaroscopy was used to discover micro-angiopathy in atherosclerotic patients with hypertriglyceridemia (types III and IV hyperlipoproteinemia). In comparison with healthy normolipemic controls, 51 of a series of 64 patients were found to have beds of dilated, congested, elongated, and tortuous capillary venular limbs and loops; and 29 of these with capillary abnormalities were found to have either fresh or old hemorrhages. Serial studies revealed that capillary hemorrhages tended to subside shortly after the hyperlipoproteinemia was controlled by a low carbohydrate diet, while the morphologic abnormalities showed little or no change for 8 to 21 months.

Additional Indexing Words:
Atherosclerosis Coronary artery disease Hyperlipemia
Capillaroscopy Micro-angiopathy

ABNORMAL small vessel patterns have been observed in a number of cardiovascular and metabolic diseases which include atherosclerosis,1 hypertension,2 congenital heart disease,3 and diabetes mellitus.4 Since it is generally known that patients with hypertriglyceridemia (types III and IV hyperlipoproteinemia) may manifest variable degrees of carbohydrate intolerance and increased proneness to atherosclerosis,5 it is postulated that certain characteristic microvascular aberrations may be demonstrable in these patients.

From the Cardiac Section of the Department of Medicine, the Robinette Foundation for Cardiovascular Research, and the George S. Klump Laboratory, Hospital of University of Pennsylvania, Philadelphia, Pennsylvania.

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Methods
Nailfold capillaries were observed and photographed with a modified Leitz binocular microscope illuminated by reflected light. Photographs of end-row capillaries were made on Kodak HS daylight Ectachrome with xenon-gas flash, powered by Leitz Microblitz 300, which was housed behind a didymium glass filter. The nailfold was chosen for study because of its easy accessibility and the possibility of visualizing the length of the capillary loop obliquely. Studies may be made in the conjunctiva, gums, and buccal mucosa, but only the tip of the capillary loop is visible in these sites. Conditions of capillaroscopy were standardized according to those employed in peripheral vascular vasodilatation test.6 Subjects were examined in sitting position with hand and arm resting on a soft pillow at heart level with a drop of emulsion oil applied to the nailfold. Preliminary investigation showed that in some patients, the abnormal capillaries may be localized in certain capillary beds. Therefore, in each subject the end-row capillaries of the second through the fifth fingers of both hands were scanned to locate area(s) of maximal abnormality. Beds with abnormal capillaries and their adjacent normal-looking capillaries were photographed with a graduated scale. The picture of the capillaries and graticule was projected by a photographic...
enlarger onto a flat surface for measurements of the vascular and loop diameters. Nailfold capillaryscopy was unsatisfactory in persons with heavily pigmented or callous skin and in those whose cuticle has been pushed back or cut on account of manual work or for cosmetic reasons.

Studies were made on 64 patients from 26 to 50 years of age with hypertriglycemia (types III and IV hyperlipoproteinemia), two patients with type I hyperlipoproteinemia, 14 patients with type II disease (essential familial hypercholesterolemia), and 64 healthy normolipemic controls closely matched in age to that of the patients. These controls had negative family history of premature atherosclerosis, diabetes mellitus, allergies, and connective-tissue disorders. Serial capillaryscopy was performed on patients at 6 to 10-week intervals for 8 to 21 months to evaluate the hypolipemic effect of a diet of 125 to 150 g of carbohydrate per day upon the vascular pathology. The diet was restrictive in refined-carbohydrates and fats with high short and medium-chain triglyceride content and, therefore, low in total calories. No restriction was imposed upon the protein and long-chain triglyceride intake.

Venous blood samples were taken after a 12 to 14 hour fast for serum cholesterol and triglyceride determinations by standard methods and for lipoprotein analysis by paper electrophoresis. Broad beta type III electrophoretic pattern was confirmed by re-electrophoresis of the isolated “floating” beta fraction at 1.006 density. Data obtained were used for phenotyping of hyperlipoproteinemias.

Lipoprotein analyses were extended to the available family members of patients under 40 years of age to establish the diagnosis of primary hyperlipoproteinemia. Carbohydrate metabolism of these patients and normolipemic subjects was evaluated by 5-hour oral glucose tolerance test (glucose dosage was calculated on the basis of 1 g/kg of ideal body weight). Blood glucose level was measured by glucose oxidase method.

Results

Blood Glucose

Only nine of the 64 patients with types III and IV hyperlipoproteinemia had fasting blood glucose levels of 100 to 110 mg/100 ml. Eleven of them had peak levels of blood glucose in the 150 to 162-mg/100 ml range within the first hour after a test meal. The mean glucose tolerance curves of the patients and controls are shown in figure 1. The early phases of the two curves are similar. In comparison with the normolipemic subject, the blood glucose curve of the patients is depressed from the second to the fourth hour of oral glucose test. The use of glucose oxidase method would account for the relatively low blood glucose values obtained in this study.

Plasma Lipids and Lipoproteins

Fasting plasma lipid (cholesterol and triglyceride) values and lipoprotein phenotypes together with other pertinent clinical data of patients and controls are presented in table 1. Twelve patients in this series had serum cholesterol values below 260 mg/100 ml, but all of them had triglyceride values above 150 mg/100 ml due to variable increases of triglyceride-rich pre-beta lipoproteins. Both beta- and pre-beta-lipoprotein fractions were increased in the remaining 52 patients. Two patients with primary type I hyperlipoproteinemia and 14 with primary type II disease were studied for comparison.

![Figure 1](image-url)
Table 1

Summary of Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Range of serum</th>
<th>Lipoprotein phenotype</th>
<th>Familial hyperlipoproteinemia</th>
<th>Positive family history</th>
<th>Coronary and/or peripheral vascular disease</th>
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<tbody>
<tr>
<td>Normolipemic controls</td>
<td>64</td>
<td>156-222</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemic patients</td>
<td>64</td>
<td>207-430</td>
<td></td>
<td>III &amp; IV</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>14</td>
<td>355-568</td>
<td></td>
<td>II</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Primary chylomicronemia</td>
<td>2</td>
<td>266-320</td>
<td></td>
<td>I</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2

(A) End-row nailfold capillaries of a patient with endogenous hyperlipoproteinemia. Venous portions of several capillaries are widened, elongated, and congested. A string of hemorrhages can be seen on the left directly below division 8 of the scale. (B) Markedly elongated, moderately widened venous limbs and loops of a number of the end-row nailfold capillaries in a patient with type IV hyperlipoproteinemia.

Figure 3

End-row nailfold capillaries of a normolipemic subject with no venous dilatation or congestion.

Nailfold Capillaries of Patients with Types III and IV Hyperlipoproteinemia

Fifty-one of the 64 patients with hypertriglyceridemia (types III and IV hyperlipoproteinemia) showed either widespread or localized capillary abnormalities in varying degrees of severity. Various combinations of the following changes were manifest in these patients: elongation, dilatation, twisting and coiling of the venular capillary limb, widening of the capillary loop, dilatation of the subpapillary venous plexus, and intravascular aggregation of the red cells. The capillary pattern of a given patient is persistent and completely reproducible. Relatively mild to moderate capillary dilatations were observed in only nine of the normolipemic controls. Small fresh and old hemorrhages arising from
the diseased capillaries were observed in 29 of the patients and in none of the normolipemic subjects. The arteriolar limbs in most of the abnormal capillaries were displaced and poorly visualized. No consistent abnormality was noted in the visible portions of the arterioles. Examples of the abnormal capillary patterns with and without hemorrhages are shown in figure 2A and B for comparison with normal capillary loops shown in figure 3. The percentage distribution of the different mean diameters of the capillary venular limbs in control and patient groups, ranging from 6μ to >30μ are presented in histograms in figures 4 and 5. The distribution patterns of the venous diameters of more normal capillary populations of both groups are similar to each other (fig. 4). Examination of the abnormal populations in both groups (fig. 5) shows that a high percentage of the patients have dilated venular limbs (>16μ), while 90% of the controls have venular diameters in the 8 to 14 μ range.

Histograms in figure 6 show no significant difference between mean loop diameters of normal-looking capillaries in both groups. Comparison of the more abnormal populations in both groups (fig. 7) shows that a high percentage of patients have significantly wider loops than those of the controls. Apparently, much of the loop widening is secondary to the venous dilatation. Localized coiling and redoubling at the apex and elsewhere of the capillary loop may give the impression of "micro-aneurysm" and "nodular" thickening. Interestingly enough, microvascular abnormal-
NAILFOLD CAPILLARIES

DIAMETER, MORE NORMAL CAPILLARY LOOPS

Figure 6
Percentage distribution of mean loop diameters of the normal-looking capillaries in normolipemic subjects (dotted bars) and in patients with types III and IV hyperlipoproteinemia (hatched bars).

Diabetic patients showed more abnormalities. In type III and IV patients, capillary changes were observed more prominently by young patients with primary types III and IV hyperlipoproteinemia. Serial follow-up studies indicate that most of these capillary morphologic changes would persist for 8 to 21 months after the hyperlipoproteinemia has been successfully controlled and 8 to 26 pounds of body weight have been lost. On the other hand, old hemorrhages were promptly absorbed and fresh diapedesis of red cells from the capillaries did not recur in the affected patients during the same periods of observation.

Nailfold Capillaries of Patients with Primary Types I and II Hyperlipoproteinemia

Studies made on two children with primary type I disease with marked chylomicronemia showed relatively normal capillary patterns. The nailfold capillaries of genetically determined type II patients and their hypercholesteremic family members were either normal or showed only increased tortuosity and coiling. No marked capillary venular dilatation and red cells stasis as described in type III and IV patients were observed in these patients.

Discussion
Several groups of investigators have reported dilatation of the efferent (venular) capillary limb, widening of the transitional limb (loop), nodular apical elongation, and other associated phenomena in the capillaries of the skin and mucous membrane of diabetic patients. Most investigators have focused attention on one or the other aspects of capillary abnormality. Kontras and Bodenbender reported morphologic changes in nailfold capillaries in over 75% of 60 diabetic children studied. The present study indicates that the capillary changes of patients with types III and IV hyperlipoproteinemia are in most parts similar to those observed in diabetic patients. Indeed, glucose intolerance and abnormal serum insulin level and insulin response to carbohydrates have been reported in patients with endogenous or types III and IV hyperlipoproteinemia.

Figure 7
Percentage distribution of mean diameters of the loops of abnormally dilated capillaries in normolipemic subjects (dotted bars) and in patients with types III and IV hyperlipoproteinemia (hatched bars).
A number of metabolic and physical factors can affect the small vessel tone. If the microvascular changes observed in patients with types III and IV hyperlipoproteinemia were in some way related to disturbance in carbohydrate metabolism, there is no evidence to suggest that a persistent hyperglycemia per se is responsible for the development of capillary abnormalities.

Comparative studies have been made on the small vascular beds of atherosclerotic and “healthy” subjects of various ages by other investigators. However, most studies did not supply information on the lipid or carbohydrate metabolism of their patients and have emphasized chiefly arteriolar changes. These attempts to designate arteriolar narrowing as the primary atherosclerotic lesion have been complicated by the demonstration of more severe narrowing of the arterioles in the hypertensive than in the atherosclerotic patients. Thus, the arteriolar changes described may be secondary to chronic effects of different chemical and physical factors upon the cellular metabolism of the vessel wall. In contrast, the persistent capillary venular dilatation, congestion, and hemorrhage observed in young patients with familial hyperlipoproteinemia may constitute one of the primary or early lesions in the development of vascular disease.

Intravascular red cell sludging has been described in atherosclerosis and hyperlipoproteinemia as well as in other physiologic and pathologic states. In the light of the present study, it may be reasonable to assume that decrease in vessel tone with capillary venular dilatation may play a role in the production of sludging phenomenon in those atherosclerotic patients with types III and IV hyperlipoproteinemia.

In a limited number of patients, through judicious exclusion of other diseases that may affect the capillaries, capillaroscopy might be helpful in the early detection of atherosclerosis and in long-term follow-up of a given abnormal finding. However, the present investigation actually serves to emphasize the fact that different metabolic abnormalities as manifested in types II, III, IV, and V hyperlipoproteinemia may produce a diversity of early vascular changes.

References

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PETER T. KUO, LOUISE Y. FENG and JOSÉ PAMINTAUN

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