



CAPILLAROSCOPIC PATTERNS IN RHEUMATIC DISEASES

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ABSTRACT

Nailfold capillaroscopy (NVC) is a simple, non-invasive, inexpensive and useful method for the analysis of microvascular abnormalities found in several rheumatic disorders. The well-known Raynaud's phenomenon is a clinical condition that should promptly lead to a microvascular analysis, in order to distinguish its primary form (functional, not disease associated) from the secondary Raynaud's phenomenon (disease associated). NVC has an exceptional predictive value in this early distinction, and this may be the best advantage this technique can offer.

Microvascular damage is a typical feature of Systemic Sclerosis (SSc) and more than 95% of the patients present architectural disorganization, giant capillaries, haemorrhages, loss of capillaries, avascular areas and neovascularization, as main microvascular abnormalities. These sequential capillaroscopic changes characterize the «scleroderma pattern» and reflect the SSc microangiopathy. In dermatomyositis and undifferentiated connective tissue disease the capillaroscopic aspects are generally named as «scleroderma-like pattern». Capillaroscopy changes have also been found in other systemic rheumatic diseases such as Systemic Lupus Erythematosus, Antiphospholipid Syndrome and Sjögren's Syndrome, further epidemiological and clinical studies are needed to better characterize and standardize nailfold capillaroscopy patterns in these disorders.

Keywords: Capillaroscopy; Raynaud's Phenomenon; Systemic Sclerosis; Microangiopathy.

RESUMO

A capilaroscopia do leito ungueal é um método simples, não-invasivo, económico e muito útil para estudo das alterações da microcirculação encontradas em várias doenças reumáticas. A presença do fenómeno de Raynaud deve conduzir a uma avaliação imediata da microcirculação para distinguir a sua forma primária (funcional, não associada a doença) da forma secundária (associada a outra patologia). Uma das grandes vantagens da capilaroscopia do leito ungueal é o seu excepcional valor predictivo na distinção precoce destas duas formas.

As lesões microvasculares ocorrem tipicamente na esclerose sistémica e mais de 95% dos doentes apresenta desorganização da arquitectura dos capilares, megacapilares, hemorragias, perda de capilares, áreas avasculares e neovascularização como alterações mais frequentemente encontradas. Estas alterações sequenciais caracterizam o «padrão de esclerodermia» e reflectem a microangiopatia da esclerose sistémica. Na dermatomiosite e na doença indiferenciada do tecido conjuntivo os aspectos capilaroscópicos são denominados genericamente como «padrão esclerodermia-like». As alterações capilaroscópicas também têm sido encontradas noutras doenças reumáticas sistémicas como o lúpus eritematoso sistémico, a síndrome dos anticorpos antifosfolípidos e a síndrome de Sjögren, mas são necessários mais estudos clínicos e epidemiológicos para melhor caracterizar padrões capilaroscópicos nestas patologias.

Palavras-Chave: Capilarocopia; Fenómeno de Raynaud; Esclerose Sistémica; Microangiopatia.

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Introduction and historical review

The story of the capillaroscopy «started» from the observations of an Italian physician, Giovanni Rastori (1766-1837), who described the close relationship between conjunctival inflammation and the presence of an «inextricable knot of capillary loops» by a magnifying glass.

During the beginning of the 20th century Brown and O'Leary used the capillaroscopic analysis to show in detail the abnormalities that characterize involvement of the microvasculature during Raynaud's phenomenon (RP) in Systemic Sclerosis (SSc).¹ In 1973 Hildegard Maricq and Carwyle LeRoy published the first paper in Arthritis & Rheumatism describing the specific capillaroscopic patterns in SSc, as well as the modification of the capillary blood flow during cold exposure both in primary and secondary RP.^{2,3} In the 21st century, Cutolo *et al.* defined three major nailfold videocapillaroscopy (NVC) patterns for SSc, which reflect the progression of the microvascular abnormalities in this condition: «early», «active» and «late» patterns.⁴ NVC represents the best method to analyze microvascular abnormalities in rheumatic diseases. In normal conditions, the microvascular pattern is characterized by a regular array of microvessels with large intra/inter-individual variability. However, absolute absence of capillary loss and giant capillaries is expected in normal pattern.

How to perform a capillaroscopy

The observation of the capillary bed is usually made at nailfold, because here capillaries run parallel to the skin surface, whereas in other areas they are perpendicular to skin surface. The room temperature should be constant, between 20-22°C, and the

patient should be kept inside for at least 15 minutes before the exam. All ten fingers should be examined, except those affected by recent local trauma. The observation is more accurate in the fourth and fifth fingers due to the greater skin transparency in these fingers. A drop of immersion oil is placed at nailfold of each finger before observation, in order to improve image resolution.

NVC is a simple, non-invasive, cheap and useful tool for the study of microvasculature, and in clinical practice it is usually performed through an incident light microscope. More recently, the videocapillaroscopic systems have demonstrated to be a sophisticated method of microvascular analysis, which can also detect blood flow in the microvessels.

Capillaroscopy: when to perform?

RP is the hallmark of microvascular involvement in several rheumatic diseases, and it is particularly important in SSc (Figure 1). The occurrence of this phenomenon should promptly lead to a microvascular analysis through capillaroscopic examination. Several criteria are helpful in distinguishing primary RP (functional, not disease associated)



Figure 1. The Raynaud's phenomenon.

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from secondary RP (disease associated):⁵

Primary RP

- Symmetric attacks
- Absence of tissue ulceration, necrosis or gangrene
- Absence of serum antinuclear antibodies
- Normal erythrocyte sedimentation rate (ESR)
- Normal aspect of nailfold capillaries

Secondary RP

- Age of onset above 30 years
- Intense, symmetrical, painful and/or associated with ischemic skin lesions
- Presence of specific autoantibodies
- Clinical features suggestive of connective tissue disease
- Evidence of microvascular alterations in capillaroscopic examination

The mean age of onset of primary RP is 14 years, with 27% beginning at 40 or later.⁶ In a meta-analysis of 10 articles⁷ about 10% of people suffering from RP who sought medical help developed a connective tissue disease (CTD) (n=639). These data suggest that it is essential to identify the patients at significant risk of developing a CTD from the wide population with RP. One of the best advantages that rheumatologists can have with NVC is its high negative predictive value for CTD (>90%) in subjects with RP. On the other hand, its positive predictive value is only about 50%, but this is higher than any other single screening test.⁸

Approximately 15 to 20% of individuals with RP who have microcirculatory alterations (assessed by NVC) and/or autoantibodies will develop a connective tissue disease within two years (not meeting criteria at baseline).⁹

The normal aspect of the capillary bed

Nailfold's capillaries in the healthy subject usually show a regular architecture, uniform shape, distribution and diameter, and most of them show a hairpin or U shaped aspect (Figure 2). An early morphological feature of SSc's microangiopathy is a striking modification of the normal capillary architecture, which can be seen in capillaroscopy. The early microvascular alterations in patients with recent onset of RP may be patchy, unilateral or even in a single finger, and that is why all the fingers should be examined.



Figure 2. The nailfold's capillaries in the healthy subject usually show a regular architecture, uniform shape, distribution and diameter; and most of them show a hairpin or U shaped aspect. (magnification 200x)

Capillaroscopy patterns: the scleroderma pattern

Microangiopathy, which is an important feature of SSc, is characterized by a sequence of events occurring in the microvessels, that can be easily assessed by nailfold capillaroscopic examination, or even better by videocapillaroscopic examination: this technique is safe, non invasive and has both diagnostic and prognostic value in the presence of RP.^{10,11}

Previous capillaroscopy studies have graded and classified microvascular damage in SSc into two major capillaroscopy scleroderma patterns, namely the «active» (presence of definite loss of capillaries – moderate or extensive) and the «slow» (capillary telangiectasias and/or extremely enlarged nailfold capillaries with no or minimal loss of capillaries) patterns.¹²

Recently, the scleroderma microangiopathy has been reclassified into three major patterns: «early», «active» and «late» pattern.⁴ The «early» scleroderma NVC pattern is characterized by relatively well-preserved capillary distribution, few enlarged/giant capillaries, few capillary haemorrhages and no evident loss of capillaries (Figure 3). Frequent giant capillaries, frequent haemorrhages, mild disorganization of the capillary architecture, moderate loss of capillaries, absent or mild ramified capillaries characterizes the «active» pattern (Figure 4). In the «late» pattern severe loss of capillaries with extensive avascular areas, together with disor-

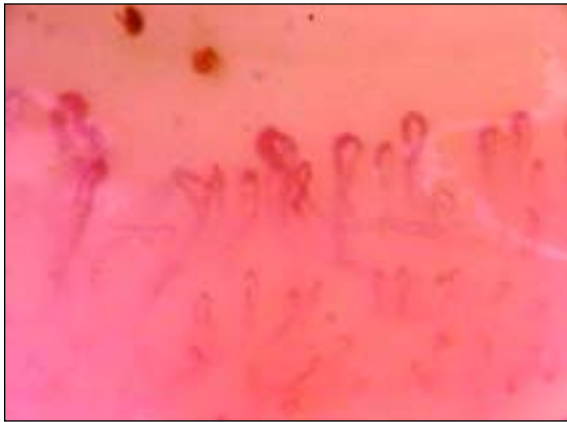


Figure 3. The «early» scleroderma NVC pattern characterized by a relatively well-preserved capillary distribution, few enlarged/giant capillaries, few capillary haemorrhages, no evident loss of capillaries (magnification 200x)



Figure 5. In the «late» pattern severe loss of capillaries with extensive avascular areas, disorganization of the normal capillary array, ramified/bushy capillaries are commonly found, as well as irregular capillary enlargement and few or absent giant capillaries or hemorrhages (magnification 200x)



Figure 4. The «active» pattern characterized by frequent giant capillaries, frequent hemorrhages, mild disorganization of the capillary architecture, moderate loss of capillaries, absent or mild ramified capillaries (magnification 200x)



Figure 6. The hallmark of the scleroderma pattern is the presence of megacapillaries (magnification 200x)

ganization of the normal capillary array, ramified/ /bushy capillaries are commonly found, as well as irregular capillary enlargement and few or absent giant capillaries or haemorrhages (Figure 5).

This classification stresses the sequential process of SSc microangiopathy, beginning with a predominantly microvascular damage which progresses into a fibrotic phase with loss of capillaries and aspects of neovascularization in latter stages. There is progressive and significant increase of the latter microvascular abnormalities during SSc, and the three NVC patterns were found to correlate with both RP and SSc duration, reflecting at least,

the possible evolution of the disease process.⁴

The NVC patterns have been correlated with different clinical features of the disease, thus playing an important part in the overall study of the disease.^{13,14} Recently, the relationship between specific autoantibodies and the patterns of microcirculatory damage in patients with SSc (limited cutaneous and diffuse cutaneous forms) was investigated: the positivity for Scl 70 antibody was more commonly found in patients exhibiting «active» and «late» NVC patterns, than in the «early» pattern patients. However, no significant correlation was found between Scl 70 presence and both RP and disease duration.¹⁵

Capillaroscopic patterns and rheumatic diseases

The hallmark of the scleroderma pattern is the presence of megacapillaries (Figure 6) and decreased capillary density. In a large recent study, 186 patients with secondary RP (65 with undifferentiated connective tissue disease (UCTD), 47 with systemic lupus erythematosus (SLE), 26 with dermatomyositis, 14 with rheumatoid arthritis (RA), 7 with primary Sjögren's syndrome (SS) and 102 with SSc) were investigated.¹⁶ A scleroderma pattern was found in 14 of 16 patients diffuse cutaneous SSc (87,5%), and in 53 of 86 patients with limited cutaneous form of SSc (61,6%). A scleroderma pattern was identified in 13,8% of UCTD, 8,5% of the SLE and 26,4% of the patients with dermatomyositis. None of the patients with RA or primary SS had this capillaroscopic pattern.

In conclusion, the scleroderma pattern is often

present in dermatomyositis, and can occasionally be found in patients with RP and UCTD, and therefore, NVC helps in the early selection of patients more prone to develop scleroderma spectrum disorders.

Dermatomyositis

A well defined pattern has been described in patients with dermatomyositis,¹⁷ and it includes two or more of the following findings in, at least, 2 nail-folds: enlargement of capillary loops, loss of capillaries, disorganization of the normal distribution of capillaries, «budding» («bushy») capillaries (seen in Figure 7), twisted enlarged capillaries, and capillary haemorrhages (seen in Figure 8).¹⁸ This pattern is often associated with scleroderma pattern and is also called «scleroderma-like pattern».

SLE

The microvascular alterations found in SLE include morphological changes in capillary loops, venular visibility and sludging of blood with variability of capillary loop length (Figure 9).¹⁹ One hundred patients with SLE were evaluated in a recent study.²⁰ In this study, both the presence of altered NVC was associated with the presence of RP ($p<0,001$) or anti U1 RNP antibodies ($p<0,01$), and also with the simultaneous presence of RP and U1 RNP antibodies ($p<0,001$). These authors also found a negative association between the presence of anticardiolipin antibodies and scleroderma pattern ($p<0,05$). Therefore, this study demonstrates a strong association between capillaroscopic

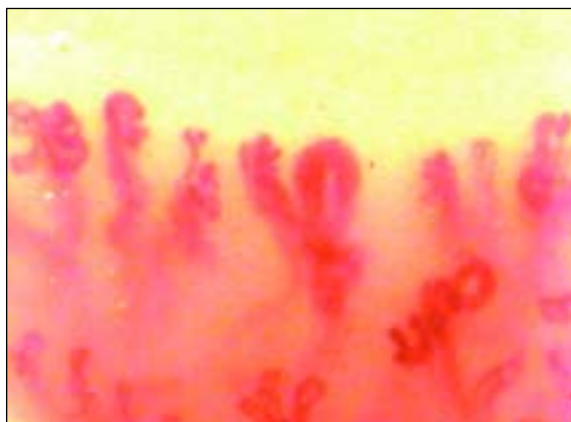


Figure 7. «Budding» («bushy») capillaries related to the neovascularization (magnification 200x)

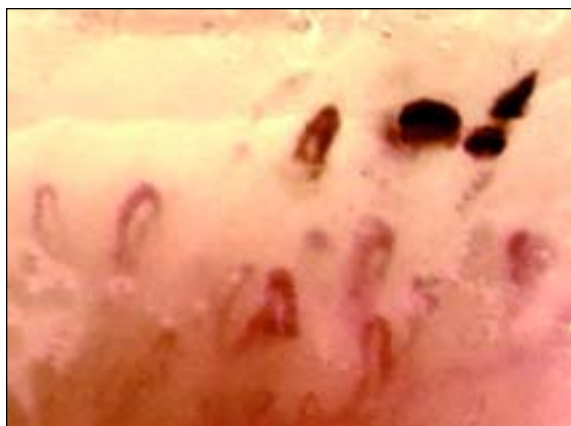


Figure 8. Capillary microhemorrhages (magnification 200x)

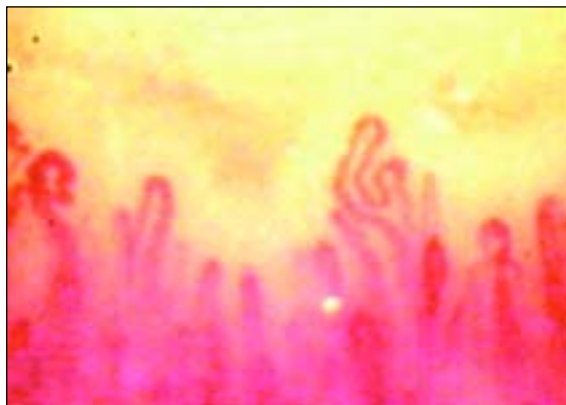


Figure 9. Microvascular alterations found in SLE include morphological changes in capillary loops, venular visibility and sludging of blood with variability of capillary loop length (magnification 200x)

abnormalities and either U1 RNP antibodies or RP in SLE patients.

A recent retrospective study²¹ in patients with SLE (n=123) analysed NVC alterations and possible association with clinical features and laboratory parameters: 35,8% of the patients showed major capillary abnormalities but no specific pattern was noted. Also, there was no association between the presence of anticardiolipin antibodies and microvascular changes. However, there was a significant correlation between SLEDAI index and the severity of capillary abnormalities ($p<0,0001$). It was also found that pathologic capillary abnormalities were increased in the presence of anti U1-RNP antibodies ($p<0,05$). These data suggest that NVC examination could be useful in identifying the more severe forms of the disease.

Sjögren's Syndrome

Microvascular abnormalities have been reported in primary SS.²² In a recent controlled study, 40 patients with primary SS (16 with RP, 14 without RP and 10 with anti-centromere antibodies (ACA)), 20 with scleroderma (disease control group) and 40 healthy controls were evaluated. Patients with SS and RP showed a higher frequency of microvascular abnormalities than those without RP. 80% of the patients with ACA showed scleroderma-type findings. Thus, nailfold capillaroscopy can be used to easily assess the microvascular changes in SS patients, especially in those with RP and those with ACA.²³

Antiphospholipid Syndrome

Microcirculatory changes were recently described in patients with primary antiphospholipid syndrome (PAPS). In a recent study,²⁴ the percentage of subjects with morphological microvascular alterations (mainly tortuosities) was 78%, compared to 21% of healthy controls. Capillary diameter was found to be significantly smaller in PAPS patients than in controls, although no difference was found in capillary density or blood flow velocity. Another study reported the presence of symmetrical microhemorrhages at NVC analysis, and these alterations were found to be particularly significant in patients with both IgG and IgM anticardiolipin antibodies (Figure 10).²⁵ The thrombotic manifestations in APS have also been related to marked microcirculatory damage, confirming the pattern (symmetrical microhemorrhages).¹⁹

In summary, NVC is a safe, inexpensive and use-

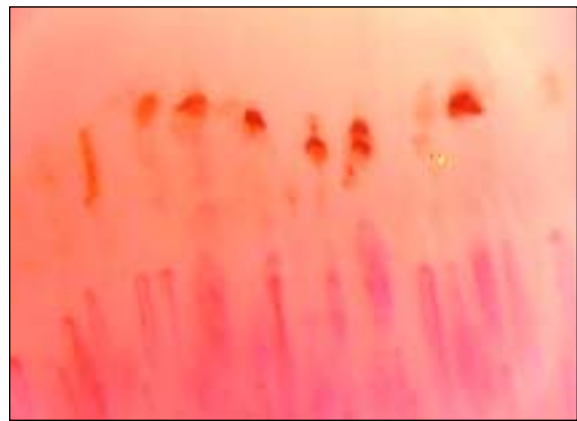


Figure 10. Symmetrical microhemorrhages at capillaroscopic analysis are found particularly significant in patients with both IgG and IgM anticardiolipin antibodies (magnification 200x)

ful technique for microvascular analysis in rheumatic diseases and has a highly negative predictive value in the evaluation of patients presenting with RP.²⁶ Its value is unquestionable in the assessment of SSc microangiopathy. In SLE minor microcirculatory alterations have been reported but the scleroderma pattern seems to be associated with the presence of RP and U1 RNP antibodies, as mentioned above. In dermatomyositis a scleroderma-like pattern has been well defined and in SS scleroderma-like findings have been associated with the presence of ACA. In PAPS microcirculatory changes (mainly tortuosities) are common and symmetrical haemorrhages have been reported specially in patients with anticardiolipin antibodies and thrombotic manifestations.

Further studies in this area are needed to better characterize NVC patterns in rheumatic diseases. NVC opens a window to the systemic microvascular damage that occurs in certain rheumatic diseases and plays an important role in the diagnosis and prognosis of SSc.

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