Nailfold capillaroscopy in systemic diseases: short overview for internal medicine

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Nailfold capillaroscopy (NFC) is now one of the main imaging tools in systemic sclerosis and imposed over time as an easy, non-invasive method for the nailfold microvascular bed assessment.

In qualitative NFC normal pattern is characterized by homogeneous, parallel fashion arrangement of the last capillaries row as well as by capillaries with hairpin or non-specific variations like tortuous and/ or crossing shape.

Nailfold capillaroscopy is strongly recommended for evaluation of all patients with Raynaud phenomenon. Appearance of giant capillaries is chronologically the first relevant finding for scleroderma spectrum disorders development (systemic sclerosis, dermatomyositis, undifferentiated and mixed connective tissue disease). Collapses of the giant loops generate microhemorrhages and further capillary loss with subsequent hypoxia, and neoangiogenesis seen as ramified/ bushy capillaries. Nailfold capillaroscopy is indicated especially in systemic sclerosis, being also included in the classification criteria.

Based on these major NFC pathologic findings (giant capillaries, microhemorrhages, avascularity and neoangiogenesis), three evolutive stages were described in systemic sclerosis, namely the early, active, and late scleroderma pattern.

In other connective tissue diseases than those scleroderma-related, like systemic lupus erythematosus, psoriatic arthritis, or antiphospholipid syndrome, the interest for capillaroscopy is growing, but the attempts of defining specific characteristics failed until now.

Besides qualitative NFC, semiquantitative and quantitative capillaroscopic assessments were proposed for more accurate evaluation. Lately, automated systems are under development. There is still need of more studies to sustain the nailfold capillaroscopy validity as diagnostic and prognostic test.

Key words: nailfold capillaroscopy, systemic sclerosis, microangiopathy, video capillaroscopy.

1. BACKGROUND

Nailfold capillaroscopy (NFC) is a non-invasive, easy to use, low cost, reproducible technique, that allows visualization of the capillary network in living tissues [1-3] and plays an important role in rheumatology clinical practice [4].

It appears that the first clinician who used a microscope to visualize the small blood vessels visible around the nails was Johan Christophorus Kolhaus in 1663 [2]. Later on, at the beginning of 1800, Giovanni Rasori used a magnifying glass to describe the capillary loops characteristics [2,5] and Maurice Raynaud presented his thesis on the local hand and feet ischemic damage in 1862 [5]. Further, efforts were done to define the stages of dilated capillaries and nailfold petechiae occurrence in different connective-tissue disorders [6]. There were many attempts to describe disease specific

capillaroscopic findings, like increased visibility in rheumatoid arthritis (RA), marked capillary dilatation in systemic sclerosis (SSc) and dermatomyositis (DM), or distinction of the subpapillary vessels with „punched-out” lesions in systemic lupus erythematosus (SLE) [7]. Maricq HR *et al.* defined the scleroderma pattern, characterized by giant capillaries and/or rarefaction and disorganization of capillaries with multiple branches formation, as well as changes of the blood flow in patients with Raynaud phenomenon (RP) [8-9].

In 2000, Cutolo M *et al.* defined three main patterns in systemic sclerosis (SSc) that are currently largely used, namely the E (early), A (active), and L (late) pattern [10]. Besides the qualitative capillaroscopy description that allows definitions of normal as well as of pathologic patterns, semi-/quantitative capillaroscopic evaluations were also developed [11,12].

The 2013 American College of Rheumatology (ACR)/ EULAR classification criteria for SSc counts 2 out of the minimum 9 points needed for the pathology classification for NFC SSc-specific findings [13]. The inclusion of the capillaroscopic evaluation in the SSc classification criteria was based on its role in early SSc diagnosis; later the capillaroscopy indications expanded (see Table 1) [8]. The 2013 ACR /EULAR proved better sensitivity and specificity when compared to 1980 ACR classification criteria, respectively 0.91 and 0.92 versus 0.75 and 0.72 [13]. There is need for more data to conclude over the NFC accuracy as a diagnosis or prognostic tool in SSc and in other rheumatic diseases [14].

Recently, standardization guidelines for capillaroscopy practice for RP and SSc were published by the EULAR study group on microcirculation in rheumatic diseases and the scleroderma clinical trials consortium group on capillaroscopy [15].

We herein present a short overview of the NFC main features and use in daily clinical practice as well as the advances done for the NFC use in other rheumatic diseases than SSc.

2. IMAGING TECHNIQUE

NFC allows the non-invasive “in vivo” examination of the peripheral microcirculation [5]. The term microcirculation refers to micro-vessels with less than 300µm diameter [11]. Instruments of

optical magnification developed for the examination of nailfold dermal papillary capillaries [16] are the stereomicroscope, ophthalmoscope, dermatoscope, smartphone devices, digital USB microscope, and digital videocapillaroscope [15].

The videocapillaroscope is most recommended based on the strengths of better images quality and improved software for image processing and measurements. The nailfold videocapillaroscope has a digital optical probe with a fixed magnification power. Some devices have low magnification power (x20), while other allow high amplification, most frequently x200 [5,8,16]. A power of magnification higher than x 60 is necessary for a good capillaroscopic image, and magnification higher than x1000 allows to observe well even the erythrocyte passage through the capillaries loops [17]. A videocapillaroscope could also provide real-time image adaptation, image storage and reproduction, further analysis and measurement of the parameters observed [18].

The patient preparation for capillaroscopy should try to elude factors with impact on microcirculation like microtrauma, onychophagia, smoking, nail lacquer or artificial nails [8]. A complete preparation for capillaroscopy includes hand washing, avoiding caffeine and smoking 6 hours before examination, and avoiding to remove the nail cuticles [19]. Giving up manicure for 15 days will avoid microtrauma of cuticula with subsequent hemorrhages and edema [17].

Table 1

Nailfold capillaroscopy indications

Indications
• All patients with Raynaud phenomenon
- Differential diagnosis: primary vs secondary Raynaud phenomenon
• All patients with Systemic sclerosis
- Diagnostic approach in systemic sclerosis
- Staging in systemic sclerosis
- Follow-up/ treatment response of patients with systemic sclerosis
• Evaluation of patients with Scleroderma spectrum disorders
• Dermatomyositis (DM)
• Mixed connective tissue disease (MCTD)
• Undifferentiated connective tissues disease (UCTD)
- Differential diagnosis (e.g. Dermatomyositis versus Polymyositis)
- Follow-up/ treatment response
- Need of screening for pulmonary involvement
• Diagnostic approach of idiopathic interstitial lung disease
After Cutolo M <i>et al.</i> [5], Cutolo M <i>et al.</i> [16], and Chojnowski MM <i>et al.</i> [30]

Also, acclimatization of the patients before examination is very important, as cold-induced vasoconstriction impede the capillaries visualization [5,8]. It is recommended for the patient to stay in a room with temperature 20–25° for at least 15 minutes before the NFC exam starts [17]. For examination, the hands are put on a table, approximately at the heart level. All fingers are examined, with the exception of the thumb [17].

The direct contact between the video-capillaroscope optic probe and the nailfold bed is done after applying neutral (vegetal) oil on the examined area, thus avoiding light reflection on the skin surface [19,17,20].

The optic probe is positioned over the nailfold and should exert no pressure [5]. Excessive pressure may interfere with blood flow by compressing the capillaries, consecutively producing loss of capillary visibility, so that the focus area might look falsely avascular [17]. This should be correctly assessed and differentiated from real avascular areas, “deserted areas” determined by pathologic capillary loss in SSc or related pathologies [17]. It is recommended to take two to four images of each nailfold after focusing on the distal layer of capillaries [19].

From the eight fingers examined, the fourth and fifth fingers most frequently provide clinically relevant information in both visibility and pathologic findings [19]. When a complete examination cannot be performed, the evaluation of both ring fingers is

considered most relevant for diagnosis, the “best two fingers combination” [10]. The correct preparation of the capillaroscopic exam significantly reduces technical errors [17]. Overall, an NFC exam should last around 15–30 minutes [19].

Efforts are done to have automated systems for capillaries evaluation, involving image-processing software, allowing automatic extraction of quantitative features, such as the automated absolute capillary number counting [21, 22].

3. CAPILLAROSCOPY PARAMETERS AND DEFINITIONS

The parameters analyzed during the NFC examination include skin transparency, venous plexus, the capillaries’ characteristics, namely distribution, density, length and diameter, presence of pathologic changes like micro-hemorrhages, neoangiogenesis, and blood flow characteristics (see Table 2) [8].

Visibility is mainly driven by skin transparency [8] and might be modified by factors like skin color, hyperkeratosis, edema and fibrosis [4]. The subpapillary venous plexus is situated deep in the nailfold base and drains all capillary venous loops [19]. The subpapillary venous plexus is visible in about 30% of subjects [1]. The blood flow is commonly faster in the subpapillary plexus than in capillaries [19].

Table 2

Parameters and definitions in nailfold capillaroscopy

Parameter	Definition
Visibility/ Skin transparency	The interface that capillaries view.
Subpapillary venous plexus	Vascular network at the nailfold base.
Capillary orientation	Capillaries direction in report to the skin surface.
Capillary density	Number of capillaries/ 1mm.
Capillary morphology	The shape of each individual capillary.
Capillary length	Distance between the capillary apex and the point where the capillary loop is no longer visible.
Capillary diameter	Width of the arterial (afferent), apical, venous (efferent) loop (especially apical loop).
Pericapillary edema	Pericapillary increase of interstitial fluid.
Microhemorrhages	Dark areas of hemosiderin on the nailfold capillary bed due to the capillary wall rupture.
Neoangiogenesis	Abnormal shapes (other shapes than hairpin, tortuous, or crossing).
Blood flow characteristics	Regular erythrocytes column, slowed down.
After Kayser C <i>et al.</i> [1], Chojnowski MM <i>et al.</i> [30], Tavakol ME <i>et al.</i> [19], Cutolo M <i>et al.</i> [5], Cutolo <i>et al.</i> [16], and Faggioli P <i>et al.</i> [8].	

The capillaries are usually distributed homogeneously and regularly in horizontal lines, which leads to a palisade- [1] or comb-like structure [16] and the distal row capillaries are perpendicular to the nail edge [1] (see Figure 1). For each examined finger, capillary density is defined by the number of capillary loops per millimeter length of the distal row [1,19]. The mean density in all fingers can be calculated [23]. The capillaries density is

one of the most important and reliable capillaroscopic parameters [15] as it might predict the development of an underlying connective tissue disease [1]. A capillaries density higher than 7 capillaries/ mm is considered normal [15,19]. Capillary density was the first NFC parameter for which automated counting systems were developed, automated count of the nailfold capillary number (AUTOCAP) [22].

Figure 1. Normal shapes: 1a. hairpin; 1b. crossed capillaries; 1c. ectasia; 1d. meandering.

The morphology of each capillary loop is described and analyzed separately. In healthy subjects, nailfold capillaries have a hairpin shape, but variations like tortuous or crossed capillaries can also be seen. Meandering capillaries have

loops crossed upon themselves several times [1]. In late stages of scleroderma spectrum disorders (SSD), twisted and bushy capillaries are found as a result of neoangiogenesis [1,12] (see Table 3; Figure 2).

Table 3

Abnormalities described in nailfold capillaroscopy

Type	Synonyms	Description
Ectasia	Ectatic loop Loop enlargement Dilatated capillary	Moderately enlarged limbs, between 4 and 10 normal size. Diameter greater than 20 μm for the venous and 15 μm for the arterial loop, but less than 50 μm
Non-specific variations	Tortuous capillaries	Serpentine branches, without crossing each other
	Crossed capillaries	Branches that cross more than one time
Meandering capillaries	Meandering loops	Loops crossed upon themselves several times
Bizarre capillaries	Bizarre loops	Atypical non-classifiable morphology, rare forms that cannot be integrate as hairpin, tortuous, or crossed.
After Bertolazzi C <i>et al.</i> [4], Kayser C <i>et al.</i> [1], Tavakol ME <i>et al.</i> [19], Cutolo M <i>et al.</i> [16], and Cutolo M <i>et al.</i> [5].

Figure 2. Pathologic capillaroscopic findings: 2a. giant capillaries; 2b. microhemorrhages; 2c. neoangiogenesis; 2d. avascular areas

The capillary length or height is not regularly performed in clinical practice, being less relevant for a final diagnosis. The capillary length is measured between the capillary loop apex and the region where the loop is no longer visible [19] and capillaries are so classified as short or long [23]. It is to note that the capillaries length of the fourth and fifth fingers is longer than that in other fingers [19]. However, the capillaries length is variable (some authors consider values higher than 300 μm abnormal) and less useful for diagnosis in clinical practice [24].

The evaluation of capillary diameter is an essential part of the NFC examination as it allows identification of giant capillaries, a marker of the scleroderma pattern. The capillary width is measured at the widest section [19] and the mean diameter is obtained by the means of three consecutive loops, giant capillaries being defined by diameter higher than 50 μm [19]. The diameters of the afferent arterial side, apical loop, and also of the efferent venous loop are measured [1]. If only one measure is done, the apical loop is preferred. The interpeak capillaries refers to the intercapillaries distance, between two successive capillaries [19].

Moreover, pericapillary edema might be described like flu contour surrounding the capillary loop. The pericapillary edema is normally absent [10]. However, the visibility is influenced by several factors as already mentioned and it is difficult to discriminate the flu contour from other causes of reduce visibility or diminished sharpness.

It was estimated that only about 40% of general population has a pattern with completely normal capillaries, while in 50% minor abnormalities are found [17]. Giant capillaries, microhemorrhages, avascular areas or neoangiogenesis are not described in healthy subjects, but as part of the scleroderma pattern and will be detailed later [12] (see Table 4).

Beside the qualitative NFC exam that allows the identification and description of specific parameters, semi-quantitative and quantitative NFC methods may provide more accurate assessments. Parameters like capillary density, capillary diameter, and a number of various capillary abnormalities can be quantitatively assessed [15,16] by counting the number of each on either side at 1 mm of the reference point on all fingers, divided by the capillaries sum score [25]. The first semi-quantitative and quantitative approaches were used to differential diagnosis of early SSc from other

rheumatic diseases [26]. The degree of the capillary enlargement was graded as follows: 0=normal, 1=borderline, more than 2 times enlargement, 3=extremely enlarged, more than 4 times enlargement [26]. Also, the capillary loss was graded as follows: A=no capillary loss, B=rare capillary loss, C=moderate capillary loss, D=extensive capillary loss [26]. The most used semiquantitative rating scale is as follows: 0=no changes, 1=less than 33% capillary alterations/reduction, 2=33 – 66% of capillary alterations/reduction, 3=more than 66% alterations or reduction /mm were tested to assess the capillaries number, enlarged and giant capillaries, microhemorrhages, and ramified capillaries in NFC [27].

4. NORMAL CAPILLAROSCOPY PATTERN – HEALTHY SUBJECTS

The qualitative NFC assessment in healthy subjects shows homogeneous capillaries distribution in the field examined. Most frequently, the capillaries are stand perpendicularly to the nail

edge [1,11]. The terminal row of capillaries is arrange in parallel fashion and grant a full length description of the capillary [11]. Under the rows of capillaries, the subpapillary venous plexus might be seen and appears of greater diameter [17].

Beside the hairpin, “U” shape morphology, some other shapes might be display in the frame of the normal pattern. The morphology of each normal capillary loop analyzed separately looks like hairpin [1,5,16,11], English letter “U” upside down [19]. The arterial afferent loop is thinner than the venous efferent one [1] (see Figure 1). Besides the hairpin shape, other two discrete abnormalities, nonspecific variations are recognized for the normal pattern: tortuous (the loops undulate but do not cross) and crossing (loops crossed once or twice) capillaries that together with the hairpin shape are considered normal [15]. Besides these three shapes (hairpin, tortuous, crossing) all the other are defined as abnormal morphologies [15] (see Table 2).

Table 4

Major pathological hallmarks of the scleroderma pattern observed in nailfold capillaroscopy

Parameter	Synonyms	Description
Giant capillary	Mega capillary	Loop diameter > 50 μ m (afferent, apical, efferent)
Microhemorrhages	Micro bleedings	Hemosiderin deposits seen as dark spots Erythrocytes microvascular extravasation
Avascular area	Capillaries loss Reduced density Deletion areas	Loss of ≥ 2 contiguous capillaries Distance ≥ 500 μ m between adjacent capillaries Less < 30 capillaries/ 5 mm
Neoangiogenesis (Ramifications)	Twisted capillaries Bushy capillaries	New vascular formation Highly heterogeneous shape Branched capillaries
After Bertolazzi C [4], Sebastiani M <i>et al.</i> [43], Tavakol ME <i>et al.</i> [19], Cutolo M <i>et al.</i> [16], After Cutolo M <i>et al.</i> [5], and Faggioli P <i>et al.</i> [8].		

Ingegnoli F *et al.* described the morphological aspects of the capillaries as hairpin shaped loop, loops with one cross, loops with more than two intersections, as well as meandering loops and proposed three main capillaroscopic patterns for normal variations found in healthy subjects, namely first one “normal” with 2–5 U-shaped loops/mm and maximum 2 tortuous loops/mm; the second one, named also “perfect normal” which consists of more or equal than 5 U-shaped loops/mm, and the third one, “unusual normal” consisting in at least any of the following: one meandering, one bushy loop, one microhemorrhage, or more than 4 crossed

loops/mm [18]. Therefore, unusual capillaries like intercrossed capillaries, tortuous capillaries, elongated capillaries, or disorganization of the capillaries might occur even in subjects without underlying SSD [17].

Counting the number of capillaries reported to distance (per mm) is important for defining normality [18]. Different authors defined various limits for the normal capillaries density, like 9–14 (average 10) capillaries/ mm [16], 7–10 capillaries/ mm [18], 9–13 capillaries/ mm [8], 6–14 capillaries/mm [17], 7–12 capillaries [28]. A recent standardization of the EULAR study group for

microcirculation in rheumatic diseases stated that more than 7 capillaries/ mm define normal density [15] (see Table 5).

Similarly, the reports for capillaries loops diameter or length are not uniform. The ectasia was initially defined as having 4–9 times higher, while the giant capillaries more than 10 times higher than normal diameter [1]. Further, the normal diameter of the afferent branch of 6–19 μm and 8–20 μm for the efferent branch, with diameters of more than 50 μm defining the mega/ giant capillaries, [1, 8, 17]. By consensus, it was recently established that a diameter of maximum 20 μm for normal diameter and 50 μm for ectasia [15]. The loop length is representing the visible part of the capillaries and normal ranges were reported by some authors of 200–250 μm [17], but also up to 500 μm [8,18],

while elongated capillaries have length of more than 300 μm , 500 μm or even 700 μm [29].

Microhemorrhages might be seen in healthy individuals in case of local trauma in which its position is closer to the nail and not related to a giant capillary recently collapsed [1].

5. PRIMARY VERSUS SECONDARY RAYNAUD'S PHENOMENON

RP is characterized by the change of color fingers that evolves in three stages (pallor, cyanosis, rubor) and reflects reversible ischemia secondary to vasospastic events commonly triggered by cold or stress [1]. RP is found in about 2–9 % of the general population [17].

Table 5

Capillaroscopic aspect in healthy subjects

Parameter	Description
Skin transparency	Allows a good visualization of the capillaries
Subpapillary venous plexus	Visible in up to 30% of healthy individuals
General view	Homogeneously sized, regularly arranged
Capillary orientation	Straight, parallel fashion, usually perpendicular to the nailfold
Capillary density	Number of capillaries over 1mm nailfold, more than 7 capillaries/ mm
Capillary morphology	Inverted “U”, hairpin shape, but also tortuous and/ or crossing capillaries (nonspecific variations)
Capillary length	Less than 300 μm
Capillary diameter	Less than 20 μm for each loop (afferent, apical, efferent)
Pericapillary edema	Absent
Hemorrhages	Absent (occasionally observed after microtrauma)
Giant capillary	Absent
Neoangiogenesis	Absent
Blood flow characteristics	Dynamic, no stasis
After Kayser C <i>et al.</i> [1], Chojnowski MM <i>et al.</i> [30], Cutolo M <i>et al.</i> [5], and Smith V <i>et al.</i> [15].	

The RP is classified as primary (idiopathic) or secondary [1]; setting in which the RP may be associated to systemic autoimmune diseases [17]. Primary RP appears usually in young people around 14 years onset age, in symmetric form with rather mild episodes that are not accompanied by trophic complications [1]. Secondary RP has often onset after 30 years, develops more intense and painful episodes that might further complicate with ischemic lesions [1].

RP is the most frequent indication for performing NFC [16]. In patients with primary, idiopathic RP, the NFC finds virtually no changes.

Moreover, the normal pattern in NFC is backed by lack of other symptoms relevant of connective tissue diseases as well as by normal ranges for acute phase reactants [30].

NFC should be carried out in all patients with RP [5,16] given that up to 15% of all patients with initially idiopathic RP might develop SSc features within 3 years [16], but there is no consensus on the frequency of this examination (some authors suggested yearly NFC in patients with RP) [5,16]. Between the parameters analyzed, the absence of capillaries with diameter higher than 30 μm correlated with low risk of SSc development [15].

Capillaroscopic indexes to predict the transition from primary to secondary RP are discussed. Therefore, based on six variables, namely capillaries density, branching, enlarged and giant loops, capillary disorganization, and microhemorrhages, an index named PRINCE (Prognostic Index for Nailfold Capillaroscopic Examination) was design to predict 5-year transition from isolated RP to secondary to SSD' RP [31]. Further, using also the antinuclear antibodies (ANA) status, Ingegnoli *et al.* [32] classified three categories of risk for the progression from RP to SSc: low risk (< 10%) involving mean number of capillaries greater than 8.4/ mm or less than 8.4/ mm and negatives ANA, intermediate risk (10–50%), and high risk (> 50%) with low capillaries density associated with ANA positivity [20,32]. This algorithm was called PRINCESS (Prognostic Rule-based Instructions using Nailfold Capillaroscopy Examination and Scleroderma-related Serology) [20,32].

In patients with already defined SSD, the RP occurrence might predict the development of local complications, severe organ involvements like pulmonary arterial hypertension, and more severe prognosis [17]. In one study including 586 patients with RP followed for 3,197 person-years, 12.6% developed definite SSc. The enlarged capillaries,

capillary loss, as well as the SSc-specific autoantibodies independently predicted a definite SSc [33].

6. SYSTEMIC SCLEROSIS

SSc is the only pathology that can be pre-clinically predicted by combination of serology and capillaroscopy findings [16]. In SSc, specific NFC changes appear and further evolve in a defined sequence that was named scleroderma pattern [30], identified in 90–95% SSc patients [30,34], one of the reasons for which NFC is included in the 2013 ACR/ EULAR classification criteria for SSc [13].

NFC enables not only the early diagnosis of SSc, but also prediction of disease progression and of complications occurrence during follow-up [35]. The “very early” diagnosis of SSc (VEDOSS) criteria contain three domains with seven items. NFC scleroderma pattern together with RP, puffy fingers, ANA, and SSc-specific antibodies are part of the “very early” diagnosis of SSc [36].

The specific NFC findings suggestive for SSc are the giant capillary and the loss of capillary, that are essential for the SSc diagnosis, followed by microhemorrhages and finally neo-vascularization [16,37] (see Tables 4 and 6).

Table 6

Capillaroscopic patterns for scleroderma microangiopathy

Pattern	Description
E –early	No evident loss of capillaries Preserve architecture Few giant capillaries Few microhemorrhages Density ≥ 7 capillaries/ mm Homogeneous distribution Diameter (apical, but any/all loops) $\geq 50 \mu\text{m}$ Dark spots
A –active	Moderate loss of capillaries Frequent giant capillaries Frequent microhemorrhages Abnormal morphology Lowered density 4–6 capillaries/ mm Diameter (apical, but any/all loops) $\geq 50 \mu\text{m}$ Dark spots Non-specific variations: tortuous/ crossing
L –late	Important loss of capillaries Severe architecture damage Abnormal morphology Neoangiogenesis Almost absent microhemorrhages Almost absent giant capillaries Even lower density ≤ 3 capillaries/ mm (avascularization) Intense disorganization Frequent abnormalities, highly heterogeneous shapes, numerous ramified and bushy capillaries
Adapted after After Cutolo M <i>et al.</i> [10], Cutolo M <i>et al.</i> [5], Cutolo M <i>et al.</i> [16], Smith V <i>et al.</i> [15], and Chojnowski MM <i>et al.</i> [30].	

The giant capillary is the earliest SSc feature and one single giant capillary is suggestive for SSc development [16]. The loop enlargement is symmetrical, both arterial and venous loops are affected and reflects the endothelial cell array damage with micro-vessel wall alteration [16]

After the capillaries collapse and red blood cells extravasation, the loss of capillaries occurs. The diminished capillaries density determines local hypoxia with subsequent locally increased growth factors and further stimulation of new vessels organization. Neovascularization is

described as capillaries heterogeneity with abnormal morphology, twisted and bushy capillaries [16] (see Figure 2).

The enlarged capillary diameter is therefore the first NFC marker for SSc. The ongoing standards state normal size capillaries for diameters having up to 20 μm , while for giant capillaries loop diameter larger than 50 μm [1]. Capillaries with loops between 20 and 50 μm are described as enlarged capillaries [1]. After reaching maximum dimensions, the capillaries collapse and produce microhemorrhages that are visible at the nailfold capillary bed as darker areas [1]. The differential diagnosis for microhemorrhages must be done with lesions due to microtrauma or capillary thromboses [24]. The shape of capillary thrombosis mirrors the capillary loop [24]. Further, the capillary loss is defined based on the capillaries density, namely lower than 7 capillaries/mm [1]. The vasculopathy progression might be accompanied by clinical overt disease manifestations [37]. Avascular areas may be focal or diffuse; more than 500 μm between two successive loops is defined as a diffuse avascular area (devascularization) [1]. Neoangiogenesis is determined by local hypoxia, appearance of new vascularization with highly heterogeneous shape and multiple branches [1] (see Table 4).

As we already mentioned, Cutolo M *et al.* described three evolutive capillaroscopic patterns, able to quantify and monitor the microvascular damage progression in SSc patients [10,38], namely E (early), A (active), and L (late) pattern [10] (see Table 6).

Capillary density seems to be the most reliable parameter, useful for SSc monitoring [15]. In the early capillaroscopic pattern, there is never observed lower density [15]. On the contrary, the next patterns, the active (4–6 capillaries/mm) and late (≤ 3 capillaries/mm) patterns, always present lowered density, meaning less than 7 capillaries/mm [15]. This simplification as “always/ never” was considered for an easier application in clinical practice [15]. The giant capillaries are specific for the early pattern, while avascularity for the late pattern [15]. Neoangiogenesis is the feature of advanced microvascular involvement, late SSc stages [16].

A fast-tracking algorithm was developed to discriminate between scleroderma and non-scleroderma pattern. The easy rule of thumb of

the fast algorithm includes capillary density and the presence of giant capillaries [39]. The presence of giant capillaries allows distinction between scleroderma and non-scleroderma pattern with over 95.6% specificity [39].

Further, the NFC changes observed might be linked to specific SSc features like specific SSc involvements [20]. Therefore, the degree of capillaries loss correlates with pulmonary arterial hypertension severity [40] and survival rates in SSc [28,41]. SSc patients with pulmonary interstitial disease presented lower median capillary density and higher degree of neoangiogenesis [42]. SSc late pattern was associated with lower forced vital capacity (FVC) [42] and the number of giant capillaries with reduced diffusion capacity of the lung [42]. However, the clinical associations that have been described for NFC are not proved to be clinically reliable, each case should be always considered separately.

Several NFC indexes were developed for prediction in SSc. The capillaroscopic skin ulcer risk index (CSURI) was developed to predict the onset of digital ulcerations in SSc patients [43]. CSURI integrates the total number of capillaries, the maximum size of the loop diameter as well as the number of mega capillaries in order to predict the skin ulcer occurrence in 3-month follow-up period [43]. A semiquantitative rating scale, named the “microangiopathy evolution score” was also proposed to assess the progression of the vascular damage. This scale sums three items, namely the loss of capillaries, disorganization of the microvascular array and the capillary ramifications [38]. The NEMO score that assesses the cumulative number of microhaemorrhages and microthromboses is used as an indicator of the steady state level of disease activity in SSc patients and also the overtime changes in disease activity [44]. Further, a composite score, Clinical data, Imaging and Patient history (CIP-DUS) for digital ulcers occurrence over 12-months follow-up period was proposed. CIP-DUS combines clinical data and disease history with NFC, colour Doppler ultrasonography and fluorescence optical imaging [45].

7. SCLERODERMA SPECTRUM DISORDERS

SSD are a heterogeneous group of pathologies, for which disease-specific features

were defined, including undifferentiated connective tissue disease (UCTD), mixed connective tissue disease (MCTD), and

dermatomyositis (DM). The microvascular alterations found in SSD are alike the ones found in SSc, (see Table 7).

Table 7

Capillaroscopy findings in other than systemic sclerosis pathologies

Pathology	Capillaroscopy findings description
Scleroderma spectrum disorders	
Dermatomyositis (DM)	Important capillaries abnormalities: giant capillaries, ramified capillaries, increase neoangiogenesis Scleroderma pattern (most cases)
Mixed connective tissue disease (MCTD)	Presence of enlarged or giant loops, avascular areas, nonspecific abnormalities, or borderline lesions Scleroderma pattern (most cases)
Non-scleroderma spectrum disorders	
Systemic lupus erythematosus (SLE)	Increased capillaries tortuosity Meandering loops Increased capillaries length Rarely, focal area of capillaries loss In some, increased subpapillary venous plexus visibility
Antiphospholipid syndrome (APS)	Symmetric microhemorrhages (especially for secondary APS) Variations of loop lengths (especially primary APS)
Sjogren's syndrome (SS)	Tortuous and irregular capillaries In some, increased subpapillary venous plexus visibility
Rheumatoid arthritis (RA)	Most frequent, increased subpapillary venous plexus visibility In some, increased capillaries tortuosity In some, increased capillaries length
After Kayser C <i>et al.</i> [1], Chojnowski MM <i>et al.</i> [30], and Lin K-M <i>et al.</i> [24]. * the attempts of defining nailfold capillaroscopic patterns or specific finding in other than systemic sclerosis pathologies failed until now	

7.1. Undifferentiated connective tissue disease

UCTD refers to connective disorders that have incomplete clinical features [46]. In one research, in 98 patients with UCTD followed up for 11 years, 24% entered in remission while 14% developed a definite connective tissue disease [47]. Alongside with cytopenia and positives ANA, the progressive changes observed in NFC were predictors for a definite connective tissue disease development [47]. 20% UCTD patients present nonspecific NFC findings [8]. When compared to early SSc, 48.7% versus 37.8% had functional alterations, while 92.0%

versus 17.1% developed definitive SSc diagnosis within five years of follow-up [48].

7.2. Mixed connective tissue disease

MCTD is systemic autoimmune disease characterized by high anti-U1-RNP titers. The anti-U1-RNP positivity in other CTD than MCTD was associated with NFC abnormalities [49]. The NFC findings in MCTD microangiopathy have a dynamic evolution [50], the NFC changes progress [51] with significant decrease over time of the moderate and severe avascular areas [50]. The term frequently used in MCTD is “scleroderma like” NFC abnormalities, and

a specific MCTD capillaroscopic pattern was not defined yet [52].

Scleroderma pattern was found in 54% [53], 63.6% [54], 70% [50,52], and up to 82% [53] of MCTD patients. 72.7% of MCTD patients might have bushy capillaries [54]. Besides bushy capillaries, the most frequent encountered parameters are the capillaries dilatations [8].

MCTD patients with scleroderma pattern are younger than those with other capillaroscopic patterns [50]. When compared to SLE patients, the NFC in MCTD demonstrates higher capillaries loss and more frequent scleroderma pattern or bushy capillaries [54]. When compared to SSc, the scleroderma pattern was less frequent and bushy capillaries were more frequent encountered [54].

The pulmonary involvement in MCTD might correlate to the NFC findings. Avascular areas in NFC were more frequent in SSc with interstitial lung disease [50], while pulmonary arterial hypertension appears more frequent in MCTD with RP and NFC changes [55]. Another study showed that the number of giant capillaries was predictor for the interstitial lung disease co-existence [56]. The pulmonary ground-glass opacity areas correspond to inflammatory lung biopsies and might be related to the capillaroscopy findings [50]. Therefore, NFC should be considered in all patients with MCTD and further, scleroderma type findings should raise concern on MCTD pulmonary involvement [56]. Some authors described improvement of the NFC microvascular pattern under immunosuppressive treatment in both SSc and MCTD [57], but more data are needed to sustain these observations.

7.3. Dermatomyositis

The pathogenic pathways involved in DM implies a complement-mediated microangiopathy that has the endothelium as target, with inflammatory processes especially in endomysia [17]. The spectrum of autoimmune myopathy is complex and so differentiating between PM and DM has lost significance [58]. However, NFC exam might help the differential diagnosis between DM and PM. The difference between DM and polymyositis (PM) in NFC reflects the underlying pathogenic processes, respectively microangiopathy versus autoimmune cytotoxic reaction centered by the T cell [30]. One systematic review that analyzed 27 selected

researches from 540 publications, reported NFC alterations in 63.6% to 88.9% DM and in up to 32% with PM [34]. Of these, scleroderma pattern was described in 27 to 57% patients [34]. Besides “scleroderma pattern” the NFC alterations found in DM are named “scleroderma-like pattern”, “scleroderma-dermatomyositis pattern”, undefined “alterations” or “vasculopathy” [34].

In DM, at least two of the following modifications: capillaries enlargement, capillaries lost, normal distribution disorganization, bushy capillaries, twisted enlarged capillaries, or hemorrhages are more frequent than in general population [8], the ectasia and bushy capillaries being the most frequent [8]. Similar to SSc, giant capillaries are more frequent in patients with less than 6 months disease durations, while ramified capillaries in longstanding disease [34]. The number of enlarged capillaries is higher in DM patients with pulmonary involvement, while enlarged capillaries and loss of capillaries are related to RP and arthritis [34]. NFC changes are usually remitting together with the cutaneous ones. The capillaroscopic pattern is more rapidly changing in DM when compared to SSc and neoangiogenesis is an indicator of longstanding disease [34].

8. OTHER THAN SDS RHEUMATOLOGIC PATHOLOGIES

In other connective tissue diseases than SSD, the capillaroscopic pattern might be normal, with nonspecific findings, or borderline changes [16]. There are defined two types of borderline capillaroscopic findings: high prevalence of abnormal shapes (neoangiogenesis, with the exception of normal hairpin, tortuous, crossing) or concomitance of microhemorrhages, abnormal shapes (neoangiogenesis), and size variations [16].

8.1. Antiphospholipid syndrome

The vascular lesions observed in the antiphospholipid syndrome (APS) are based on a non-inflammatory vasculopathy [59]. The NFC findings in APS are not specific and a characteristic pattern was not defined yet. When compared to controls, APS patients presented significantly smaller capillaries diameters (for the

afferent, apical or efferent loop) [59]. While the capillaries density did not differ between controls and patients with primary APS, the frequency of bushy capillaries, crossing capillaries and other morphological alterations was more frequent in the later [59]. The NFC exam was done comparatively, trying to find out features that might differentiate primary APS of secondary to SLE APS cases, but failed to be found [60],[61]. Also, splinter hemorrhages are specifically described in APS.

One important aspect in APS patients is capillary thrombosis that might be falsely interpret as microhemorrhages [62]. In microvascular thrombosis, the dark zone takes the shape of the capillary loop [62]. The NFC changes seems to be related to the prevalence of the large vessels thrombotic events [60].

In patients with other than SSc rheumatologic diseases, microhemorrhages were associated with anticardiolipin (aCL) and anti-beta2-glycoprotein I (a β 2GPI) antibodies [63]. Also, in another research, from 343 patients with various rheumatic diseases, microhemorrhages were found in 149 NFC exams were correlated with the APS serology in these patients [64].

8.2. Systemic lupus erythematosus

NFC abnormalities are described in around 30% SLE cases [65]. A systematic review regarding NFC approach in SLE included a total of 14 original articles [29]. The authors described in SLE: normal pattern (with regular distribution of typical hairpin capillaries), non-specific pattern (including abnormalities that do not fulfill the scleroderma pattern definition), and scleroderma pattern (giant capillaries, hemorrhages, avascularity) [29]. Five of the studies included in one systematic review tried to define a specific SLE pattern based on the following features: increased capillaries loop length, increased tortuosity and meandering, well visualized subpapillary plexus, dilatated capillaries without avascular areas [29].

Among the SLE-related antibodies, only the anti-Ro/ SS-A antibodies were related to NFC changes, lower capillaroscopic density respectively [29], even if it was previously suggested that SLE patients with anti-U1-RNP present more often scleroderma pattern with enlarged loops and avascular areas, while those with

microhemorrhages more prevalent APS antibodies [65].

8.3. Sjogren's syndrome

Around 30% of the patients with primary SS develop RP [66]. Regarding the NFC findings in primary SS, one study that included 61 consecutive patients found normal pattern or non-significant capillaries alterations in 59% of the cases. Moreover, 29.5% primary SS patients expressed non-specific abnormalities, while 11.5% a scleroderma-like pattern [66]. Another study that evaluated 136 patients with primary SS, reported normal in 41%, non-specific in 27%, and scleroderma pattern in 10% cases [67]. Also, the NFC changes were more frequent in patients with SS and RP, 40% versus 10% [67].

When comparing primary SS with healthy subjects, non-specific capillaries abnormalities like crossed capillaries to more specific ones like confluent hemorrhages and pericapillary hemorrhages are found [68]. Hemorrhages were found in 31.2% and pericapillary hemorrhages in 18.7% patients, while 2 out of 16 patients with primary SS and RP had scleroderma like pattern [68]. All patients with primary SS who were positive for antcentromere antibodies had modified NFC exam and among them, 80% a scleroderma like pattern [68]. Also, capillaries density was inversely correlated with the RP presence in primary SS [68]. Giant or bushy capillaries are not generally found in SS [69]. There are also reports that do not found NFC changes in primary SS, but only dysregulation of the reactive hyperemia response, an increased time to reach the maximum capillary red blood cell velocity [70]. The attempts to identify differences between the NFC images in SS compared to SLE [71], with cutaneous vasculitis development [72], or to anti-Ro/SS-A, anti-La/SS-B failed [67].

8.4. Psoriatic arthritis

The vascular injury could play a role in psoriasis pathogenesis [73] which starts with the vascular endothelium activation [74]. About 32.4% of the patients with psoriatic arthritis (PA) have RP [75]. When compared to controls, the amplitude of the capillaries loop was higher, the

capillaries density was lower, the number of twisted capillaries and the tortuosity was higher in psoriasis with/ without AP [74]. In almost 60% of the AP patients tight terminal convolutions of the examined capillaries were found [75].

Analyzing the NFC in 46 patients with psoriasis versus 50 controls, lower capillaries density, increased avascular areas, and increased number of abnormal capillaries were reported [76]. Even if the skin involvement in psoriasis is not associated with NFC changes found more frequent avascular areas in patients with nail involvement [76]. Also, another research including 44 patients with PA and 44 age- and sex- matched control subjects, found diminished capillaries density in patients with nail disease as well as in those with nail and distal interphalangeal joint involvement [73]. Both arterial and venous capillary loops diameter were smaller in patients with distal interphalangeal joints involvements [73]. Other authors reported higher frequency of tortuous capillaries when comparing 34 patients with psoriatic nail disease with 15 healthy controls [77]. In patients treated by Cyclosporine, improvement of the skin thickness, erythema, scaling, and infiltration degree, were followed by amelioration of the NFC images [78]. Compared to RA, the capillaries abnormalities like mega capillaries, hemorrhages, ramifications, avascular areas seem to be similar in PA and RA, but the number of twisted capillaries is higher in AP when compared to RA [74].

8.5. Rheumatoid arthritis

RP is found in 22.3% to 30.6% patients with RA [75,79]. Microvascular changes have also been described in RA, but most findings are non-specific [80]. The NFC contribution to a definite diagnosis in patients with early arthritis is considered [81].

When compared to AP or control subjects, the diameters of capillaries loops are higher in RA. The trend of expansion of the efferent loop is an early manifestation of the micro-circulation vascular damage [74]. From a total of 430 RA patients examined for 4 years, 20.9% showed scleroderma pattern [82]. Other authors reported 14.5% RA patients with scleroderma pattern [75].

After performing NFC in 210 patients with RA compared to 50 healthy subjects, higher frequency of tortuosity, dilated and bushy capillaries was reported [79]. The NFC

alterations identified in RA patients were not correlated with the ACPA positivity or RA disease activity as assessed by DAS28, but only with RP occurrence [79]. In another research involving RA patients, more prominent subpapillary plexus (69%) and elongated capillaries (58%) were the most frequent NFC alterations [75]. Also, dilatated capillaries were more frequent in RA patients with RP, 78.9% versus 62.8% [75]. Compared to healthy subjects, the capillaries density has lower values in RA patients. The capillaries density negatively correlated to the C-reactive protein and positively with the HDL-cholesterol and the cardiac index, being so related to the cardiovascular risk [83].

9. THE CAPILLAROSCOPY REPORT

In 2019 the Pan-American League of Associations for Rheumatology (PANLAR) reached a consensus for the standards of capillaroscopy report [4].

The PANLAR recommended that the capillaroscopy report should contain: the patient data (including diagnostic suspicion, work type, habits, medications – a summary of conditions that might affect the capillaroscopic image), RP's onset time, and also characterization of visibility, subpapillary venous plexus, architecture, capillaries density, description of giant capillaries, avascular areas, bushy capillaries, microhemorrhages, ectasia and other abnormalities like thrombosed capillaries, tortuous, crossed and bizarre capillaries. And finally, the NFC-based diagnosis should be noted in the final examination report as well as management suggestions and relevant images.

10. CONCLUSION

Lately, important advances have been made for the NFC standardization and its use indications gradually expanded. Also, systematic reviews for NFC use in pathologies including SSc, SLE or DM were published.

The capillaroscopic assessment is recommended in patients presenting with RP, allowing differential diagnosis and early recognition of associated underlying pathologies, as well as in all SSc patients for both diagnosis and treatment follow-up at least yearly. There is still need of data regarding the NFC validity as diagnostic and prognostic tool.

Capilaroscopia periunghială este una dintre metodele paraclinice importante în evaluarea sclerodermiei sistemice, ce s-a impus în timp, fiind o metodă neinvazivă ce permite descrierea patului microvascular.

Calitativ, aspectul capilaroscopic normal este caracterizat printr-o aranjare omogenă, paralelă a anselor capilarelor așezate pe ultimul rând, la fel ca și prin prezența de capilare în ac de păr sau care prezintă variații nespecifice ca formele tortuoase și/ sau încrucișate.

Capilaroscopia periunghială este recomandată pentru evaluarea tuturor pacienților care prezintă fenomen Raynaud. Cronologic, apariția capilarelor gigante este primul indiciu relevant pentru dezvoltarea unei afecțiuni din spectrul patologiilor de tip scleroderma (sclerodermie sistemică, dermatomiozita, boala nediferențiată și boala mixtă de țesut conjunctiv). Colapsul anselor gigante produce microhemoragii și, mai departe, pierderea de capilare cu ischemie secundară și neoangiogeneză, ce poate fi observată ca apariție de capilare ramificate, cu aspect arborescent. Capilaroscopia periunghială este utilă în special în sclerodermia sistemică, fiind de altfel inclusă în criteriile de clasificare ale acestei patologii.

Plecând de la aceste caracteristici importante (capilare gigante, microhemoragii, avascularitate și neoangiogeneză), trei stagii evolutive au fost descrise în sclerodermia sistemică, și anume tipar precoce, activ și tardiv.

În alte boli de țesut conjunctiv decât cele care au caracteristici comune cu sclerodermia sistemică, cum ar fi lupusul eritematos sistemic, artropatia psoriazică sau sindromul antifosfolipidic, interesul pentru capilaroscopie este în creștere, dar încercările de a defini caracteristici specifice în aceste boli au eșuat până acum.

În afara aprecierii calitative, sunt propuse și metode de evaluare semicantitativă și cantitativă în capilaroscopie. Recent, sisteme automate sunt în curs de dezvoltare. Cu toate acestea, sunt încă necesare studii suplimentare care să susțină utilitatea capilaroscopiei ca test diagnostic și prognostic.

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