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How to perform and interpret capillaroscopy

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A B S T R A C T

The essence of capillaroscopy is to examine, noninvasively and safely the morphology of nailfold dermal papillary capillaries using a magnification system (microscopical lenses). Capillaroscopy may be performed with lenses with low (×20) and with high magnification (×200 up to ×600). The video-capillaroscope consists of an optical/digital probe which is moved to the finger of the patient and allows direct contact with the nailfold. Through qualitative assessment a normal capillaroscopy can be distinguished from a pathognomonic abnormal one due most frequently to systemic sclerosis (SSc). This pattern recognition relies on evaluating the morphology of the capillaries, their density (number) and dimensions 'at sight' of the capillaries and their architecture. In SSc three progressive capillaroscopic patterns have been described ('early', 'active' and 'late'). Quantitative assessment (quantitation of certain characteristics and semi-quantitative scoring) of the capillaroscopic pictures may also be performed. Qualitative and semi-quantitative assessments are used to predict SSc clinical complications. In other connective tissue diseases (CTDs) prospective clinical studies resulting in indices which can predict future clinical complications have not been published, as yet.

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Introduction

Capillaroscopy: not only an old but also an actual technique

In 1663, Johan Christophorous Kolhaus was the first clinician to use a primitive microscope to observe the small blood vessels surrounding the nails and Giovanni Rasori (1766–1873), using a magnifying glass, first described the close relationship between conjunctival inflammation and the presence of an "'inextricable knot of capillary loops." [1] From the time that Maurice Raynaud (1834–1881) presented his thesis in Paris (1862) on local ischaemic damage of the hands, feet, nose and tongue, capillaroscopy became recognised as an important investigation to visualise the microvascular involvement, which is the key feature of Raynaud's phenomenon (RP) (Fig. 1) [2].

In the 20th century important steps were taken with this tool. In this way, for example, capillaroscopy was shown to be able to distinguish primary Raynaud's phenomenon (PRP) from secondary Raynaud's phenomenon (SRP) due to systemic sclerosis (SSc) [3–5]. In addition, techniques to perform capillaroscopy were optimised [6,7].

Recent interpretation of capillaroscopic images and consensus on when and how to use capillaroscopy is mainly influenced by the landmark papers published by the late Maricq and the present Cutolo Team as will be attested below.

What is nailfold capillary microscopy (capillaroscopy)?

The essence of capillaroscopy is to examine, noninvasively and safely, the morphology of nailfold dermal papillary capillaries. This is achieved by looking through the epidermis at the nailfold bed, after application of a drop of oil [8].

In the nailfold distal capillary row the dermal papillae run parallel to the surface of the nail. Subsequently the capillaries of the distal row are visible in their whole length and appear as red, hairpin-shaped loops (consisting of an afferent limb, a transitional (or apical) limb and an efferent limb) that parallel the axis of the finger in a healthy subject (Fig. 2A).

In SSc and diseases of the scleroderma spectrum ('early' SSc (see below), mixed connective tissue disease (MCTD), dermatomyositis (DM) and polymyositis (PM)) there is prominent microangiopathy (see below), which can readily be detected by capillaroscopy. These specific capillaroscopic changes are, in combination with serological testing of the patient, paramount in two situations:

One, in differentiating primary from SRP due to SSc and, two, in predicting in a Raynaud's cohort, without any other sign of a CTD, those patients who will develop SRP due to SSc in the future (see

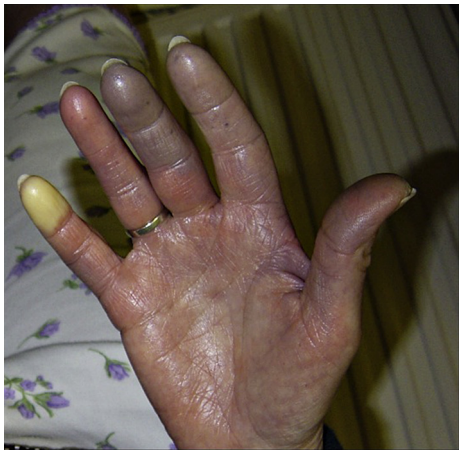

Fig. 1. Patient affected the Raynaud's phenomenon. Note the three phases: white, blue and red.

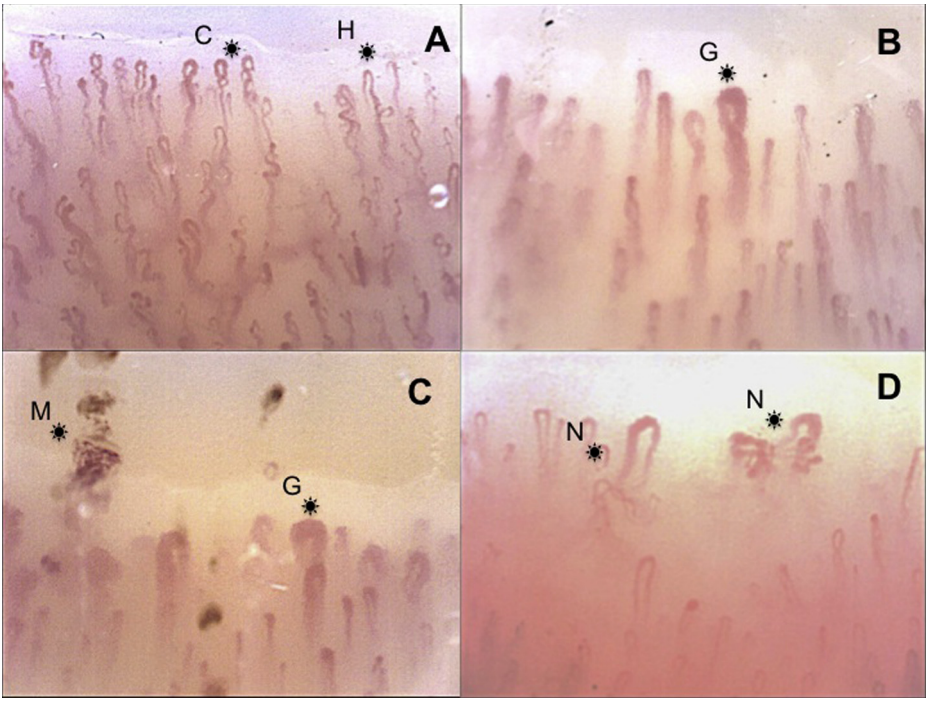

Fig. 2. A) Normal capillaroscopic picture as assessed qualitatively. Note the regular array of the capillaries and the normal: hairpin shape (H) and aspecific variations: crossing once or twice (C). B) "Early" scleroderma pattern. Note the present of giant capillaries (G). There is no loss of capillaries. C) "Active" scleroderma pattern. Note the presence of the combination of giant capillaries, loss of capillaries and microhaemorrhages (H). D) "Late" scleroderma pattern. Note the presence of neoangiogenesis (N) and loss of capillaries.

below) [4,5].In CTDs other than SSc, capillaroscopy is not paramount in the diagnosis [9]. The reason for this is that in those CTDs capillaroscopy may show normal, nonspecific or borderline changes. These changes will be defined below.

How to perform capillaroscopy

Capillaroscopy may be performed with a lens with low (×20) and with high magnification (e.g., ×200). The instruments with low magnification allow a global evaluation of the entire nailfold area (wide-field capillaroscopy). These instruments allow a panoramic vision of the whole nailfold microvascular network [10]. One example of an optical instrument with low magnification is the stereomicroscope (e.g., magnification ×14) (Fig. 3/picture 1).

Of note, with this technique the seminal descriptive papers concerning the scleroderma pattern were described by Maricq et al. last century (see below). Alternative choices are the dermatoscope and ophthalmoscope (Fig. 3/pictures 2 and 4) [11].

The video-capillaroscope not only allows low magnification, but also has the advantage of having sequential high magnifications (i.e., magnifications ×100, ×200 and ×600) which enable detailed observations of separate capillaries (Fig. 3/picture 3). Another advantage of the video-capillaroscope is that it consists of an optical probe which is moved to the finger of the patient and allows direct contact with the nailfold (Fig. 4). This facilitates examination of patients with SSc and severe finger flexion contractures [8].

When using the video-capillaroscope with a magnification of ×200, four consecutive images of 1 mm (in the middle of the nailfold) are usually taken [12].

Fig. 3. Different devices for the capillaroscopic analysis. The widefield microscope (1). The dermatoscope (2). The video-capillaroscope (3). The ophthalmoscope (4).

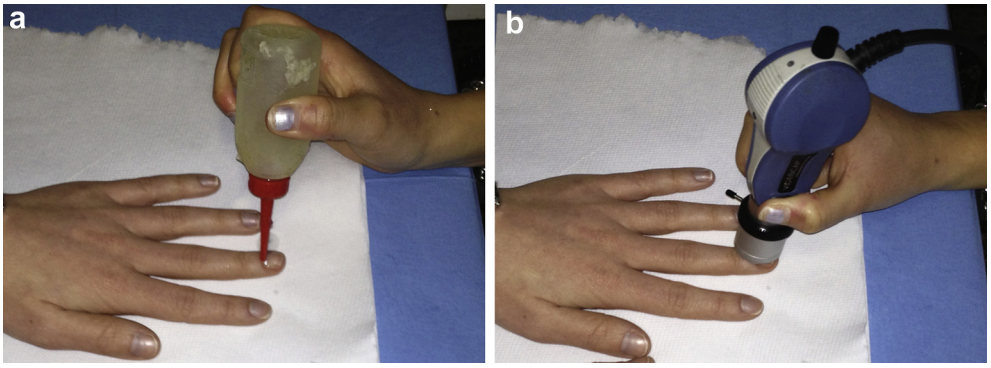

Fig. 4. The nailfold videocapillaroscope. a) Application of a drop of oil on the nailfold bed of the patient. b) Direct contact between the videocapillaroscope and the nailfold bed of the patient.

Qualitative assessment of capillaroscopic images

In qualitative assessment (i.e., pattern recognition) an overall interpretation is given after commenting on the visibility of the image, the morphology of the capillaries, the density and dimensions 'at sight' of the capillaries and the architecture.

Qualitative assessment readily allows distinction between a normal capillaroscopic image (Fig. 2A) or one showing nonspecific changes from an abnormal capillaroscopy due to a scleroderma spectrum disease (Fig. 2B–D) (see below).

All mentioned capillaroscopies have attested reliability in discerning normal capillaroscopy (in a healthy population) from the specific changes found in SSc and the other diseases belonging to the scleroderma spectrum through pattern recognition [13].

(Semi-) quantitative assessment of capillaroscopic images

Manual or (semi-) automated measurements can be made of certain characteristics of individual capillaries, in between others, of dimensions and density. Both quantitation of capillaroscopic parameters per linear millimetre as well as semi-quantitation (giving a score between 0 and 3 per capillaroscopic parameter) is being used in associative and prediction studies between capillaroscopy and clinical aspects of SSc (see below) [14].

Number of fingers to be studied

Qualitative assessment is used in screening for SSc in patients with RP (see below). As there may be a high variability in morphology in patients with SSc per nailfold (as not necessarily all nailfolds are affected by the scleroderma pattern), it may be opportune to screen every nailfold in a patient with RP (usually four or two per hand, excluding the thumb) [2].

In quantitative assessment (see below) studies are published based on the examination of one nailfold (e.g., finger 4 of one hand) and also based on quantitation of several nailfolds.

When and why to perform capillaroscopy

The main indication to perform capillaroscopy is investigation of a patient with RP. In this way a patient with SSc, in which there is a high prevalence of RP, can be readily distinguished by capillaroscopy from a patient with PRP (not related to a condition) or RP due to a CTD other than SSc. This is because the vast majority of patients with SSc have pathognomonic changes on capillaroscopy (see below, the scleroderma pattern). In addition, patients with RP as their only presenting symptom but who will develop other features of SSc in the future can be detected years before their clinically overt disease appears by simple screening using the combination of capillaroscopy and serology (see below) [4].

What is considered normal

A normal capillaroscopic pattern, by qualitative assessment, is characterised by a homogeneous distribution of hairpin-shaped capillaries as a 'comb-like structure', with a density of between 9 and 14 capillaries per mm (average 10 per mm) (Fig. 2A).

However, there is a wide intra- and inter-individual variability within a normal population. In this way tortuous and crossed capillaries may occur in high prevalence within a normal population.

Shapes, other than hairpin, tortuous and crossing (i.e., abnormal shapes due to neo-angiogenesis) should always occur in very low prevalence to be able to speak of a normal capillaroscopic image. Further, variations in dimensions of the capillaries (i.e., ectasia: diameter of a limb between 20 and 50 μm, see below) should occur in low prevalence [15]. The exact percentage of 'low prevalence' allowed within the normal population has been described for the wide-field technique, but not, as yet for the video-capillaroscopic technique.

What is considered abnormal due to SSc and other diseases of the scleroderma spectrum

The majority of patients with clinically recognisable (i.e., skin involvement) SSc show a very characteristic combination of capillary abnormalities in the nailfold, which can easily be assessed through qualitative assessment (i.e., pattern recognition).

Maricq et al. described with the wide-field technique (magnification: ×12–14) the scleroderma pattern defined as two definitely enlarged capillaries in at least 2/10 evaluated fingers [3].

Cutolo stated with the video-capillaroscopic technique that the presence of even one giant capillary should alert the clinical rheumatologist to underlying SSc [16].

Of note, the terminology of the wide-field technique is in line with the terminology of the video-capillaroscopic technique. In this way, the one quantitative study performed by Maricq in quantifying her 'definitely enlarged' capillaries reported comparable apical diameters as those defined by Cutolo as 'giant' capillaries.

Both terminologies refer to an apical diameter of at least 50 μm [17]. Additionally, the largest prospective study describing the microvasculature abnormalities in patients prone to develop definite SSc (more specifically those patients with both a scleroderma pattern and SSc-specific antibody at baseline, whilst demonstrating no sign of any CTD other than the presence of RP (i.e., early SSc according to LeRoy) attested the presence of giant capillaries to be the first specific microvascular sign in an 'early' SSc population [4].

These scleroderma-type changes are also seen in diseases other than clinically recognisable SSc such as patients with 'early' SSc (see below), DM, MCTD and undifferentiated connective tissue disease (UCTD).

Maricq et al. suggested that all these diseases may share some common pathogenetic factors and referred to these diseases as the family of scleroderma spectrum (SDS) disorders. Of note, out of all diseases belonging to the scleroderma spectrum, SSc is the sole one that can be pre-clinically detected by the combination of capillaroscopic and serological screening (see below).

In 2000, Cutolo et al. qualitatively assessed the nailfolds of an SSc cohort with patients fulfilling the American College of Rheumatology (ACR) criteria for SSc using the nailfold video-capillaroscopy (NVC) technique (magnification ×200) (Fig. 4).

According to the different proportions of the hallmark parameters of the scleroderma pattern (giants, capillary loss, micro-haemorrhages and ramifications; definitions, see below) Cutolo et al. defined three patterns as 'early', 'active' and 'late' [5].

What about patients with CTDs other than SSc and diseases of the SDS?

In contrast to SSc and diseases of the SDS, the other CTDs, such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), etc., do not have 'unique' capillary patterns. In these CTDs capillaroscopic images may be normal, show nonspecific findings or borderline changes.

A capillaroscopic image is interpreted as having borderline changes in two situations. First, when abnormal shapes (i.e., 'neo-angiogenesis', shapes differing form the normal (hairpin) and nonspecific variations (tortuosities or crossing)) occur in high prevalence within one subject. Second, when several of the following abnormalities occur together: shape abnormalities (neo-angiogenesis), confluent micro-haemorrhages or variations in dimension [15,18].

'Early' diagnosis of SSc

When patients with SSc meet the ACR criteria, they already have 'clinically recognisable' scleroderma (skin involvement) that can be classified as belonging to either the limited cutaneous (LcSSc) or the diffuse cutaneous subset (DcSSc). Patients with 'clinically recognisable' SSc have increased morbidity and mortality [2].

As yet, no treatment has been proven by randomised controlled trials to halt the natural progression of the 'clinically recognisable' disease. Consequently, efforts are being made to study the disease 'early', before the 'clinically recognisable' disease has set in and irreversible damage has occurred. LeRoy and Medsger proposed in 2001 criteria for the 'early' diagnosis of SSc, with RP as the single major criterion

[19]. These criteria incorporate SSc-specific auto-immune antibodies and microvascular techniques, more specifically the 'scleroderma-type' changes on capillaroscopy.

Like the ACR criteria, the LeRoy and Medsger criteria include patients with 'clinically recognisable' SSc (with skin involvement) LcSSc and DcSSc. However, in addition to that, they also allow patients to be included earlier before skin involvement has occurred.

Koenig et al. validated these LeRoy criteria in his recent prospective study of patients with RP but no other sign of any CTD at baseline [4]. In this study he described that patients with 'early' SSc changes progressed to SSc in 47% after 5 years and in 79% after 15 years. When both predictors are present the likelihood for development of SSc is highest. In this way 65.9% of patients with RP and both the scleroderma pattern on capillaroscopy and additionally an SSc-specific antibody develop SSc within 5 years. However, when only one of these two predictors is present the likelihood is much lower at $<$30%.

For this last-mentioned subgroup LeRoy and Medsger did not propose additional symptoms/signs/laboratory or investigational findings as inclusion or exclusion criteria in the prediction of SSc, which is a caveat of the 'early' LeRoy criteria.

Recently, new criteria were suggested by the EULAR Scleroderma Trials and Research group (EUSTAR), more specifically the VEDOSS criteria (Very Early Diagnosis of SSc) which try to circumvent this pitfall [20]. They consist of the following clinical symptoms and instrumental findings: RP, puffy swollen fingers turning into sclerodactyly, abnormal capillaroscopy with scleroderma pattern and positive anti-centromere (ACA) and anti-topo-isomerase (anti Scl-70) antibodies. These VEDOSS criteria are in line with the LeRoy criteria for 'early' SSc but differ as to the extent of cutaneous disease. The VEDOSS criteria have still to be validated.

How to interpret nailfold capillaroscopy in clinical practice in SSc

As mentioned previously, peripheral microangiopathy in SSc can be easily recognised and studied early in the disease course by the detection of the most important capillaroscopic changes associated with the presence of this secondary RP. These microvascular SSc alterations appear in a dynamic progression and represent the morphological expression of the pathophysiology of the disease that, together with the microvascular damage, will result in tissue fibrosis. The major morphological parameters that characterise SSc are the giant capillaries and the associated micro-haemorrhages when they start to collapse, the loss of capillaries and the neo-vascularisation (neo-angiogenesis) [8].

Giant capillaries and irregular enlargements

Homogeneously enlarged microvascular loops (giant capillaries) are the earliest and most striking feature of this secondary RP [4]. The enlargements show a characteristic symmetrical shape involving both afferent and efferent branches of the capillary, or a horse-shoe shape (with the diameter of the transitional limb being wider than the other two limbs) [16].

The detection of even a single loop with a homogeneous increase in diameter to $>$50 μm (giant) at the level of the nailfold should be considered a potential marker of microangiopathy related to an early SDS [16].

Generally, the capillary dilatations represent the first sign of micro-vessel wall damage (altered endothelial cell array).

The presence of homogeneously enlarged microvascular loops (giant capillaries) may be preceded and/or associated with irregularly enlarged microvascular loops (non-homogeneous capillary enlargements) that indicate an early partial damage of the capillary wall.

Micro-haemorrhages

Nailfold micro-haemorrhages are also linked to the altered integrity of the micro-vessel wall and altered endothelial cell array and they appear as an easily detectable dark spot.

Practically, micro-haemorrhages that arise from microvascular extravasation of red blood cells from the capillary loop (giant capillary close to collapse) migrate and bridge the appearance of giant capillaries, their incoming collapse and the subsequent loss of capillaries.

Of note, micro-haemorrhages may also occur in other CTDs and are a nonspecific finding. In addition they may be related to capillary thrombosis as in the antiphospholipid syndrome (APS) [18].

Capillary loss and avascular areas

A decreased number of capillary loops is characteristic of SSc. Through quantitative assessment, a decreased capillary density has been shown to be most predictive of secondary RP due to a scleroderma spectrum disease. More specifically, the loss of capillaries to a number <30 capillaries per 5 mm (in one nailfold) has a specificity of 92% [21].

The extensive disappearance of capillaries can generate large avascular areas, which have a desert-like appearance in the nailbed microvascular array. Loss of capillaries could be relevant in determining the severe tissue hypoxia that is involved in the development of digital skin ulcers and other clinical complications in SSc.

In patients with recent onset of RP, the appearance of rapidly progressive capillary loss can represent the first dramatic capillaroscopic evidence of destruction of the micro-vessels and the development of severe SSc [16].

Neo-angiogenesis (e.g., ramifications)

Capillary loss creates tissue hypoxia and local production of vessel growth factors (such as vascular endothelial growth factor, VEGF), which may be hypothesised to stimulate the formation of new capillaries – neo-angiogenesis.

The features of capillary neo-formation may be extremely heterogeneous and when appearing in high prevalence within a subject is seen almost exclusively in patients with late SSc, secondary RP associated with DM or MCTD.

Neo-angiogenesis characterises almost solely the advanced scleroderma 'late' capillaroscopic pattern.

The main morphological hallmark of (neo-)angiogenesis in advanced SSc is the clustering of twisted capillaries, with pronounced heterogeneity in shape and size, winding together with bushy capillaries. Rather than trying to describe the heterogeneity of morphology where (neo-)angiogenesis exists, an easy rule of thumb is to classify all shapes which are not 'normal' (hairpin) or 'nonspecific' (tortuous, crossing once or twice) as neo-angiogenetic.

(The count of neo-angiogenetic (new) capillaries should be done carefully in order to avoid mis-interpretations; of note giant capillaries almost never occur in late SSc, only possible abnormal dilatations of neo-angiogenetic microvessels.) These last easy rule-of-thumb definitions have been first used in a large pan-European study, evaluating the predictive capacity of capillaroscopy for digital ulcers in a prospective follow-up of SSc patients [31].

The scleroderma patterns

The above-discussed microvascular alterations characterise the scleroderma pattern and have been recently classified by Cutolo et al. into three defined and different NVC patterns that include an 'early' pattern (few giant capillaries, few capillary micro-haemorrhages, no evident loss of capillaries and relatively well-preserved capillary distribution), an 'active' pattern (frequent giant capillaries, frequent capillary micro-haemorrhages, moderate loss of capillaries, absent or mild ramified capillaries) and a 'late' pattern (almost absent giant capillaries and micro-haemorrhages, severe loss of capillaries with extensive avascular areas, neo-angiogenesis with ramified/bushy capillaries and intense disorganisation of the normal capillary array) [5]. (Fig. 3(b)–(c)).

As SSc is a disease with progressive obliteration of the microvasculature, the borders of the three NVC scleroderma patterns are delineated by more progressive loss of capillaries.

The reliability between different observers for classifying images has recently been attested [13].

(Semi-) quantitative assessment in SSc

Capillaroscopic characteristics can be quantified (counted per linear millimetre) or semi-quantified by giving a score between 0 and 3 per linear millimetre and calculation of a mean score over all evaluated fields. Both are being used in associative and prediction studies between capillaroscopy and clinical aspects of SSc (see below).

The semi-quantitative scoring has been attested to be reliable for the following parameters: loss of capillaries and giants and micro-haemorrhages and is calculated as follows. For loss of capillaries the scores are obtained by calculation of the percentage of loss versus the number of normally expected capillaries per millimetre: (0 = no changes, 1 = <33% of capillary alterations/reduction, 2 = 33–66% of capillary alterations/reduction, 3 = >66% of capillary alterations/reduction, per linear millimetre). Two or four fields per finger are evaluated. A mean score of capillary loss is obtained by adding all the scores and dividing the number of fields that have been evaluated, usually 16 or 32 per patient.

For the other capillaroscopic parameters the scores are calculated versus the numbers of capillaries that have been counted in the field of evaluation [14].

Reporting the capillaroscopic findings

The capillaroscopy report is the final statement of the examination, and it is the most important part of the capillaroscopic assessment. In the report, all the capillary features and abnormalities should be summarised in order to allow the reader (general practitioner and specialist) to better understand all the aspects of the microangiopathy.

The reader should be enabled to imagine the capillaroscopic pattern, as if he was performing the examination himself. Therefore, conclusions should be given, even if the report does not encompass a final definite diagnosis.

The following parameters should always be reported – morphology: normal shapes, hairpin; nonspecific changes: tortuosities and crossing (once or twice), neo-angiogenesis; density; dimensions: normal, ectasia or giants and the presence or absence of haemorrhages [8,22].

Optionally some other characteristics may be described (even though the literature has not attested the reliability concerning their interpretation).

In this way the capillaroscopist may comment on the following: skin transparency, dermal papillae, sub-papillary plexus, apical ectasia and capillary blood flow. The careful assessment and score of any of these items may provide important information.

The skin transparency may be reduced in non-white subjects, as well as in the presence of fibrosis or skin thickening, and this may reduce the quality of the pictures.

The number of capillaries inside each dermic papilla may vary under different clinical conditions: the papilla may be empty in scleroderma or contain more than two capillaries in hypoxic clinical conditions. The sub-papillary venous plexus is usually well evident in patients with rheumatoid arthritis, as well as in children; on the other hand, its dilation is common in acrocyanosis. Small apical capillary enlargements, variations, are frequently observed in normal subjects. On the contrary, the efferent (venous) capillary branch enlargement is often described in acrocyanosis, as well as in SLE patients.

Conclusions should either state a definite capillaroscopic diagnostic address, when possible, (e.g., normal, nonspecific changes or scleroderma pattern) or describe, in summary, the ‘non-specific’ capillary abnormalities (i.e., borderline changes, see above).

In scleroderma patients, also the stage of the microangiopathy should be reported: the ‘early’, ‘active’ or ‘late’ pattern (see above) [8,13,14,23,24].

It may be important (especially for the follow-up of the patient) to add (semi-)quantitative scores for the SSc-characteristic capillaroscopic findings (capillary loss, giants, haemorrhages and neo-angiogenesis). An example of a capillaroscopic report is shown in Fig. 5.

Of note, the capillary blood flow cannot be quantified by nailfold capillaroscopy, even if the capillary column of red blood cells may be observed moving inside the capillaries from the arteriolar to the venous branch; only qualitative (morphologic) information may be collected concerning blood flow (regular, slowed down).

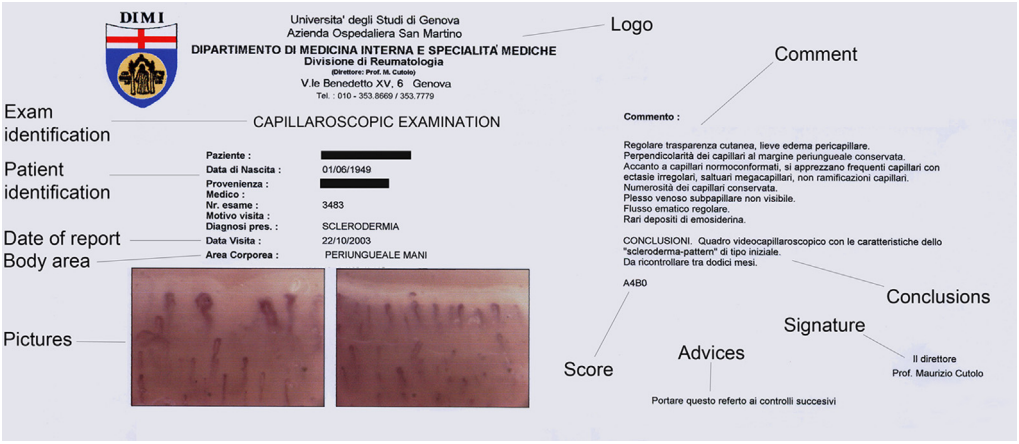

Fig. 5. Example of a capillaroscopic examination report as is adopted at the Academic Unit of Clinical Rheumatology of Genova (patient data deleted to respect the privacy).

The blood flow is usually slow in patients with RP and scleroderma micro-angiopathy, as well as in subjects with other vasospastic conditions. Laser techniques, such as laser Doppler flowmetry and laser speckle contrast analysis (LASCA), may be employed to quantitate blood perfusion at peripheral sites [25–27].

Finally, the capillaroscopic examination may be extended by undertaking further serological testing. In addition, a follow-up visit should be incorporated into the report: after 3 months in the borderline cases, after 6 months in early scleroderma or in drug-treated scleroderma patients and after 12 months in PRP.

Clinical applications of capillaroscopic assessment in RP and in SSc

In RP both qualitative and (semi-)quantitative assessment play an important role. Qualitative assessment by itself is enough to make a differential diagnosis between primary RP and SRP due to SSC [28]. Quantitative assessment attests a microvascular evolution in patients with 'RP ± a scleroderma pattern on capillaroscopy' and/or an SSc-specific antibody ('early SSc'), prone to develop SSc.

In this way quantitative assessment has attested giant capillaries to be the first capillaroscopic alteration in a Raynaud's population which met the criteria for 'early' SSc. Capillary loss (see above) occurs the moment that clinically overt SSc sets in.

Further, in an SSc population itself both types of assessment have merits. In this way the natural evolution during follow-up over time of the capillaroscopic images of an SSc population has been described and is characterised by diminishing of the prevalence of giants and capillaries and augmentation of neo-angiogenesis, as assessed (semi-)quantitatively [14]. In addition, the qualitatively assessed scleroderma patterns may also evolve over time [24].

Both qualitative and (semi-)quantitative capillaroscopic assessments are associated with clinical complications in SSc. In this way associations with pulmonary arterial hypertension, interstitial lung disease, peripheral vascular disease and also with the severity of peripheral vascular disease, heart and lung involvement assessed by the disease severity scale of Medsger have been attested [28].

In addition, capillaroscopy seems to be a putative biomarker for future complications in SSc such as digital trophic lesions [29,30].

These path-finding studies encouraged the European rheumatology community to set up a multicentre study (CAP study) to investigate the role of capillaroscopy in predicting new digital ulcers, 6 months after the baseline capillaroscopic visit [31]. The early results confirm the predictive and prognostic role of video-capillaroscopy at least in SSc patients.

Conclusions

Video-capillaroscopy, being a safe and reliable technique, is considered fundamental for the early differentiation of the transition from primary to secondary RP through the detection of the different and progressive scleroderma patterns [32].

Validated scoring of the capillaroscopic markers of the scleroderma patterns is recommended for the follow-up of SSc patients.

The prognostic and predictive value of capillary density (number of capillaries) is becoming an index of outcome in patients affected by SSC.

Conflict of interest

No conflict of interest from the authors.

Practice Points

- Patients affected by Raynaud's phenomenon should always be examined by nailfold capillaroscopy at least once a year, as 15% of them after an average period of 3 years might develop systemic sclerosis (SSc).
- Changes in the number of capillaries (decrease) in SSc patients as evaluated by nailfold capillaroscopy are predictive of clinical complications (i.e., digital ulcers) as recently validated.
- The nailfold capillaroscopic analysis must be extended in each patient or suspected patient to all eight fingers in order to detect correctly the early morphological markers of microvascular damage.

Research Agenda

As recently done with specific autoantibodies, further larger-scale studies, both cross-sectional and longitudinal, are required and are ongoing to examine the associations between capillaroscopic findings and other parameters/biomarkers of disease (i.e., angiogenic/static factors).

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