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.

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 31 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 ulcers 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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mounted on a microsyringe is advanced into
the subepidermal layer by hand or by means
of a micromanipulator. 0.01 ml of FITC-dex-
tran 150 000 (Pharmacia) is injected. The flu-
orescent deposit is visualized under the fluo-
rescence microscope with epiillumination (Wild-
Leitz). A sensitive television camera (Cadmium
Selenide Vidicon, Siemens) records the dy-
namic filling of the lymphatic capillaries from
the original dye deposit on videotape (Grun-
dig 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 net-
work 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 cut-
taneous reflux and of dye passage from lym-
phatics into the interstitial space.

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

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

Fig. 2b Most of the dye molecules left the capillary fragments colouring interstitial space (24 min 31 s after subepidermal injection).
patients, however, the permeability of lymphatic capillaries was clearly increased. The fragmented, 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
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 the lymphatic capillary network remains intact in primary lymphedema (2, 6). Like in CVI the extension of the network filled by the dye significantly increased because of a deficit in transport of collectors and precollectors. Phenomena of cutaneous reflux occur in both diseases on the microcirculatory level (Fig. 5).

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

Literature

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


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