

Chapter 11

Capillaroscopy

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Capillaroscopy

Capillaroscopy is a noninvasive imaging technique that is used for the *in vivo* assessment of the microcirculation. Its principal role in rheumatology and dermatology is to differentiate the primary and secondary forms of Raynaud's phenomenon (RP) associated with connective tissue disease [1]. Capillary microscopy can be performed with various optical instruments such as the ophthalmoscope, dermatoscope, photomacrography system, stereomicroscope, conventional optical microscope, and the videocapillaroscope. The nailfold videocapillaroscope (NVC) with handheld device has the advantages that it is easy to learn and is a handheld device (=probe) which can be used in situations in which the use of the traditional microscope may be less convenient (such as in patients with finger flexion contractures) and its relatively high magnification (200–500x) is advantageous compared to the older widefield technique (Fig. 11.1).

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Fig. 11.1 A videocapillaroscope that is used in detecting the microcirculation at the level of the nailfold bed

Capillaroscopic Detection of the Early Microvascular Alterations That Are Markers of Secondary Raynaud's Phenomenon

The morphologic changes that characterize the microvasculature in the scleroderma-spectrum diseases at the level of the nailfold have been extensively described – giant capillaries, microhemorrhages, loss of capillaries, neovascularization, and avascular areas (Fig. 11.2) [2].

The microvascular alterations have been recently reclassified in systemic sclerosis (SSc) into three defined and different NVC patterns:

1. An “early pattern” (few giant capillaries, few capillary microhemorrhages, no evident loss of capillaries, and relatively well-preserved capillary distribution)
2. An “active pattern” (frequent giant capillaries, frequent capillary microhemorrhages, moderate loss of capillaries, absence or mild ramified capillaries with mild disorganization of the capillary architecture)
3. A “late pattern” (almost absent giant capillaries and microhemorrhages, severe loss of capillaries with extensive avascular areas, ramified/bushy capillaries, and intense disorganization of the normal capillary array) [3] (Fig. 11.3)

The marked increase in capillary size is the most characteristic feature of the nailfold capillary bed (giant capillary) in early secondary RP. In particular, the detection of enlarged and giant capillaries, together with microextravasation (hemorrhage) of the red blood cells in the nailfold, most likely represents the first morphologic sign of the altered microcirculation in systemic sclerosis.

The shape of the widened capillaries is largely heterogeneous, but giant capillaries with a homogeneous enlargement (diameter over 50 μm) are an absolute marker

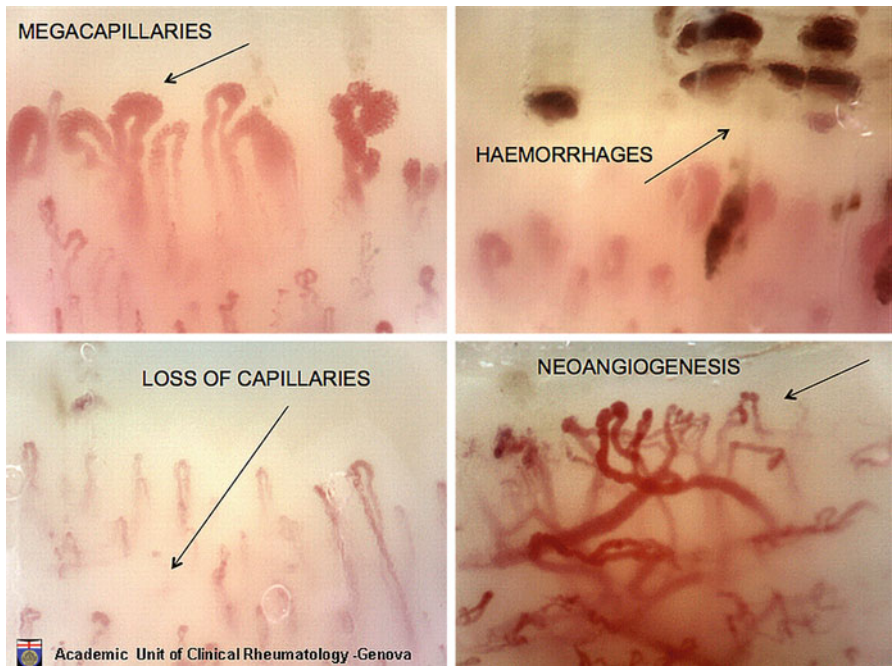


Fig. 11.2 Different microvascular alterations (i.e., *giant capillaries*, *microhemorrhages*, *loss of capillaries*, and *neovascularization*) that characterize the secondary Raynaud's phenomenon

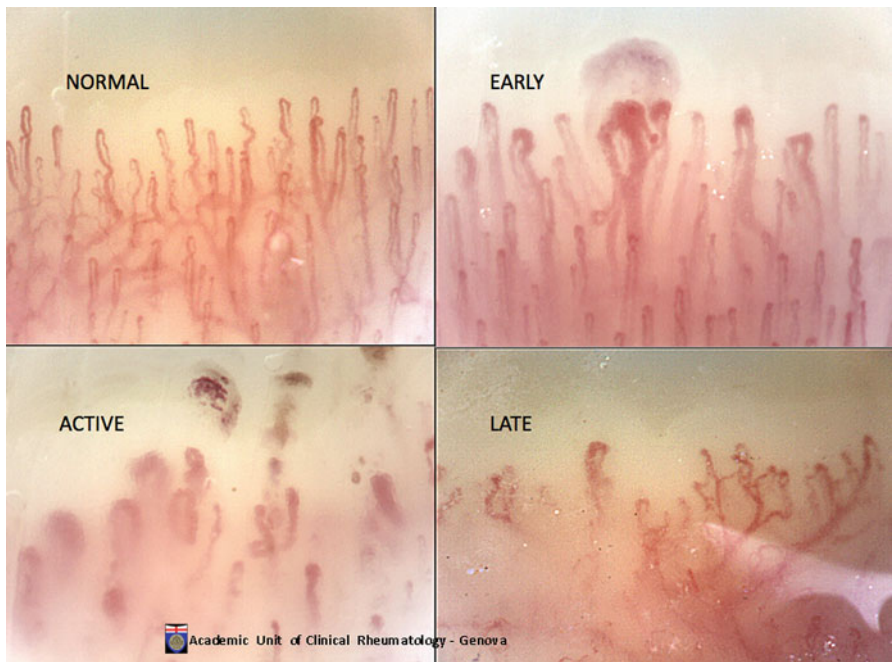


Fig. 11.3 The three scleroderma patterns (*early*, *active*, *late*) compared to the microvasculature in a normal health control subject

of the scleroderma capillaroscopic pattern. This picture characterizes the “early” (initial) SSc capillaroscopic pattern (Fig. 11.3) [4]. As the pathophysiological process of SSc progresses into fibrosis, the capillaroscopic analysis most likely reflects the effects of tissue hypoxia/massive capillary destruction, then increased loss of capillaries and avascular areas are observed, together with bushy capillaries indicating neoangiogenesis. This advanced stage of the systemic sclerosis is characterized by the “late” capillaroscopic pattern (Fig. 11.3). We know that patients with the “early” capillaroscopic pattern may have had RP for many years, and a transition from primary to secondary RP may be expected in almost 15 % of subjects in an average time of 29 months [5].

To quantify the microvascular changes, a practical system to score these capillaroscopic alterations in systemic sclerosis patients has been proposed recently and validated [6, 7]. Studies on nailfold capillary changes over time or in response to therapy are currently ongoing.

Learning to Use Capillaroscopy

Recent preliminary experience indicates that technical and operative skills in capillaroscopy, using a videomicroscopy system, can be achieved in approximately five nonconsecutive hours by an untrained specialist, in the context of a self-teaching program under expert supervision [8]. The beginner’s performances show that self-efficacy increases with practical experience, and image quality is reached in up to 70 % of learners by the third session [8].

Scleroderma Capillaroscopic Patterns and Serum Autoantibodies in Systemic Sclerosis

Regarding the anti-endothelial cell antibodies (AECA), these have been detected significantly more frequent in SSc patients with the “late” capillaroscopic pattern compared to the “early” and “active” patterns ($p < 0.05$) [9]. Concerning the anti-topoisomerase I (anti-Scl70) and anticentromere (ACA) antibodies, anti-Scl70 were found more frequent again in SSc patients showing the “active” and “late” patterns, whereas ACA especially in patients with the “early” pattern [10].

In a large prospective study, enlarged/giant capillaries, capillary loss, and more SSc-specific autoantibodies independently predicted definite SSc [11]. The authors reported associations between certain patterns of capillary abnormality and different specific autoantibodies. Anti-CENP-B and anti-Th/To antibodies predicted enlarged/giant capillaries; these autoantibodies and anti-RNAP III predicted capillary loss. Interestingly, each autoantibody was associated with a distinct time course of microvascular damage, as gauged by capillary enlargement or capillary loss.

At follow-up, 79.5 % of patients with one of these autoantibodies and abnormal findings on nailfold capillary microscopy at baseline had developed definite SSc. Patients with both baseline predictors (abnormal capillaroscopy and an SSc-specific autoantibody) were 60 times more likely to develop definite SSc.

Finally, the association of specific antinuclear antibodies positivity and the presence of the NVC scleroderma pattern have been proposed as biomarkers for the very early diagnosis of SSc together with clinical symptoms (i.e., Raynaud's phenomenon and/or puffy fingers) [12].

Possible Predictive Value of Capillaroscopy for Clinical Outcome in Systemic Sclerosis Patients

Systemic sclerosis microangiopathy correlates with disease subsets and the severity of peripheral vascular, skin, and lung involvement; in particular, patients with the "late" pattern showed an increased risk to have active disease and have moderate/severe skin or visceral involvement compared to patients with "early" and "active" capillaroscopic patterns [13].

Skin ulcers are a common vascular complication of SSc and seem now recognized in association with rapidly progressive capillary loss and the "late" NVC pattern, characterized by progressive avascular areas. An association with trophic lesions and loss of capillaries, as assessed by semiquantitative scoring, has also been reported [14]. Very recently, in 130 SSc patients examined at entry and after 20 months of follow-up, the diffuse cutaneous SSc phenotype with avascular areas on capillaroscopy represented, among other factors (e.g., increased IL-6), the major risk factor for ulcer development [15].

A recent study developed a capillaroscopic skin ulcer risk index (CSURI) that might predict the onset of new digital ulcers by using NVC analysis in patients with SSc [16]. However, this index is complex and time consuming, and the authors found that also the simple decrease of capillary number alone is sufficient as marker. A more recent simple capillaroscopic index (day-to-day DU index), prognostic for digital trophic skin lesions and based just on loss of capillaries alone, has been published showing high sensitivity and specificity [17].

Digital ulcers have been associated with significantly reduced blood flow at fingertips; in addition, SSc patients with the scleroderma "active" and "late" NVC patterns showed decreased blood flow velocity (65.5 % and 66.2 % reduction, respectively), and in particular, the reduced blood flow velocity was significantly associated with capillary ramification and capillary loss [18].

Ideally, future studies examining associations between digital ulceration and nailfold capillaroscopic patterns should consider digital tip ulcers and extensor surface ulcers. Recent studies showed that nailfold capillary density and its decrease are associated with the presence of lung involvement and severity of pulmonary arterial hypertension in systemic sclerosis patients [19, 20].

Conclusions

Videocapillaroscopy is considered fundamental for differentiating between primary and secondary Raynaud's phenomenon [1–3, 5]. The validated scoring of the capillaroscopic markers of the scleroderma patterns is supported for follow-up of systemic sclerosis patients, at least already in some centers [6, 7]. The prognostic and predictive value of capillary density is becoming an index of outcome in patients affected by systemic sclerosis [21, 22]. As with specific autoantibodies, further larger-scale studies, both cross-sectional and longitudinal, are required and are ongoing to examine further the associations between capillaroscopic findings and other parameters/biomarkers of disease.

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