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Review article

Nailfold capillaroscopy: relevance to the practice of rheumatology

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ABSTRACT

Nailfold capillaroscopy is a simple, low-cost method, that is extremely important in the evaluation of patients with Raynaud's phenomenon and of patients with systemic sclerosis (SSc) spectrum diseases. Besides its importance for the early diagnosis of SSc, nailfold capillaroscopy is a useful tool to identify scleroderma patients with high risk for development of vascular and visceral complications and death. The inclusion of capillaroscopy in the new classification criteria for SSc of the American College of Rheumatology (ACR) and European League Against Rheumatism (Eular) gives a new impetus to the use and dissemination of the method. In this paper, we present a didactic, non-systematic review on the subject, with emphasis on advances recently described.

Capilaroscopia periungueal: relevância para a prática reumatológica

Palavras-chave:
Capilaroscopia
Fenômeno Raynaud
Esclerose sistêmica

RESUMO

A capilaroscopia periungueal é um método simples, de baixo custo, e de extrema relevância na avaliação de pacientes com fenômeno de Raynaud ou portadores de doenças do espectro da esclerose sistêmica (ES). Além de sua importância para o diagnóstico precoce da ES, constitui instrumento útil na identificação de pacientes esclerodérmicos com risco elevado para o desenvolvimento de complicações vasculares, viscerais e de óbito. A inclusão da capilaroscopia nos novos critérios para classificação da ES do Colégio Americano de Reumatologia (ACR) e da Liga Europeia Contra o Reumatismo (Eular) dá novo impulso para a utilização e disseminação do método. No presente artigo, pretendemos apresentar uma revisão didática, não sistemática, sobre o tema, com ênfase nos avanços recentemente descritos.

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Introduction and brief history

Vascular changes characterized by functional and structural abnormalities of the microcirculation play a central role in the pathogenesis of systemic sclerosis (SSc) and may also be present in dermatomyositis (DM) and in the SSc spectrum diseases.[1] Nailfold capillaroscopy (NFC) is a non-invasive, inexpensive and reproducible imaging method allowing the evaluation of structural changes in the peripheral microcirculation. It is mainly used in the differentiation of primary and secondary Raynaud's phenomenon (RP) and in the diagnosis of SSc.[2,3]

The history of capillaroscopy started 400 years ago, when JC Kolhaus described the possibility of visualization of capillary loops of the nailfold region through a rudimentary system of optical magnification.[3] However, only in the second half of the 20th Century NFC begins to be used more systematically in the evaluation of RP, in particular, thanks to the studies of Hildegard Maricq and Edward Carwile LeRoy, who described in 1973 specific capillaroscopic patterns of SSc and related diseases.[4] In Brazil, the method was introduced and standardized in the 80s by Luís Eduardo Coelho Andrade.[5] In recent years, researchers have turned their attention to the NFC because of new evidence of the importance of the method for early diagnosis of SSc and its prognostic value. In addition, NFC has recently been incorporated into the new classification criteria of the ACR/EULAR 2013 for SSc, confirming the importance of the method in the diagnosis of the disease.[6] In this paper, we present a didactic, non-systematic review on the subject, highlighting the indications of NFC and clinical implications of its main findings in the daily practice of the rheumatologist.

Indications of capillaroscopy in rheumatology

Patients with RP represent a common diagnostic challenge in the practice of Rheumatology, with a broad differential diagnosis. Moreover, they constitute the main indication for NFC. RP is an exaggerated physiological response of the microcirculation of the extremities, face to precipitating factors such as exposure to cold or emotional stress. Its classic presentation includes three phases: (1) the first is represented by ischemia, when the fingers assume a white color; (2) then, with the occurrence of blood stasis, the extremities turn to a blue color (cyanosis); (3) and finally the red color appears, indicating the stage of reperfusion. RP may be primary, or secondary to a number of conditions and diseases. Primary RP is a benign condition characterized by functional changes of blood vessels and/or their innervation, and by definition does not progress to an irreversible tissue damage. Diagnostic criteria for primary RP were proposed in 1992 by LeRoy et al., and included the presence of a normal NFC.[7] More recently, new criteria were proposed, including: (1) the presence of a clinical diagnosis of biphasic RP; (2) a normal NFC; (3) a physical examination with no findings suggestive of a secondary cause for RP (ulceration, gangrene, necrosis, sclerodactyly, calcinosis or skin thickening); (4) no history of autoimmune rheumatic disease; and (5) negative or low-titer ANA.[8]

At the other extreme, in patients with RP secondary to SSc spectrum diseases, RP attacks tend to be more severe and may be associated with complications such as ulceration, scarring, gangrene and/or digital amputation. Various rheumatic diseases may present with RP, including, in addition to SSc, systemic lupus erythematosus (SLE), dermatomyositis/polymyositis (DM/PM), mixed connective tissue disease (MCTD), rheumatoid arthritis, Sjögren's syndrome, vasculitides and antiphospholipid syndrome. However, RP assumes greater importance in the scleroderma spectrum of diseases. Notably, RP is often the first manifestation of the disease in about 75% of patients with SSc, besides being associated with significant morbidity and increased therapeutic difficulties.[9–11]

In this context, NFC plays a key role in the distinction between primary and secondary RP, and can also aid in clinical and evolutionary characterization of these subjects, as well as reducing costs with an unnecessary workup.[12–14] A meta-analysis showed that 12.6% of patients initially identified as suffering from primary RP develop a secondary cause for this phenomenon.[10] Another recent study showed that approximately 20% of these patients progress to a definitive or suspected diagnosis of secondary RP at a 10-year follow-up.[9] Different studies have been uniform in assigning to NFC a crucial role in monitoring the transition from primary to secondary RP.[15–18] A meta-analysis by Spencer-Green et al. showed a positive predictive value of 47% for the presence of alterations in NFC, a value higher than the predictive value for the presence of autoantibodies (30%).[10] When presence of specific autoantibodies in SSc were associated with abnormal capillaroscopy findings, the positive predictive value for the development of SSc reaches 79.5% in 15 years.[18] The main indications for NFC are summarized in Table 1.

Technical aspects

Equipment

Didactically, we can enumerate three possibilities for the visualization of the terminal row of capillary loops (Fig. 1):

(1) Stereomicroscope: magnification capacity 10–50 times; allows the realization of panoramic NFC. With the stereomicroscope, it is possible an overall assessment of nailfold beds, to register qualitative and quantitative parameters.[5,19] This remains the main method still used

Table 1 – Main indications for capillaroscopy.

(a) Evaluation of patients with Raynaud's phenomenon
(b) Monitoring the transition from primary to secondary RP
(c) Early diagnosis of SSc
(d) Differential diagnosis of SSc-related conditions, such as localized SSc and eosinophilic fasciitis, which usually have a normal capillaroscopic pattern
(e) Detection of severe microangiopathy and prognostic evaluation in SSc
(f) Monitoring of treatment and disease activity in dermatomyositis

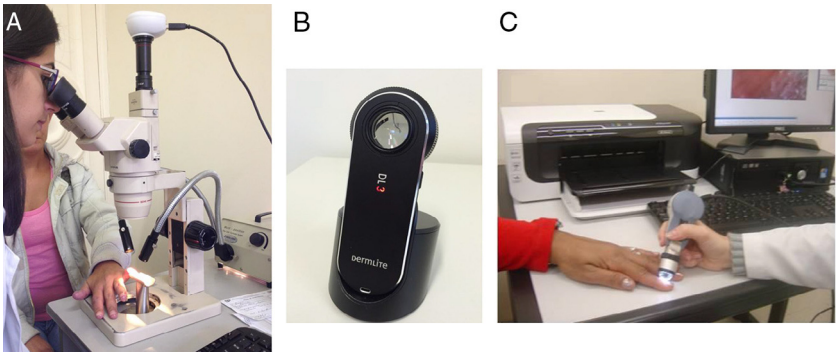

Fig. 1 – Devices that can be used for nailfold capillaroscopy: stereomicroscope (A); dermatoscope (B); videocapillaroscope (C).

today in national and international centers, due to its ease of use and low cost.

(2) Ophthalmoscope and dermatoscope: provide images with lower magnification and quality. These techniques can be an alternative to the bedside exams, or as a form of screening in medical offices that do not have a stereomicroscope or a videocapillaroscope[20,21]; and

(3) Videocapillaroscopy: consists of the combination of a microscope with a larger magnification lens coupled with a digital video camera. This technique provides a significantly higher increase (200–600-fold) compared to the stereomicroscope; and, with the aid of specific softwares, allows a precise measurement of capillaroscopic parameters (capillary length, width and density).[13,22] One of the disadvantages of the technique is the loss of panoramic view of the capillary loops; only one area of the nailfold region may be examined at any given time.

Recently, a study from our group, comparing videocapillaroscope versus stereomicroscope, showed similar diagnostic performance and reproducibility of the two methods.[22]

How to perform the examination

Whichever method is used, initially the patient must remain in an acclimatized room for 15–20 min with its temperature around 20–22 °C. For better visualization of the capillaries, a drop of immersion oil is placed on the cuticle of the fingers to be evaluated. The periungual region of the ten or eight fingers (excluding the thumb) should be examined. In this region, the distal row of capillary loops protrudes into the dermal papillae, allowing a longitudinal view of its three (afferent, efferent and transition) segments, arranged in a direction parallel to the skin surface.[23]

The following parameters are routinely evaluated: number of loops/mm, number of dilated capillaries (with ectasia and/or megacapillaries), devascularization, the presence of micro-hemorrhages, and meandering, tortuous or branched capillaries. The presence of devascularization can be assessed by the number of loops/mm or by a devascularization score, graded 0–3, where 0 corresponds to the absence of devascularization, and 3 to extensive areas of avascularity. Capillaroscopic parameters may also be graded using the method proposed by Cutolo et al., in which the capillary abnormalities are graded according to their intensity, as follows: score 0 – no changes; score 1 – <33% of capillary changes; score 2 – 33–66% of capillary changes; score 3 – >66% of capillary changes.[24] By convention, an abnormal capillaroscopic finding is considered significant if it is observed in at least two fingers of the individual.[12,13,25]

Capillaroscopic patterns

Normal capillaroscopic pattern

In healthy individuals, the capillaries have homogeneous size, shape and color, and are arranged transversely across the cuticle (Fig. 2A). The capillary loops may present discreet morphological variations, such as crossed or meandering loops (with intertwining). The subpapilar venous plexus can be seen in varying extent in approximately 60% of the population, with greater visibility expected in children and in white

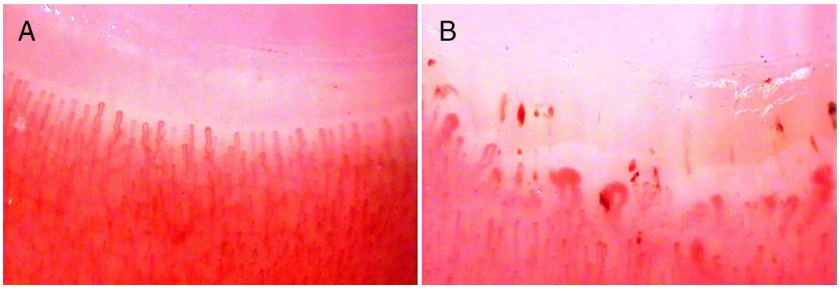

Fig. 2 – Images of capillaroscopy with a normal capillaroscopic pattern (A) and with SD pattern, in which presence of micro-hemorrhages, dilated capillaries, megacapillaries and avascular areas can be observed (B).

people.[5,19] The normal capillary density, obtained by counting the number of loops in one millimeter, ranges from 7 to 12 capillaries, averaging 9 capillaries/mm; most researchers consider as a parameter of normality in adults the presence of ≥9 loops/mm.[22,25] A small number of capillary dilations (ectasia) may also be observed, but the finding of megacapillaries or areas of devascularization should be considered abnormal, except in the latter case, if the devascularization is associated with traumatic microscars in the periungual region. Similarly, small areas of micro-bleeding with focal distribution can be observed in healthy individuals, associated with everyday microtrauma. During the exam, it is useful to consider that there is great variation in the shape and size of the capillary loops among healthy individuals, and even among fingers of the same person. Therefore, in these cases a misdiagnosis of microangiopathy should be avoided. Thus, the training and development are essential factors in the formation of capillaroscopists.[26]

SD (scleroderma) pattern

First described by Maricq et al., the SD pattern corresponds to a set of typical NFC changes characterized by the presence of dilated capillaries (ectasia and/or megacapillaries), loss of capillary loops, with consequent reduction in the number of capillaries, micro-bleeding and neoangiogenesis (branched capillaries) (Fig. 2B).[4,27] The SD pattern is present in 83–98% of cases of SSc, although it is also observed in MCTD, DM and in overlap syndromes.[13,28]

Additionally, Cutolo et al. classified capillaroscopy changes associated with SD pattern in three stages: recent, active and late.[24] In the "recent" pattern, micro-hemorrhages, and ectasia (including megacapillaries) predominate, with a relatively preserved capillary distribution and with no significant devascularization. These findings are crucial for early diagnosis of SSc. In the "active" pattern, an increase in the number of giant capillaries (megacapillaries) and micro-hemorrhages are observed, in association with a moderate loss of capillaries and mild distortion of capillary architecture. The "late" pattern is characterized by a severe loss of capillaries and by extensive avascular areas, neoangiogenesis and disorganization of capillary architecture. In this study, the late pattern changes correlated with the duration of RP and diagnosis of SSc.

Nonspecific microangiopathy

Nonspecific changes characterized by the presence of elongated or tortuous capillaries, discreet presence of dilated capillaries and increased visibility of the subpapilar venous plexus are described in a number of conditions. Their real significance must be interpreted within the clinical context of each patient.

Capillaroscopy in autoimmune rheumatic diseases

Systemic sclerosis

As previously mentioned, approximately 90% of patients with SSc exhibit the SD pattern in NFC. A microangiopathy typical of SSc is found in the early stages of the disease, often only when RP is present. The correlation between capillaroscopic findings and the duration of the disease is controversial. Some authors describe a more pronounced presence of dilated capillaries and micro-hemorrhages in the early years of disease, and a more intense disorganization and devascularization in later stages. However, it is not uncommon to find patients with many years of illness and little devascularization; on the other hand, patients with little disease duration and intense degree of devascularization and disorganization of the capillary architecture can also be seen.[2]

SSc is a chronic disease associated with high morbidity and mortality. In this sense, it has been increasingly emphasized the need for an early diagnosis of the disease, when there is as yet no evidence of fibrosis of internal organs and of irreversible damage.[6,13,28] In this scenario, NFC acquires its great practical importance. It is noteworthy that the ACR (1980) classification criteria for SSc, based mainly on clinical manifestations of a well-established disease, did not allow its early recognition. In this context, LeRoy and Medsger proposed in 2001 criteria for the early diagnosis of SSc, which include a combination of clinical (Raynaud's phenomenon), imaging (nailfold capillaroscopy with SD pattern) and laboratory (presence of SSc-specific autoantibodies) data.[29]

Recently, the Research Group on Scleroderma from EULAR suggested preliminary criteria for the very early diagnosis of SSc using the same three domains, with the addition of the presence of swollen fingers and a positive result for antinuclear factor.[30]

Corroborating the importance of NFC in the diagnosis of SSc, ACR and EULAR proposed in 2013 new criteria for the classification of SSc.[6] According to these new criteria, the patient is classified as having SSc if he/she get a total of nine or more points among those eight items listed in Table 2, with a sensitivity of 91% and specificity of 92% in a cohort study, compared to a sensitivity of 75% and specificity of 72% with the application of the 1980 ACR criteria.

Systemic lupus erythematous

Capillaroscopy changes in SLE are less specific than in SSc, being characterized by the presence of tortuous and meandering capillaries, bizarre loops and a prominent subpapilar plexus, leading some authors to postulate the presence of a typical capillaroscopic pattern.[31] The presence of alterations in NFC is more frequent in patients with SLE presenting RP.[32] However, 50% of patients with SLE have normal NFC. SD pattern is a less common finding and has been described in 2–9% of patients.[33,34] In these patients, there seems to be a correlation between the presence of SD pattern, fingertips vasculitis and anti-U1-RNP antibodies.[34,35]

Recently, recommendations for the screening and detection of pulmonary arterial hypertension in patients with autoimmune rheumatic diseases suggested that patients with SLE with characteristics of SSc spectrum of diseases, for example, the presence of NFC with SD pattern, should also perform an annual screening for the diagnosis of pulmonary arterial

Table 2 – Classification criteria for SSc proposed by ACR and EULAR (2013).[6]

Item	Sub-item	Valor
Skin thickening of the fingers, proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (only consider the higher score)	Sclerodactily of the fingers (distal to the metacarpophalangeal joints)	4
Fingertip lesions (only consider the higher score)	Puffy fingers	2
Raynaud's phenomenon	Digital ulcers	2
Autoantibodies specific for SSc (anti-centromere, anti-RNA polymerase III, anti-topoisomerase I [anti-Scl70])	Fingertip pitting scars	3
Telangiectasias		3
Abnormal nailfold capillaroscopy		3
Pulmonary arterial hypertension and/or interstitial lung disease		2

hypertension, suggesting a major role of NFC in identifying this subtype of patients.[36]

Dermatomyositis and polimyositis

The prevalence of DM/PM in RP ranges from 10 to 60%, but the presence of complications such as digital necrosis is rare.[37] The SD pattern is observed in about 20–60% of patients with DM/PM, with more frequent and pronounced findings in DM than in PM; it correlates with the presence of RP and interstitial pulmonary involvement.[38] The presence of branched capillaries is more common in DM, but their presence is not specific and can also be found less frequently in patients with SSc. In studies with juvenile DM, the SD pattern is most common, having a positive association with severity and clinical and laboratory activity of the disease.[39–41]

Mixed connective tissue disease

RP is one of the initial manifestations of the disease, occurring in approximately 85% of patients with MCTD and is also part of the main classification criteria for this disease.[42] SD pattern is observed in 50–65% of cases. A correlation between capillaroscopy findings and pulmonary involvement in MCTD is also described.[43]

Undifferentiated connective tissue disease (UCTD)

The term UCTD is used when, in the presence of clinical manifestations suggestive of systemic autoimmune disease, a shortage of clinical and/or laboratory data does not allow the characterization of a specific clinical entity. The follow-up of this group of patients points to a clinical outcome for SSc, SLE, rheumatoid arthritis or Sjögren's syndrome in 30% of cases. Nagy et al. found a prevalence of 13.8% for SD pattern in 65 patients with UCTD and suggested that NFC be performed in all cases of UCTD with the aim of identifying patients at higher risk for progression to SSc or to its spectrum diseases.[33]

Primary Sjögren syndrome (SS)

In SS, the capillaroscopic findings differ, depending on the presence or absence of RP, present in 13–30% of patients.[44,45] In primary SS without RP, NFC is normal in more than half of patients; the other patients present nonspecific capillaroscopic findings, including the presence of tortuous, irregular capillaries and of a more evident subpapilar plexus. When there is presence of RP, most patients also show nonspecific capillaroscopic findings. The SD pattern was described in two of 16 patients (12.5%) with SS in one study.[46] In the subgroup of patients with SS and with positivity for anticentromere, the researchers found a prevalence of 80% of the SD pattern, indicating a potential for subclinical overlap with SSc.[46]

Rheumatoid arthritis (RA)

In patients with RA there is no description of a SD pattern.[2] Some studies show the presence of changes of uncertain relevance in a proportion of patients, such as the presence of elongated capillaries.[2]

Antiphospholipid syndrome (APS)

Presence of microbleeding distributed symmetrically is described in APS patients and in SLE patients with presence of IgG and IgM anticardiolipin antibodies, suggesting a direct damage of vascular endothelium triggered by these antibodies.[47,48]

Capillaroscopy as a marker of severity of systemic sclerosis

Despite some controversial results, capillaroscopy also assumes an important role in evaluating the severity of the disease, visceral involvement, and prognosis of patients with SSc. In 1976, Maricq et al. previously had found a correlation between morphological changes of NFC and the number of organs involved by the disease.[49] Over the years, most studies found a correlation with the degree of microangiopathy evaluated by NFC and peripheral vascular, cutaneous and pulmonary involvement.[2,16,50] Recently, a study of two cohorts of Belgian and Italian patients found an association between the severity of capillaroscopy patterns and risk of severe clinical involvement. Nine systems and/or organs (peripheral vascular, general, skin, joints, muscles, gastrointestinal tract, lung, heart and kidneys) were evaluated according to Medsger severity scale. There was an association between risk of serious visceral injury and early, active and late patterns, and the risk was higher in patients presenting the late pattern.[51]

Digital ulcers are common vascular complications in patients with SSc. Different studies have demonstrated an association between the score of capillary loss or more severe changes in NFC and increased risk for development of digital ulcers.[52,53] A recent study proposed a capillaroscopic

index (CSURI) to predict the emergence of new ulcers in SSc patients.[53] Taken together, these results suggest the NFC routine use in patients with SSc, aiming the identification of patients with increased risk for development of this complication.

Regarding pulmonary involvement, a study found a significantly lower capillary density in patients with pulmonary arterial hypertension associated with SSc, compared with patients without pulmonary hypertension.[54] In another study, Bredemeier et al. found a correlation between higher scores for avascular areas and ground-glass opacities in 91 patients with SSc.[55]

Finally, a study from our group demonstrated an association between risk of death and higher scores for devascularization (>1.5) in NFC in a group of 125 patients with SSc.[56]

Conclusions

Capillaroscopy is an extremely useful and reliable method for the differential diagnosis between primary and secondary RP. Additionally, the use of NFC may aggregate information about the disease severity and degree of visceralization in patients with SSc. Currently, two methods are most used for performing NFC: panoramic nailfold capillaroscopy, using a stereomicroscope, and videocapillaroscopy, which uses larger magnifications and a computerized system of image acquisition.[3] Both have advantages and disadvantages; however, they are equivalent for the identification of classical abnormalities, allowing the recognition of three patterns: normal pattern, nonspecific microangyopathy and SD pattern.[23] The inclusion of capillaroscopic abnormalities in the new classification criteria of the ACR/EULAR for SSc gives a new impetus to the use and dissemination of capillaroscopy. The education and training of rheumatologists qualified to perform the capillaroscopy was an issue neglected for years, with prevalence of self-teaching. EULAR promotes regular courses in capillaroscopy. In Brazil, the first course of capillaroscopy in autoimmune rheumatic diseases was conducted in 2011 by the Discipline of Rheumatology of *Universidade Federal de São Paulo*. Dissemination, training and improvement of the method must remain in the specialty agenda.

Conflicts of interest

The authors declare no conflicts of interest.

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