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Lymphatic Microangiopathy: A Complication of Severe Chronic Venous Incompetence (CVI)*

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Summary

The lymphatic capillary network was visualized by fluorescence microlymphography (subepidermal injection of 0.01 ml of FITC-dextran 150 000 under a fluorescence microscope) in the medial ankle region of 21 patients with chronic venous incompetence (CVI) and of 15 healthy controls. In severe CVI leading to trophical changes of the skin lymphatic microangiopathy was detected. Obliterations of parts of the superficial capillary network, phenomena of cutaneous reflux and increased permeability of capillary fragments occurred. These findings contrast to primary lymphedema where the rete remains intact in most cases.

Visual lymphography by vital dyes has been used by various authors to depict the small skin lymphatics accessible at a macroscopic level (4, 8, 12). Fluorescence microlymphography adds the possibility to study the true lymphatic capillary network by videomicroscopy in an almost atraumatic way (2, 6). After subepidermal injection of 0.01 ml FITC-labelled dextran 40 000 or 150 000 the lymphatic capillaries are visualized under the fluorescence microscope.

In the present study the findings of fluorescence microlymphography applied to the medial ankle region are described in 21 patients with CVI and compared to a group of 15 healthy controls.

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Method, patients and controls

21 patients (mean age 51 years) with chronic venous incompetence were included in the study. 14 were women, 7 men. A total of 32 fluorescence microlymphographies were performed (11 studies on both legs). In 20 legs chronic venous incompetence developed as a consequence of deep venous thrombosis. In the remaining 12 legs primary varicose veins with insufficient perforators were diagnosed. According to the degree of severity the cases were attributed to one of the three stages defined by *Widmer* (14). Stage I is characterized by slight ankle swelling and dilated foot veins (n = 5), stage II by induration, hyperpigmentation and hyperkeratosis (n = 12), stage III by additional ulcera including healed ones (n = 15).

Edemas of cardiac or nephrotic origin were excluded by appropriate tests. Phlebography was indicated in 3 cases. The examination by Doppler-ultrasound revealed obstruction of the deep veins in 8 legs, insufficiency of the deep thigh and calf veins in 18 legs. Insufficient perforator veins were diagnosed by clinical examination and by Doppler-ultrasound in 26 legs. A history of previous deep vein thrombosis was found in 20 legs.

The control group consisted of 15 healthy volunteers (mean age 31 years).

The *technique of fluorescence microlymphography* using a video microscopy system (1) has been described in detail (2, 7). A steel microneedle with an outer diameter of 0.2 mm

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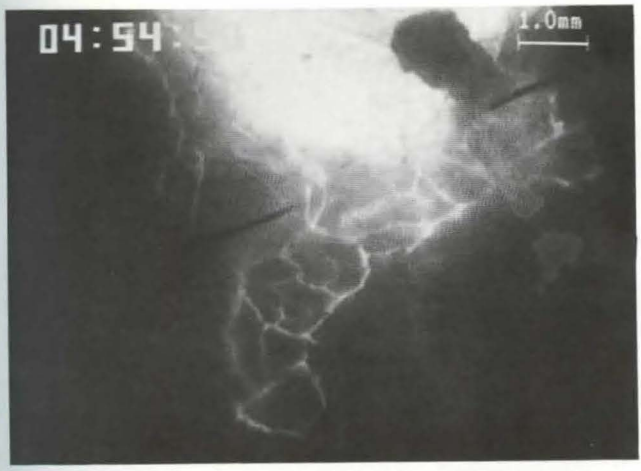

Fig. 1a Lymphatic capillary network 4 min and 54 s after subepidermal injection of FITC-dextran (picture taken from the television monitor). The distal half of the original dye deposit is seen in the upper part of the figure. The expansion of the dye in the network is limited.

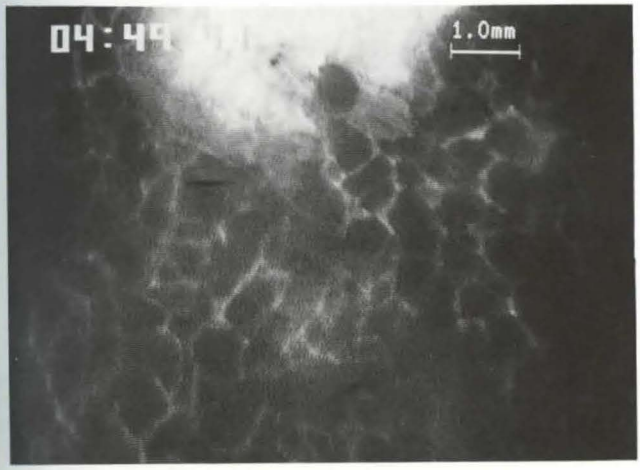

Fig. 1b Increased expansion of FITC-dextran filling an extended field of the lymphatic capillary network in a patient with CVI stage I

mounted on a microsyringe is advanced into the subepidermal layer by hand or by means of a micromanipulator. 0.01 ml of FITC-dextran 150 000 (Pharmacia) is injected. The fluorescent deposit is visualized under the fluorescence microscope with epiillumination (Wild-Leitz). A sensitive television camera (Cadmium Selenide Vidicon, Siemens) records the dynamic filling of the lymphatic capillaries from the original dye deposit on videotape (Grundig BK 204). The microscope is mounted on the arm of a heavy support (6) which allows exact positioning of the lenses (objectives 1/0.04 and 2.5/0.08) in a three dimensional way. The final magnification on the television monitor was 55 and 158 times respectively. After the microinjection of the dye 4–5 cm above the medial ankle the filling of the network from the deposit was recorded on video tape for 5–8 min and then every ten minutes up to one hour. Photographs were taken from single frames on the television screen.

The expansion of the dye in the lymphatic network was measured systematically in the four directions. The morphology was assessed during the maximal filling period. Care was taken to observe eventual phenomena of cutaneous reflux and of dye passage from lymphatics into the interstitial space.

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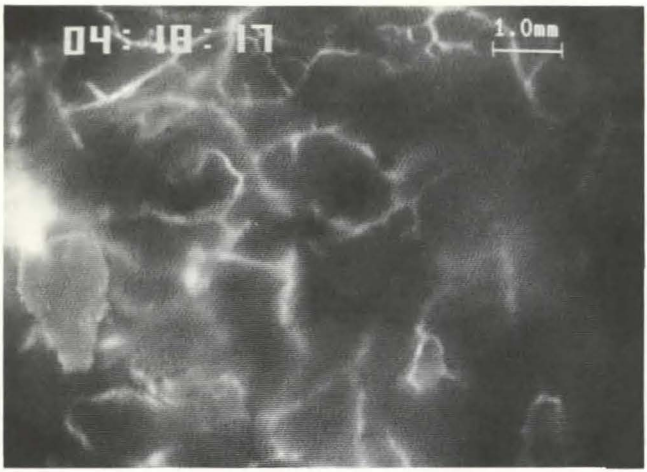

Fig. 2a The lymphatic capillary netwo in severe CVI is partially obliterated. ly fragments of the network are filled (4 min 18 s after subepidermal injecti

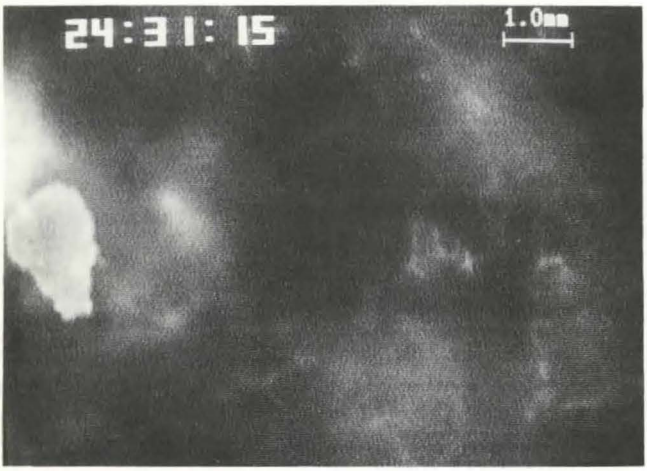

Fig. 2b Most of the dye molecules ha left the capillary fragments colouring t interstitial space (24 min 31 s after su epidermal injection)

Results

1) Morphology of lymphatic capillaries

In cases with chronic venous insufficiency without trophic changes (stage I) no changes of capillary morphology were observed. The propagation of the dye, however, was significantly enhanced (see below).

In cases complicated by trophic changes (stages II and III) in the medial ankle region the superficial network of lymphatic capillaries was damaged. The meshes which form a regular network in the healthy controls (Figure 1a) and in patients with stage I (Fig. 1b) are interrupted, only partially filled or completely obliterated (Fig. 2 and 3). Fragments of the dye may be filled quite far away from the deposit. In cases with no filling of lymphatic capillaries at all the dye moved into the interstitial space without clear cut pathways (Fig. 4). A cloudy diffuse fluorescence appeared in the interstitial space originating from the deposit of FITC-dextran.

2) Permeability of lymphatic capillaries

In the healthy control group the meshes of the superficial lymphatic capillary network visualized contained dye for more than one hour. No or only minor leakage of FITC-dextran 150 000 was observed. In some of the

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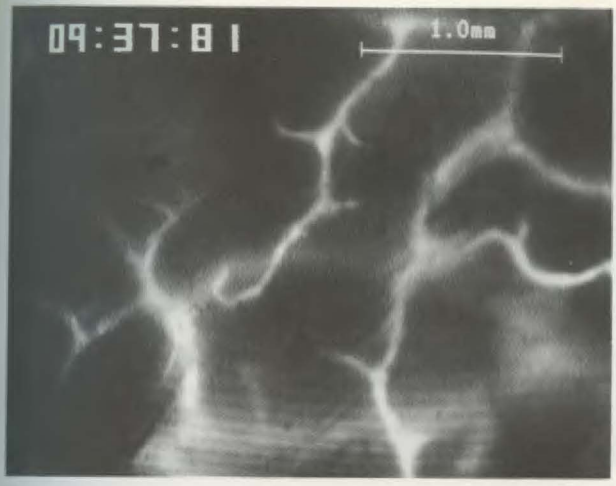

Fig. 3 Part of the lymphatic capillary network in a patient with severe CVI. The interruptions of the network are clearly delineated

Fig. 4 Original dye deposit and cloudy migration of the tracer into the interstitial space without filling of capillary fragments. Patients with CVI stage III

patients, however, the permeability of lymphatic capillaries was clearly increased. The fragmentated, partially obliterated network was only visible for 20–40 min after subepidermal injection of the dye. Later on, the lymphatic capillaries became invisible. The high molecular dextran accumulated in the interstitial space forming cloudy spots (Fig. 2a and b). At the end of the observation period (one hour) the dye was still detected in the interstitial space.

3) Cutaneous reflux

Phenomena of cutaneous reflux were observed in 4 patients. The dye moved into the deeper, invisible structures starting from the original deposit and reappeared from below in the superficial structures. Where no reticular network of lymphatic capillaries was preserved, the dye filled the pericapillary halo area of the blood capillaries (Fig. 5).

4) Expansion of the dye

As mentioned briefly the dye expanded to larger skin areas in patients than in normals. In the latter the maximal propagation in one of the four directions reached 7.8 ± 2.6 mm, in the patients with CVI 25.4 ± 21.6 mm. These differences in dye propagation were statistically significant ($p < 0.005$). They were

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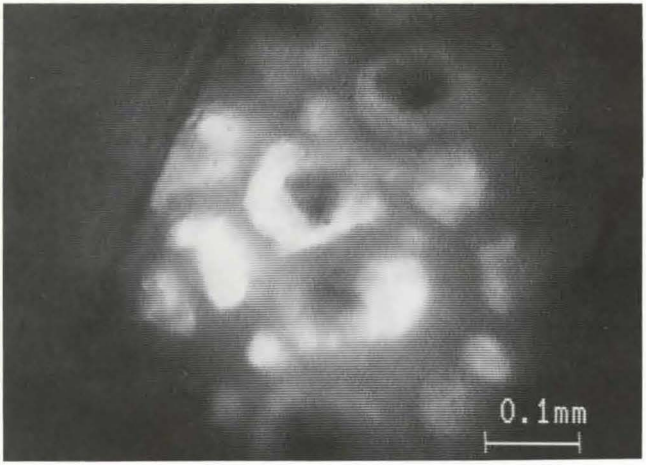

Fig. 5 Cutaneous reflux of the dye an area far away from the original d posit. FITC-dextran accumulates in halo section surrounding dilated blo capillaries (dark dots)

observed in patients with all degrees of severity.

Discussion

The blood capillaries in chronic venous insufficiency are coiled, dilated and surrounded by a halo (5). In some areas spots of white atrophy develop. They are characterized by avascular fields with enlarged and tortuous capillaries on their borders (3). The ultrastructural changes in CVI include obliterated segments, widened interendothelial clefts and passage of erythrocytes through the capillary wall (10, 13).

There are only few reports which point to lymphatic factors involved in severe CVI. Measurements with isotopes revealed a deficit of lymphatic drainage in skin areas showing trophic changes (11). Small lymphatic vessels detected by macroscopic observation were rarefied in these areas (4). In addition, the present study using fluorescence microlymphography documents lymphatic microangiopathy in severely altered skin.

In microangiopathy due to CVI the superficial lymphatic capillary network (9) is partially or almost completely obliterated (Fig. 2a, 3 and 4). The preserved fragments often exhibit enhanced permeability to FITC-dextran 150 000 (Fig. 2a and 2b). Both mechanisms prevent effective lymphatic clearance of the interstitial space.

In contrast to these findings in severe CVI lymphatic capillary network remains intact primary lymphedema (2, 6). Like in CVI th extension of the network filled by the dye significantly increased because of a deficit i transport of collectors and precollectors. Ph nomena of cutaneous reflux occur in both eases on the microcirculatory level (Fig. 5).

It may be concluded that trophic changes i severe CVI are of mixed venous and lymph tic origin. The mechanism of damage to the lymphatic microvessels is not yet establishe Recurrent infections were reported in only one half of patients with lymphatic microa giopathy.

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