Clinical Rheumatology (2022) 41:3629–3640
https://doi.org/10.1007/s10067-022-06354-1

REVIEW ARTICLE

Nailfold capillaroscopy: tips and challenges

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Received: 7 June 2022 / Revised: 22 August 2022 / Accepted: 23 August 2022 / Published online: 30 August 2022

Abstract

Although nailfold capillaroscopy (NFC) appears to have a bright future in clinical practice, the lack of familiarity with the technique and how to interpret its outcomes is major barriers which have made nailfold capillaroscopy an underutilized method in standard clinical practice. Traditional methods for assessment and measurement of capillary patterns, density, and blood flow are falling behind and face some challenges. In fact, there have been calls for improvement, hence the recent publication of the standardization of NFC by the EULAR Study Group on Microcirculation in Rheumatic Diseases. Nailfold capillaroscopy has the advantage of being a non-invasive technique that provides a window into the digital microcirculation. This paved the way for a rapidly growing interest in using capillaroscopy parameters as outcome measures in research. In standard clinical practice, whilst its main application is in the identification of an underlying systemic sclerosis spectrum disorder in patients presenting with Raynaud's phenomenon, its use has expanded to include other clinical features possibly suggestive of an underlying connective tissue disease. This article presents the challenges, provides tips, and highlights the exciting potential of nailfold capillaroscopy in standard practice.

Keywords Blood flow · Challenges · Connective tissue disease · Microangiopathy · Musculoskeletal diseases · Nailfold capillaroscopy (NFC) · Raynaud's phenomenon · Standards · Systemic sclerosis · Tips

Introduction

Observing microcirculation in the capillaries of the living skin has highlighted the importance of microcirculation as a central target organ, both in critical illness and a marker of inadequate response to therapy. Microcirculation is the final destination of the cardiovascular system which plays a vital role in the homeostasis process. It also provides oxygen and hormones as well as nutrients to the cells, and in the meantime, it eliminates the metabolic waste [1]. Its direct contact with the parenchymal cells, as well as its value in providing clinically relevant information, has provided enough evidence for microcirculation to be the most important component of the cardiovascular system.

Microvascular dysfunctions represent an integral primary pathology in several illnesses such as rheumatic diseases (particularly connective diseases), cardiac, blood, and endocrine disorders (particularly hypertension and diabetes mellitus). In systemic sclerosis, it seems to represent the underlying pathology basis of progression towards a systemic fibrotic disease [2, 3]. Furthermore in Raynaud's phenomenon, assessment of nailfold microcirculation assists in demarcating primary from secondary Raynaud's which can be linked to the underlying connective tissue disease. A meta-analysis concluded that capillaroscopy is the best predictor biomarker for the transition from a primary to secondary Raynaud's [4].

Nailfold capillaroscopy is a simple, non-invasive, safe, reliable, and inexpensive tool to morphologically study the nail microcirculation [5]. It is usually performed manually by trained

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healthcare professionals and particularly rheumatologists. Having good experience with the NFC technique is vital as the window of opportunity of early systemic sclerosis (SSc) diagnosis might be missed. Unfortunately, so far, most of the work done on NFC relies on subjective evaluation, and the scores calculated are based on qualitative or semi-quantitative assessments. This highlights the real need for a targeted NFC assessment approach using an objective technique which not only would facilitate early diagnosis but also track changes as well as progression over time. This in turn would pave the way for widening the NFC clinical application beyond early diagnosis to monitoring of the disease activity status and response to therapy [6].

This article presents the challenges, provide tips, and highlights the exciting potential of NFC in standard practice. It will start by discussing the nailfold image acquisition and interpretation, the best equipment to use, and which fingers to be assessed. The article will then discuss the potential for precise acumen between normal and abnormal capillaries and how recent approaches for semi-automated and automated analysis have been developed based on the earlier published data on qualitative, semi-quantitative, and quantitative analysis. The article will conclude with discussing the structural versus functional assessment of the capillaries and the challenge of NFC reporting as well as the integration of NFC into the rheumatology fellow curriculum.

Search strategy

Studies published from January 2000 up to March 2022 have been gathered from "PubMed," "Embase," and "Cochrane" databases by employing a systematic literature search. The inclusion criteria include the following: systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational studies including cohort, case control, and cross-sectional studies. The exclusion criteria are as follows: editorials, commentaries, conference abstracts, and non-evidence-based narrative/personal reviews, as well as manuscripts lacking the English version. The duplicate references have been excluded. All the relevant literature in English language has been searched. Boolean operators "AND" and "OR" together with keywords such as "capillaroscopy," "nailfold capillaroscopy," "video nailfold capillaroscopy," and "nailfold video capillaroscopy" have been included to ensure the specificity of the search.

The search results have been reviewed and discussed by two independent reviewers. The full texts of articles that seemed to comply with the set of criteria in this study were obtained and checked for relevancy by the reviewers. The discrepancies between the abstract and the content of a manuscript were discussed as necessary, and a discretionary decision was made as to include or exclude a specific article.

Equipment

One of the major challenges in testing nail microcirculation is the device used for assessment. Being an in vivo imaging tool, the nailfold capillaroscope is expected to provide a magnified view of the nailfold microcirculation structural aspects. Initially, ophthalmoscopes and traditional microscopes have been used in clinical practice. Their advantages are that they are widely available, there are low-cost options, and they require minimal training. Similarly, dermatoscopes are portable devices which enable nailfold capillary viewing. Whilst dermatoscopes come at intermediate cost, in contrast to ophthalmoscopes and traditional microscopes, the 3 equipment (the traditional microscope, ophthalmoscope, and dermatoscope) only provide low magnification power. The stereo microscopes have been used in several centers as they are handy and easy to use with higher magnification power and of intermediate cost. However, stereo microscopes cannot be used for patients with joint contractures [7, 8].

By using an adapted dermatoscope or macrophotography lens, smartphones can be adapted for capillaroscopy. The use of the smartphone dermatoscope and smartphone lens was assessed. Whilst being novel and relatively inexpensive portable devices, both tools showed acceptable performance even in the novice hands. When tested for their ability to distinguish "non-scleroderma" from "scleroderma patterns," both devices showed high specificity but a lower sensitivity when compared to the wide-field microscope [9]. Based on that, it has been suggested that both the smartphone and the dermatoscope may be used as screening tools when the gold standard, the NFC, is not available.

The digital video capillaroscope (DVC) is the gold standard device. It is composed of an optical microscope combined with a digital video camera and connected to a computer. The facility of combining co-axial illumination of the field together with a highly sensitive camera facilitates the acquisition of high-resolution quality images. Furthermore, digital filters, e.g., gray scale, watershed, and top-hat filters, can be applied to separate the relevant areas from the image background. With the aid of software, the standard computers can be used to assess the acquired images and quantitatively score them [10]. Despite being the most expensive option, it has the advantages of being a portable, handheld probe which can be used in the clinic as well as for bedside examination, even for those patients with severe flexion contractures [11]. Whilst there is a broad range of magnification power ranging between 50 × and 500 ×, the most commonly used devices are those with magnification power of 200 ×. At magnifications higher than 600x, the blood cells inside the capillaries can be visualized.

The DVC has also shown reliability in discriminating the normal capillaroscopy exam from the specific patterns

reported in systemic sclerosis [7]. However, under certain conditions such as when the patient's skin around the nail is thick, video capillaroscopy does not provide comprehensive images of nailfold microvasculature [12, 13]. Due to the fact that tissues strongly scatter light, the penetration depth of most of the commonly used optical microscopy tools is limited to approximately 200 μm [9]. In concordance, the penetration of the bright-field microscopy used for capillaroscopy may even get shallower (few tens of micrometers) [14]. Consequently, the arterioles and venules lying below the capillary loops may never be observed. The use of linkage fluid (immersion oil, ultrasound gel, etc.) increases the transparency and resolution of the attained images.

Nailfold video capillaroscopy has some extra advantages such as the real-time control of the image obtained, the fidelity of image storage and reproduction, the advanced image analysis, and the measuring features [15]. A further advantage is the presence of a contact probe with polarized light microscopy which allows an easier visualization of the microcirculation [16]. Moreover, the training period for the use of the video capillaroscopy is brief because of the simplicity of the equipment [17]. In comparison to the fixed stand microscope system which cannot be used for hand deformities, the portable USB system capillaroscope makes the examination feasible in such cases. Though other devices are also available to analyze the microcirculation in detail, including flow Doppler ultrasonography and laser Doppler perfusion imaging, in general the video capillaroscope remains the most appropriate device for both clinical and research purposes and is considered the preferred option for standard practice as it can be used with the widest range of patient population. [18].

In addition, the "mesoscopic" technique has been described as an ideal approach to achieve robust and complete imaging of the nailfold microvascular structure. This approach means it is possible to view and record images at depths of at least 1–1.5 mm in order to reach the whole of the skin depth. This is applicable whilst maintaining a resolution of ~ 5–10 um so that it is possible to see the smallest capillaries and venules as well as the arterioles that lie under the epidermis regardless of its thickness [14]. However, whilst optical coherence tomography (OCT) meets this imaging need and has been used to assess nailfold microcirculation by researchers [19–21], adapting this technique to see the microvasculature reduces the axial resolution severely. This has been attributed to the inherent imaging artifacts which then leads to a penetration depth of only #450 um [22]. Therefore, the ability of OCT to provide highly accurate 3-dimensional images of the nailfold microvascular structure was hampered by these drawbacks [23].

An alternative approach for microcirculation imaging is the clinical ultra-wideband raster scan optoacoustic mesoscopy (UWB-RSOM). This is a more powerful technique that has been recently developed with the ability to resolve the skin microvascular structure in label-free mode and a resolution around 10 μm [22, 24–26]. UWB-RSOM can reach a penetration depth of 5 mm whilst keeping high resolution. Its contrast mechanism is based on light absorption. Bearing in mind that hemoglobin is one of the strongest visible light absorbers in tissue, this gives UWB-RSOM technique superior microcirculation imaging capabilities in contrast to the other label-free mesoscopic techniques such as the optical coherence tomography or high-frequency ultrasound imaging [22]. The nailfold microvascular structure was assessed in a recent study using ultra-wideband raster scan optoacoustic mesoscopy. Results established the potential role of UWB-RSOM for analyzing SSc-relevant markers [27].

However, in general, the video nailfold capillaroscopy remains to be the most widely available non-invasive tool for the assessment of the microvascular structure which occurs in systemic sclerosis as well as other connective tissue or systemic diseases.

Lastly, one of the major challenges in standard practice is in the acquisition of a nailfold capilloroscope. Perhaps this is one of the causes why nailfold capillaroscopy is barely used in routine clinical practice. One of the key reasons is the perception that the equipment needed to perform and document NFC is very expensive. Whilst this is true for high-end automated systems, these are not required in a typical clinical setting. High-end USB capillaroscopes adequate for formal NFC assessment in standard practice are available at costs that are entirely affordable (€600–700). These systems are very easy to use and provide image capture and magnification levels of that are ideal for NFC assessment. Such pricing may help to break down the resistance to purchasing systems for routine use in a clinical practice.

Image acquisition

The overall reliability of the NFC procedure is influenced by the main factors of image acquisition — their interpretation — particularly when acquired at several time points. The target area for video recording in standard clinical practice is the distal layer of the capillaries that lie under the papilla. In standard practice, capillaroscopy images are acquired at several time points. After focusing the instrument, normally, one still image and a 10-s video frame are captured at the midline of a nailfold.

Consequently, only one quarter of the nailfold area can be covered by each capillaroscopic image in standard imaging. A software that merges adjacent images has been developed to facilitate building up of a panoramic "mosaic" of the entire nailfold at 300 × magnification in order to obtain

a wider view of the nailfold area [28]. This series of partially overlapping images (about 4–12 images) taken from the very left to the right are expected to cover the whole nailfold. The reliability of image acquisition is vital particularly in longitudinal studies or when the patients are monitored for disease progression or response to therapy. Having a wide panoramic mosaic view of the whole nailfold is crucial for pattern recognition [29] and essential for quantitative measurement. Considerable heterogeneity in capillary appearances across a nailfold has been reported [27], which consequently would impact negatively on the capillaroscopy outcomes and scores; therefore, selecting only a 1-mm section would be unrepresentative.

Modern software is also able to merge a sequence of 16 video frames; hence, it enhances image quality [6]. This technique enables tackling of the challenge of "ghost capillaries" (Fig. 1g). This term refers to some of the capillaries which are difficult to visualize as they are not perfused. This is based on the fact that capillary walls are invisible and that what is visualized and imaged is the column of red blood cells within the capillary. This has consequent implications for quantitative analysis of the images such as capillary density and width.

Which fingers should be assessed?

As the use of capillaroscopy becomes more popular in standard clinical practice, a key question for busy healthcare professionals is "how many fingers should be assessed?" The challenge is that nailfold morphology can differ significantly between nailfolds and abnormalities may only be visible in some but not all fingers. It is generally accepted that if abnormality exists in any finger/nailbed, then that patient has abnormal nailfold capillaries and graded according to the abnormality in that individual finger.

The gold standard for nailfold capillaroscopy is to assess eight fingers, omitting the thumbs (which are often difficult to visualize/classify the capillaries) [30]. Several studies were carried out to assess for the option of assessing lesser fingers. A study [31] suggested that if a clinician is pressed for time, the best two-finger combination is both ring fingers, giving a sensitivity of 59.8% for detecting either giant vessels or an abnormal image grade. A four-finger combination of both middle and ring fingers increases the sensitivity to 66.7%. However, this was not based on quantitative analysis but on the presence of either giant capillaries or an "early," "active," or "late" SSc pattern [32]. Other studies suggested the fourth and fifth fingers of both hands for having the highest skin transparency; therefore, it was concluded that the most precise morphologic evaluations can be obtained from these two fingers [33, 34].

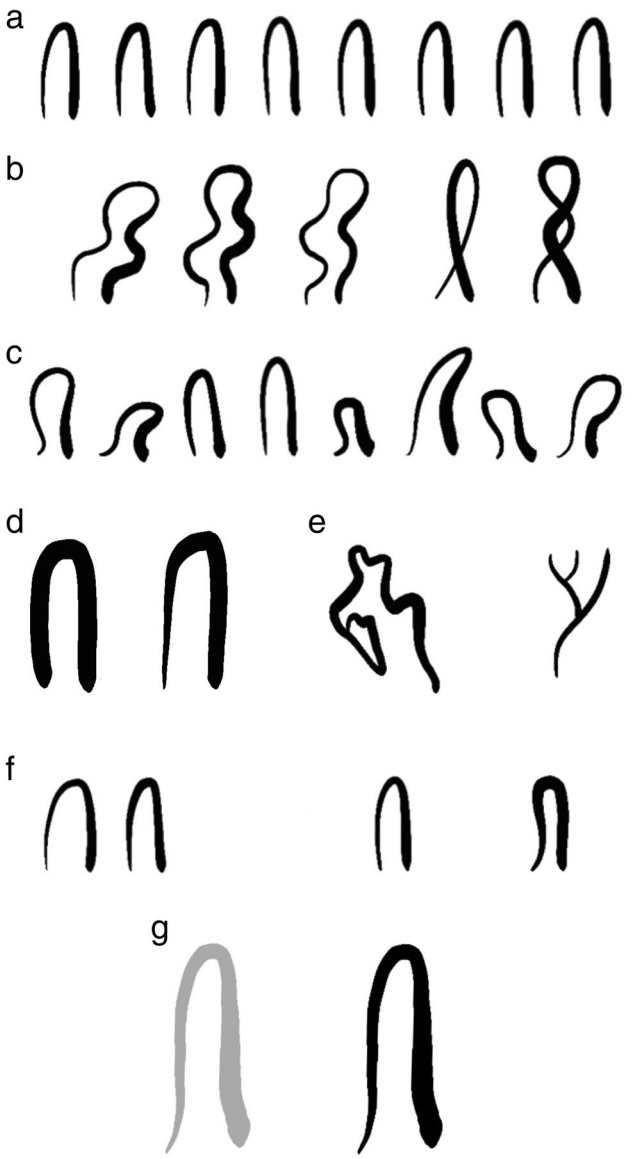

Fig. 1 Patterns of nailfold capillaries: **a** normal capillary arrangement (7 capillaries/1 mm); **b** nailfold capillary, non-specific variation; **c** architecture, capillary disarrangement; **d** diameter, capillary regularly enlarged–irregularly enlarged; **e** morphology, serpentine-branched; **f** density, enlarged capillary and avascular areas; **g** a "ghost" capillary can be viewed in sequential video frames (panoramic mosaic of the whole nailfold)

In a conclusive trial, it can be suggested that the optimal number of nailfolds to be examined is likely to be linked to the question being asked. In a study [35] carried out to predict digital ulcer risk using capillaroscopy, results revealed that eight fingers (at least one field per finger) should be assessed, whereas another study [36] suggested that examining the middle finger of the dominant hand was adequate. Another work carried out to monitor changes in the nailbed microcirculation in response to therapy supported the imaging of eight fingers [37].

Image interpretation

Interpretation of the NFC images is another major challenge in standard practice. Not only for its value in making the diagnosis and follow-up of systemic sclerosis patients, but also for its usefulness in other connective tissue diseases (though its value remains controversial in the later cohort of patients). Therefore, it is vital to optimize the NFC outcomes and its predictive ability, bearing in mind that several patients are referred for capillaroscopy assessment particularly those with Raynaud's phenomenon. To achieve such a target, NFC images should be interpreted jointly with the autoimmunity blood tests results, and on occasions, a gradual follow-up may even be required to monitor the changes in the capillaroscopic pattern over time, particularly in those patients whose immunology profile show positive ANA > 160 titer [38, 39]. Earlier research studies revealed that the presence of a non-pathological capillaroscopy pattern together with negative autoantibodies profile has a high predictive negative value leading to the ruling out of a systemic disease [40, 41].

The normal appearance of the nailbed which will also identify primary Raynaud's phenomenon and distinguish it from secondary Raynaud's appears in the form of non-dilated capillaries which are parallel to one another and perpendicular to the nailbed. A normal NFC does not present with neoangiogenesis, microhemorrhages, or giant capillaries. In regard to cut-off measures for what is a "normal" capillary density (Table 1), a wide range of densities was reported in healthy controls which tended to be in the range of 7–10/mm. As far as the normal capillary dimension, normal capillary width of limbs was reported to be < 20 μm, with the absence of large confluent bleedings, as well as "non-specific abnormalities" (Table 2) [42]

Patients with "early" SSc should have Raynaud's phenomenon plus SSc-specific antibodies (e.g., anti-CENP-B, anti-Th/To, anti-topo I, or anti-RNAP III) and/ or a "scleroderma pattern" on nailfold capillaroscopy [40–43]. The early scleroderma pattern is characterized by the presence of capillary afferent and efferent loop dilatations in addition to giant capillaries (> 50 μm), with the maintenance of a normal capillary density and without any microhemorrhages

Table 1 Normal nailfold capillaroscopy pattern

Normal (healthy pattern)	Description
Visibility/view	Homogenous size, regular alignment of the capillaries (Fig. 1a)
Orientation/pattern	Parallel, perpendicular to the skin, and straight
Density	> 7 capillaries/1 mm
Morphology	Hairpin shape, inverted "U"
Morphology variation	Tortuous and/ or crossed capillaries
Length	< 300 um
Diameter	< 20 um (afferent, apical, efferent) per each capillary loop
Subpapillary venous plexus	Can be seen in up to 30% of healthy subjects
Edema	Absent
Hemorrhage	Absent (can be seen if there is history of trauma)
Giant capillary	Absent
Neoangionesis	Absent
Blood flow	Dynamic, no stasis

Table 2 Non-specific nailfold capillaroscopy pattern

Parameter	Non-specific variation of the normal pattern	Description
Visibility/view	Tortuous capillaries:	Undulated loops but do not cross
	Crossed capillaries (Fig. 1b)	Loops crossed once or twice
Orientation/non-specific abnormal morphology	Ectasia (dilated/enlarged capillaries) (Fig. 1d)	Moderate enlargement of the limps; range, 4 and 10 normal sizes
Density	Meandering capillaries	Loops crossed upon themselves several times
Morphology	Bizarre capillaries	Atypical non-classifiable morphology, rare forms that cannot be integrate as hairpin, tortuous, or crossed
Morphology variation	Peri-capillary edema	Like flu contour surrounding the capillary
Diameter	Slightly increased diameter	Diameter greater than 15 μm for the arterial loop and 20 μm for the venous but less than 50 μm

[42]. The active scleroderma pattern is characterized by the presence of capillary dilatations. Trombetta et al. [44] suggested a threshold value of 30 μm for "average" capillary diameter (the average of the largest arterial, apical and venous diameters in each image, across at least 16 images, as a predictor of systemic sclerosis development in patients with Raynaud's phenomenon), neoangiogenesis, or avascular areas accompanied by capillary microhemorrhages. The late scleroderma pattern is characterized by the presence of mega-capillaries, reduction of capillary density, vascular areas, and neoangiogenesis (Table 3) [45].

However, whilst identifying the normal as well as the specific systemic sclerosis patterns represents the undisputed facts, the non-specific NFC patterns remain a challenge. A variety of "non-specific" capillary abnormalities have been observed in association with different connective tissue as well as systemic diseases; however, no "unique" capillary patterns have been identified in association with a specific disease. Non-specific abnormalities may appear in variable forms such as lowered capillary density, change in capillary dimension (e.g., "elongated" capillaries, "widened" loops), prominence of the subpapillary plexus, hemorrhages, and abnormal shapes (e.g., "bushy" capillaries, "bizarre" capillaries) [46]. These abnormalities on their own are not predictive of any distinct condition and may be referred to as "non-specific abnormalities." The fact that "non-specific abnormalities" appear in primary Raynaud's may sometimes represent a challenge in differentiating primary from secondary Raynaud's. Generally, when these abnormalities appear in isolated or uncommon patterns, they may represent variation of normal. On the other hand, when the abnormalities are frequent or when several abnormalities occur in one individual, they are suggestive of an underlying connective tissue disease [42].

The normal, non-specific, and the specific patterns

It was estimated that only about 40% of the general population has a pattern with completely normal capillaries, whilst in 50%, minor abnormalities are found [47]. In healthy subjects, nailfold capillaries have a hairpin shape, but variations like tortuous (serpentine loops without crossing each other) and crossing (capillaries that cross more than one time) have been identified for the normal pattern. In addition to these three shapes (hairpin, tortuous, crossing), all the other patterns are defined as abnormal morphologies. Meandering capillaries (another pattern which has loops crossed upon themselves several times) is considered one of the non-specific patterns. By themselves, these morphology abnormalities are not specific or predictive of any defined disorder. On the other hand, giant capillaries, microhemorrhages, avascular areas, or neoangiogenesis are not described in healthy subjects but as part of the scleroderma pattern. In late stages of scleroderma spectrum disorders (SSD), twisted and bushy capillaries are found as a result of neoangiogenesis [42] (Table 4).

Scleroderma spectrum disorder

In addition to its role in the diagnosis of SSc, NFC assessment has also been of value for the diagnosis and monitoring of scleroderma spectrum diseases. These include dermatomyositis (DM), polymyositis (PM), mixed connective tissue disease (MCTD), and undifferentiated connective tissue disease (UCTD) [48]. The "scleroderma spectrum" diseases might represent a challenge to healthcare professionals carrying out NFC to assess their patients. In the study carried out by Cutolo et al. [49], it was reported that the characteristic abnormalities of SSc which may occur in other "scleroderma spectrum" diseases should be defined as "scleroderma-like pattern" microangiopathy. These affects about 20 to 40% of patients with idiopathic inflammatory myopathies more often in DM than in PM. In contrast to the scleroderma spectrum diseases, the other connective tissue diseases, e.g., systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, and antiphospholipid syndrome, do not have "unique" capillary patterns, and a variety of "non-specific" capillary abnormalities have been reported, including change in the capillary dimensions (for example, elongated widened or elongated capillaries), lowered capillary density, prominence of the subpapillary plexus, hemorrhages, or abnormal shapes (e.g., "bushy" capillaries, "bizarre" capillaries) [46, 50]. By themselves, these abnormalities are not predictive of any defined condition and can be referred to as "non-specific abnormalities." Furthermore, whilst capillary abnormalities (avascular fields, giant capillaries, reduced capillary density, and capillary oedema) were closely related to an ANA titer > 1:160, a weaker correlation was found between capillary abnormalities and ANA subsets including U1RNP antibodies (MCTD), anti-SSA(Ro), and anti-SSB(La) (Sjogren's syndrome) [51].

Scoring: qualitative, semi-quantitative, and quantitative assessment

Remodelling of the blood vessels by changing their number, length, diameter, tortuosity, and wall thickness reflects permanent structural changes in the microcirculation over time or consequent to illnesses. With age, the capillaries have a tendency to become dilated and tortuous in older adults though their shapes may remain unchanged for several years. On the other hand, diseases might induce changes in

Table 3 Scleroderma capillaroscopy pattern

Parameter	Scleroderma pattern	Description
Pattern	Early (no obvious loss of capillaries: normal capillary density > 7 capillaries/mm, preserved architecture)	Density: > 7 capillaries/1 mm linear. Few giants (homogenously enlarged all three capillary limbs with diameter > 50 µm). Morphology: hairpin shaped capillaries. Hemorrhages: present (few dark spots)
	Active (moderate loss of capillaries: low capillary density < 7 capillaries /m) combined with giant capillaries	Density: 4–6 capillaries/1 mm linear. Dimension: presence of giants (frequent, diameter > 50 µm). Morphology: hairpin shaped capillaries with presence of abnormally shaped capillaries (tortuous/crossed) (Fig. 1c) Frequent microhemorrhage: present
	Late (loss of capillaries combined with abnormal shapes. Severe architecture damage. Giant capillaries never seen)	Density: < 3 capillary/1 mm (avascularization) Dimension: not measured because of abnormal shape. Morphology: disorganization, presence of abnormal shaped capillary (several bush and ramified capillaries) Neoangiogenesis Hemorrhage: absent
Density	Avascular area (Fig. 1f)	Loss of capillaries, reduced density: loss of contiguous capillaries. Distance > 500 µm between adjacent capillaries. Less than 30 capillaries / 5-mm
Morphology	Neoangiogenesis Ramified capillaries:	Twisted or bushy capillaries: new vascular formation, highly heterogenous shape, branched capillaries (Fig. 1e) There are abnormal connections between arterial and venous limbs or different capillaries
Morphology variation	Hemorrhage	Micro-bleeding: hemosiderin deposits appear as dark spots. Erythrocyte microvascular extravasation
Diameter		Giant capillaries: enlarged all three capillary limbs with diameter > 50 µm

Table 4 Capillaroscopy microangiopathy pattern: scleroderma spectrum disorder vs non-scleroderma spectrum disorders

Scleroderma spectrum disorders	Non-scleroderma spectrum disorders
Dermatomyositis (DM): -Observed in 20–40% of the patients -Increased neoangiogenesis (bushy, dendriform vessels) -Moderate derangement of the vascular architecture with a relatively low number of avascular areas -A characteristic feature: presence of giant ramified vessels -Significant correlation between capillaroscopic changes and DM activity (CK serum level) -Capillaroscopic abnormalities seem to be related with disease duration: in the first 6 months of disease duration, capillary density is usually reduced, and giant capillaries are frequent; after that period, scleroderma pattern becomes more common -Dynamic changes of the capillaroscopic pattern in response to therapy	Rheumatoid arthritis: -Prominent subpapillary plexus -Elongated capillaries -Increased capillaries tortuosity (may be seen) Psoriatic arthritis: -Tight terminal convolutions -Shortened capillaries -Lower density (compared to healthy subjects) Systemic lupus erythematosus -Increased capillaries tortuosity -Prominent venous plexus -Elongated capillaries -Meandering loops -Rarely, focal area of capillaries loss -In some, increased subpapillary venous plexus visibility -A correlation between NFC abnormalities and clinical and laboratory parameters was established -A relationship between NFC score and SLE activity was reported
Mixed connective tissue disease (MCTD) -Observed in 50–60% of the patients -Presence of enlarged or giant loops -Avascular areas/capillary drop out (but less than SSc) -Neoangiogenesis -Nonspecific abnormalities or borderline lesions -Usually associated with a positive anti-RNP antibody	Sjogren's syndrome -Tortuous and irregular capillaries -In some, increased subpapillary venous plexus visibility Antiphospholipid syndrome (APS): -Symmetric microhemorrhages (especially for secondary APS) -Variations of loop lengths (especially primary APS) Vasculitis -Microhemorrhages -Avascular areas Diabetes mellitus -Tortuosity -Capillaries with bizarre shapes -Loop dilations -Avascular areas -No differences were reported between type 1 and 2 DM -Microvascular complications detected with NFC were correlated with diabetic peripheral neuropathy

the peripheral circulation in early stages. Monitoring of such changes is vital in the disease monitoring process. Scoring of the NFC images represents a challenge in the standard practice. Although the possibility of obtaining more information from a quantitative approach is attractive, the visibility of these changes through capillary microscopy has prompted the use of a qualitative approach [52].

In qualitative assessment (i.e., pattern recognition), an overall interpretation is given after observing the visibility of the image, the morphology of the capillaries, and the density and dimensions "at sight" of the capillaries and their architecture. However, in contrast to the qualitative assessment that facilitates the differentiation between a normal capillaroscopic image and nonspecific changes from an abnormal capillaroscopy due to a scleroderma spectrum disease, semi-quantitative and quantitative NFC methods may provide more accurate and measurable valuations.

Capillary density, diameter, and the number of the variable capillary abnormalities can be assessed quantitatively by counting the number of each on either side at 1 mm of the reference point on all fingers [53]. Such semi-quantitation, which is mainly based on giving a score between 0 and 3 per capillaroscopic parameter, has been used in association and prediction studies between capillaroscopy and clinical aspects of systemic sclerosis. Another semi-quantitative scale was suggested in the study carried out by Maricq's study [54]. A semi-quantitative rating scale was used to score microvascular parameters such that 0 = no changes, 1 = ≤ 33% of capillary alterations/reduction, 2 = 33–66% of capillary alterations/reduction, and 3 = ≥ 66% of capillary alterations/reduction, per linear mm. This was found to be a sensitive tool to monitor and quantify the systemic sclerosis microvascular damage within the three qualitative NFC patterns (i.e., "early", "active" and late") [55].

In NFC quantitative assessment, capillaroscopic characteristics (i.e., capillary: density, dimension, and morphology as well as absence/presence absence of hemorrhages) are standardly evaluated per quantity unit such as per linear mm.

Capillary density as quantitatively assessed by NFC has been reported to be the most reliable capillaroscopic parameter and has been implemented for the prediction of disease progression as well as to monitor response to therapy in this patients' cohort [55–58]. Furthermore, several predictive scoring systems in systemic sclerosis have relied mainly on capillary density to provide its estimated score. These include the "Capillaroscopy Skin Ulcer Risk Index" (even though the strongest predictor for future development of digital ulcers is the positive history of digital ulcers), the "Microangiopathy Evolution Score" (MES), and the simple day-to-day risk index, to predict digital trophic lesions in systemic sclerosis [55, 59, 60].

Although being the most precise, the quantitative approach was reported to be time-consuming and difficult to use in clinical practice [10]. This paved the way for the development and introduction of automated and semi-automated NFC analysis and scoring. Automation of measurement has the advantage of removing the subjectivity from the NFC image assessment and enabling almost instant image analysis. One of the recently introduced automated systems is the "Manchester system" which includes a "video-microscope mounted on a software-controlled three-axis motorized stage together with image acquisition and analysis. This permits a series of high-magnification images to be captured rapidly as the microscope is moved under software control across the nailfold (~ 1 min per finger). A high-quality static whole nailfold capillary image mosaic is generated by automatic connection of the images from which fully automated measurements of the capillary structure and flow are derived. The structural measurements include capillary density, mean capillary width (the mean of the individual capillary widths), maximum capillary width (the largest of the individual capillary widths), and shape score (the mean vessel tortuosity) as well as derangement score (the angular dispersion of the capillaries). These structural measurements are combined to give an abnormality score, which allows patients with systemic sclerosis to be distinguished from those without (healthy controls and patients with primary Raynaud's phenomenon), with an area under the receiver operating characteristic (ROC) curve of 0.919" [6].

Blood flow measurement: moving from structural to dynamic functional assessment

Most of the published research and clinical applications of NFC focused on analysis of the NFC images which merely describes the microvascular structure. On the other hand, capillary flow which reflects an aspect of function potentially provides extra insight into the disease (e.g., systemic sclerosis) pathogenesis, measurement of the disease activity, and response to management. In the study carried out by Mugii et al., RBC velocity was reported to be reduced in both systemic sclerosis and dermatomyositis patients compared to healthy controls, although the difference was not significant in dermatomyositis patients [61, 62]. Furthermore, the red blood cell velocity was found to be sensitive to change. In the study carried out by Mugii et al., blood flow in the fingernails was increased after treatment with alprostadil in systemic sclerosis patients [61] as well as in hypertensive patients treated with moxonidine and cilazapril therapy [63], reflecting its applicability for functional assessment of the fingernail microcirculation. Adding the functional assessment represented by the blood flow to structural measurements, was reported to enhance the ability to discriminate between systemic sclerosis patients and those with primary Raynaud's or healthy controls [64].

Measurement of the capillary blood flow is by itself a challenge. Early studies estimated the flow at manually selected points or vessels which leads to subjectivity of the assessment process. This might be complicated further if a small number of vessels were selected for the blood flow valuation which might be unrepresentative of the whole nailfold. Automated structure and flow measurement was reported to be a promising tool in nailfold capillaroscopy [64].

New research suggested that laser Doppler is a tool which can be used to assess the digital blood flow. This has the potential to enhance the understanding and management of peripheral vasculopathy in patients with Raynaud's phenomenon and systemic sclerosis. Laser Doppler imaging (LDI) and laser Doppler flowmetry (LDF) — two variants of laser Doppler — have been studied to evaluate digital blood flow. LDI uses a method to scan with a distant light source and detector, whereas LDF uses optical fibers to carry the light to and from the tissue. The LDF measures the microcirculatory blood flow through a very small volume of tissue and the LDI scans a larger tissue area. LDI cannot continuously measure skin blood perfusion because of the scanning time, whereas LDF can measure it continuously [65]. On another note, the severity of lactic acid build-up in the systemic sclerosis patients, measured by fingertip lacticemy, was assessed as indicative of the degree of the perfusion impairment. Early studies revealed that the lacticemy results correlated negatively with the LDI score [66].

Reporting

The report is an integral part of the NFC, and its uniform use can help in the correct interpretation of the findings in standard daily practice as well as research. A barrier for further evaluation is the lack of consensus on how and what to document of the outcomes/findings of the NFC procedure. When describing NFC methods and outcomes, there was a variation of the level of details reported in the different research studies. This makes the interpretation and comparison of results quite challenging. In turn, this highlighted the need to have a standard model for the format and content of the NFC report in rheumatology which represents a crucial and integral aspect of the NFC examination.

Based on the general recommendations on the correct reporting of NFC imaging, it has been concluded that a "good" report of medical imaging should be described by the eight Cs: clarity, correctness, confidence, concision, completeness, consistency, communication, and consultation [67]. In addition, two features that are attributes to a "good" imaging report are timeliness and standardization.

NFC is a highly operator-dependent imaging tool, which by itself highlight the need for having a standardized objective and reproducible reporting model. A relevant step towards standardization of NFC could be the adoption of a shared model/template of reporting the NFC findings. However, because of the lack of literature on this topic, standardization of NFC report is hard to obtain. An international consensus for the format and content of the NFC report in rheumatology for use in standard daily clinical practice has been produced by the Capillaroscopy Study Group of the Pan-American League of Associations for Rheumatology (GECAP) to address the gap in the NFC process [68]. Ingegnoli et al. [69] recently carried out a study to seek consensus on the reporting standards in NFC methodology for clinical research in rheumatic diseases and to propose a pragmatic reporting checklist [69]. A reporting checklist of 33 items, based on practical suggestions made (using a Delphi process) by international participants, has been developed to provide guidance to improve and standardize the NFC methodology to be applied in future clinical research studies. The study concluded that to harmonize and facilitate NFC reporting, the next step forward towards standardization is to develop a NFC reporting core set building upon the recently published expert consensus from the EULAR SG MC/RD. This outlined on the one hand the definition of the variable capillaroscopic characteristics to be evaluated (density, dimension, abnormal shape, and hemorrhages) and on the other hand dealt with categorizing the capillaroscopic image as a scleroderma pattern or not (normal images versus images with non-specific abnormalities) [70–72].

Integration of nailfold capillaroscopy into the rheumatology fellow curriculum

Despite the increased clinical relevance and the high impact of the NFC if utilized by properly trained rheumatologists, several rheumatology fellowship programs do not currently have a standardized curriculum in this. In Europe, where capillaroscopy is still more prevalent, the earliest capillaroscopy courses took place only just over a decade ago [73]. The first American College of Rheumatology (ACR) study group dedicated to "capillaroscopy and rheumatic diseases" took place in 2010 [74]. In some countries, e.g., Germany, formal training in nailfold capillary imagery/interpretation is part of rheumatology residency. In England, NFC was a recommended procedure to learn as published in Curriculum for Rheumatology Training, Royal College of physicians [https://www.jrcptb.org.uk/sites/default/files/Updated%20Rheumatology%20Curriculum%20Draft%2014122020.pdf]. A biannual teaching course set up by the EULAR study group was launched recently by EULAR [https://emeunet.eular.org/capillaroscopy.cfm] aiming at educating the trainees how to use the NFC equipment, to reinforce the learned techniques during clinic and consult service visits and to assess the accrual of knowledge through pre- and post-tests and through patient-based assessments.

Conclusion

NFC represents the best method to analyze microvascular abnormalities in autoimmune rheumatic diseases. The term microangiopathy includes a variety of pathological changes including decreased numbers of capillaries, dilated capillary loops leading to the formation of mega-capillaries, the areas of avascularization, and the presence of ramified loops and microhemorrhages. The evaluation of nailfold capillaroscopy is not only of value in early diagnosis of autoimmune rheumatic diseases but also may represent a tool for the prediction of microvascular systemic affection, e.g., heart involvement. However, although classification systems and scores for capillaroscopy interpretation have been published, there is a lack of homogenization for the procedure, especially in the way and place the images are taken, the counting of the capillaries, and the measuring of their size. This article has included a summary of some of the challenges that NFC faces and provides tips towards how to optimize the NFC process in the standard practice as well as research.

Declarations

Conflict of interest The authors declare no competing interests.

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