

# Indications and results of videocapillaroscopy in clinical practice

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## ABSTRACT

Nailfold videocapillaroscopy (NVC) is one of the best diagnostic non-invasive imaging techniques to evaluate microcirculation in vivo and is increasingly employed in the field of rheumatology. Indeed, at present, the most important utility of NVC is in the identification of microvascular involvement in many rheumatic diseases, particularly in systemic sclerosis. More recently, this technique has been shown to be applicable to the study of many other extra-rheumatic diseases, such as arterial hypertension, diabetes mellitus, acromegaly, hyperthyroidism, cardiac syndrome X, primary biliary cirrhosis, Crohn's disease, psoriasis, familial Mediterranean fever.

This article sets down the methodology of examination and normal pattern of capillary vessels and reviews the applications of NVC in clinical practice and its results in rheumatic and non-rheumatic diseases.

**Key words:** videocapillaroscopy, rheumatology, systemic sclerosis, Raynaud's phenomenon, microcirculation involvement

## INTRODUCTION

Nailfold videocapillaroscopy (NVC) is now considered one of the best diagnostic non-invasive imaging techniques capable of studying microcirculation in vivo [1,2]. Over the last 20 years, utilization of NVC has been increasingly employed in the field of rheumatology and this technique is currently extremely useful in the identification of microvascular involvement in many rheumatic diseases, particularly in systemic sclerosis (SSc) and related disorders. At the same time, NVC has proved valuable in several other extra-rheumatic diseases.

The aim of the present article is to review the applications of NVC in clinical practice and its results in rheumatic and non-rheumatic diseases.

## NAILFOLD VIDEOCAPILLAROSCOPY: METHODOLOGY OF EXAMINATION AND NORMAL PATTERN

A fixed PAL colour video-camera equipment with contact optical lens forms the apparatus for NVC. The source of light is provided with halogen cold light transmitted by means of optical fibres. The images are observed on a high definition colour monitor (17 inches) and digitally stored on a computer hard disk, with the consequent possibility of immediate printing for reports and sending images via modem for comparative evaluation of the different patterns. The images can also be processed by means of software integrated with the image digitizer board. Exploiting the board technology, the program takes full advantage of the quality and format characteristics of the multiple video outputs of the videocapillaroscopy. The program is a highly sophisticated piece of software, though extremely easy and flexible to use. It can be used both for research purposes and in clinical practice providing rapid information on retrieval capabilities and the visualization of previously acquired images. Digital filters such as grey scale, watershed and top hat can be applied to the images to

separate relevant areas from image background. The filters can also be applied in succession. The software allows extremely precise measurements to be made, taking into account image magnification. Specifically, length, diameter, area and density can be measured and the measurements stored in the image itself. A millimetre grid can be applied to the whole image or to a portion of it with the grid step varying according to the magnification used during image acquisition, a useful function to calculate capillary density. One of the main advantages of NVC is that the contact probes make it possible to explore areas of skin surface, impossible to observe with traditional systems. Indeed, the video-camera equipment with optical contact probes may be easily moved to any body surface, including the conjunctiva and lip mucosa. Furthermore, the power of optical probes can range from 100x to 1000x magnification, though magnification of 200x is routinely employed in clinical practice.

The nail bed is normally utilized to study the micro vessels *in vivo* because of the easy approach with the specific probe; furthermore, capillary vessels at nail bed level are parallel to the cutaneous surface and it is thus quite easy to obtain valuable images.

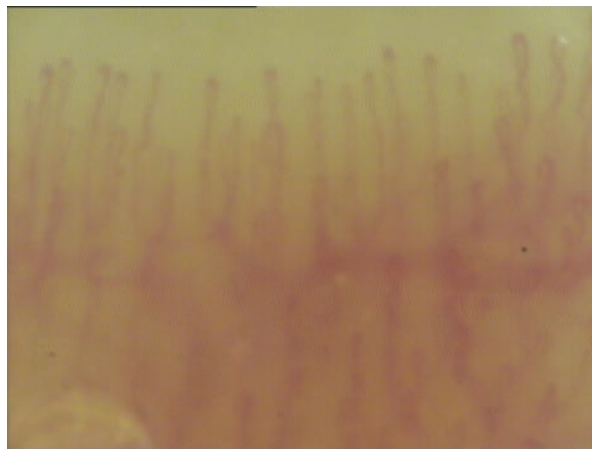
The patient should be seated with hands placed down on the examination table; environmental temperature should be between 21 and 24 degrees centigrade and the patient should refrain from smoking at least one hour before the examination. All the surfaces to be investigated must be uncovered at least 20-30 minutes before the examination in order to balance the body temperature with the environment. To obtain the best optical view it is necessary to put one droplet of cedar oil on the nail bed. Nailfold capillaroscopic examination should be carried out on all fingers, as morphological alterations of capillaries can be circumscribed in the initial phases of disease. However, the best visibility of the nailfold capillaries is generally to be found at the 4<sup>th</sup> and 5<sup>th</sup> fingers of the non-dominant hand.

NVC allows: a) evaluation of capillary vessel architecture; b) evaluation of morphology, distribution and number of capillary vessels; c) evaluation of capillary inflow and outflow characteristics.

The normal pattern of capillary vessels is as follows:

- characteristic appearance like a hairpin or upside down U;
- regular distribution and homogeneous morphology of small vessels;
- one to three capillary vessels in each dermal papilla;
- the number of capillary vessels at the periungueal level is 9 to 13/mm (mean);
- the diameter of blood column at the level of the arterial border ranges from 5 to 16  $\mu$ ;
- the diameter of blood column at the level of the venular border ranges from 7 to 18  $\mu$ ;
- mean length of the periungueal capillary visible tract is approximately 400  $\mu$ .

**Figure 1. Normal pattern of capillary vessels.**



## NAILFOLD VIDEOCAPILLAROSCOPY: PATHOLOGIC PATTERNS

NVC allows many types of micro vessel abnormalities to be identified. Main pathologic patterns are related to: architectural disorder, increase in the vascular loop diameter, decrease in capillary density, neoangiogenesis (ramifications, tortuosity, branching), microbleeding/microthrombosis, decrease of blood flow speed. In healthy subjects tortuosity, microbleeding and the diameter of the loop may be slightly increased; these aspects may be aspecific [2,3].

Architectural derangement of the nailfold microvascular network includes: altered capillary distribution, shape heterogeneity of the loops and irregular capillary orientation. This pattern represents one of the characteristic elements of microvascular involvement in connective tissue disease.

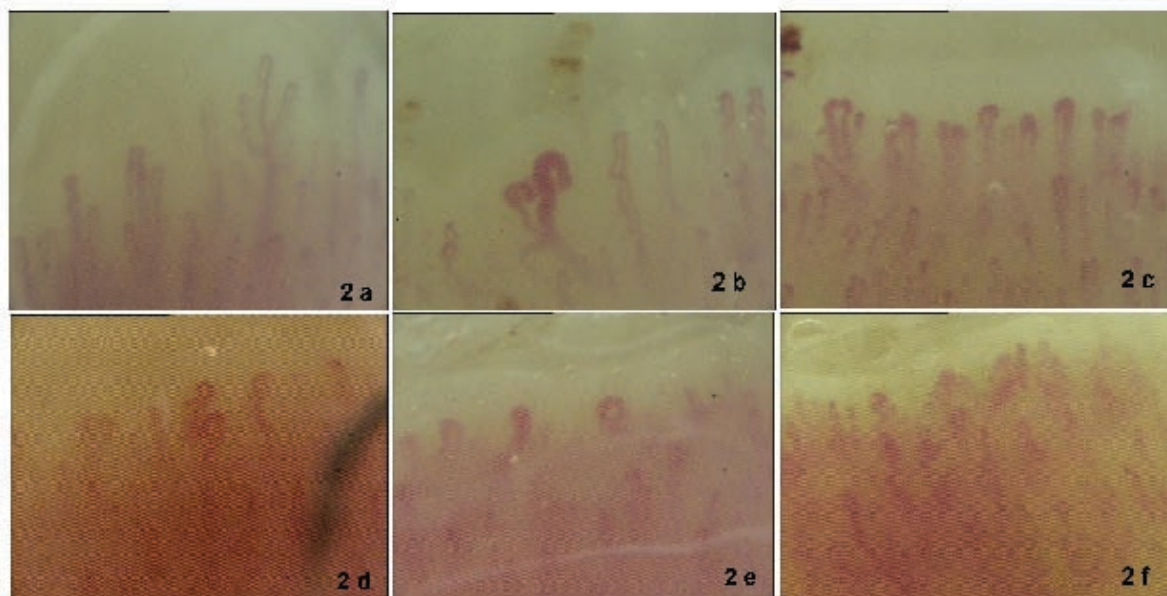
Enlarged loops, on the basis of their shape, can be divided into two types: homogeneous and irregular. In the latter there is only a circumscribed increase of the capillary diameter (micro-aneurysm). Homogeneously enlarged loops with a diameter > 50  $\mu$ m, are known as megacapillaries.

Capillary loss is characterized by progressive reduction in capillary density. An avascular area is the absence of capillaries for an area > 500  $\mu$ m or the loss of two contiguous capillaries; confluence of many avascular areas leads to so-called "deserted areas".

Angiogenesis can reasonably be considered as an attempt to compensate capillary loss. It may take the form of tortuosity (single or multiple crossovers: "8" loops, "treble clef" loops, "corkscrew" loops), branching ("antler" loops, "chandelier" loops, "cactus" loops, "trefoil" loops), anastomosed loops ("bush" loops, "glomerular" loops, "ball" loops) [3] (Fig. 2).

**Figure 2. Pathologic patterns:**

**a:** Tortuosity and enlarged loops. **b:** Megacapillary and capillary loss. **c:** Enlarged loops and microbleeding. **d:** Branching. **e:** Enlarged loops and capillary loss. **f:** Tortuosity.



## CAPILLAROSCOPY IN RHEUMATIC DISEASES

In patients affected by SSc, the most typical nailfold NVC pattern of microangiopathy, the so-called “scleroderma-pattern” (SP), is commonly observed [4,5,6]. It is characterized by irregularly enlarged capillaries, giant capillaries (capillary diameter >50 micron of both arteriolar and venular branches), microbleedings, reduced capillary number with avascular areas, capillary architecture disorganization, as well as ramified capillaries. The giant capillary is pathognomonic of the scleroderma pattern. Three distinct NVC patterns of microangiopathy have been described in SSc patients: “early”, “active” and “late”, which do not normally coexist at the same time. “Early” SP is characterized by irregularly enlarged capillaries, a few giant capillaries and haemorrhages; capillary architecture is almost regular without significant loss of capillaries.

In the “active” pattern frequent giant capillaries and haemorrhages may be observed and mild loss of capillaries and capillary architecture disorganization with a few ramified capillaries.

Severe loss of capillaries with avascular areas, capillary architecture disorganization and ramified capillaries are typical abnormalities of “late” SP.

Furthermore, a semiquantitative scale may be employed to score each capillary abnormality (score 0-3: 0 = absence of abnormalities; 3 = higher number/degree of abnormalities) [7]. The three patterns correlate with the duration of the disease and represent the evolution of SSc microvascular damage (Fig. 3).

Clinical features of SSc such as the presence of different subsets of skin involvement (ISSc and dSSc) are also found to correlate with NVC patterns: patients affected by ISSc were found to have shorter disease duration, as well as showing more frequently “early” or “active” NVC patterns. Conversely, patients affected by dSSc showed longer disease duration and mostly the presence of an “active” or “late” NVC pattern [8]. A correlation was also found between capillaroscopic pattern and blood findings [9]: interesting studies related anti Scl-70 and anti-centromere antibodies to NVC patterns [10], anti-U1-RNP antibodies to SP in SLE with Raynaud’s phenomenon [11] and reduced levels of the angiostatic factor endostatin to the presence of giant capillaries in SSc [12].

The three patterns also correlate with kallikrein serum levels, a potent angiogenic agent [13].

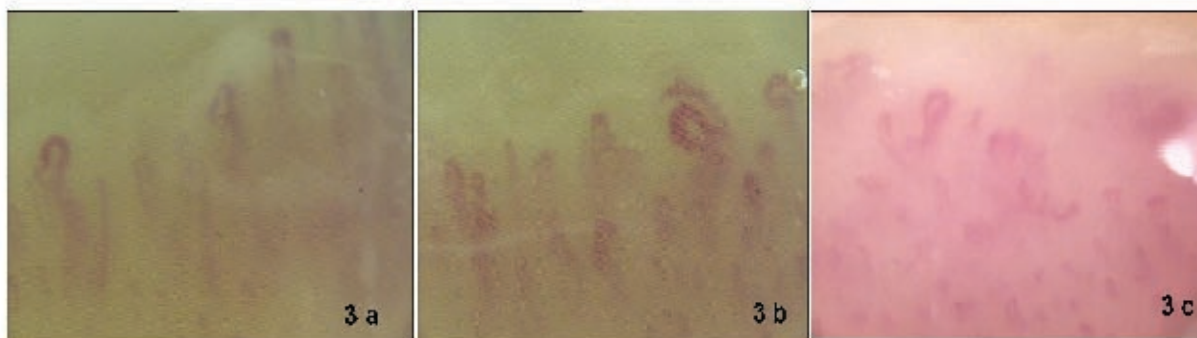
Furthermore, in patients with SSc, nailfold capillary abnormalities correlate with pulmonary arterial hypertension as well as clinical and laboratory findings indicating pulmonary hypertension [14].

A recent study found that the severity of video-capillaroscopic abnormalities is associated with lung disease activity in systemic sclerosis, particularly when the disease duration is relatively short [15].

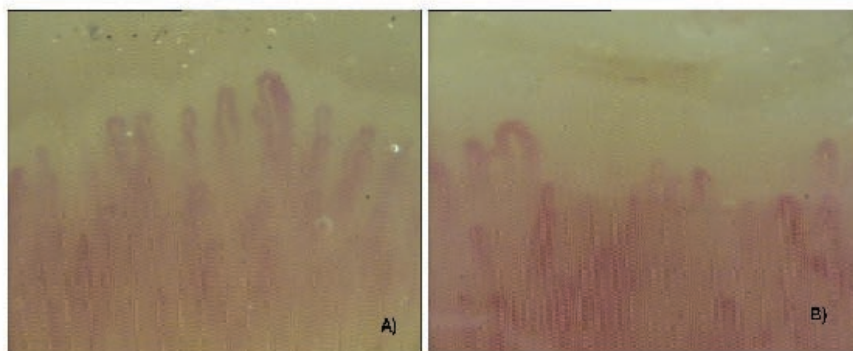
SP may be observed in various connective tissue diseases such as dermatomyositis (DM), mixed connective tissue disease (MCTD), undifferentiated connective tissue disease, overlap syndrome and presclerodermic Raynaud’s phenomenon [16,17].

In DM a greater extent of ramified capillaries is often evident at nailfold videocapillaroscopy examination when compared to SSc (Fig. 4-a). In addition, in MCTD, many ramified capillaries often coexist along with giant capillaries,

**Figure 3. Scleroderma patterns:**  
**a: Early. b: Active. c: Late.**



**Figure 4. a: Dermatomyositis. b: Undifferentiated connective tissue disease.**



and capillary disorganization is extensive. Moreover, it may be impossible to distinguish between a capillaroscopic pattern of undifferentiated connective tissue disease and one of SSc. In some undifferentiated connective tissue disease patients, the capillaroscopic pattern may be characterised by non-specific features of microangiopathy, such as a predominance of tortuous capillaries, homogeneously enlarged loops, non-homogeneity of morphology and orientation. In these patients a follow-up capillaroscopic examination is advisable in order to evaluate the possibility of the development of microvascular changes (*Fig. 4-b*).

Though patients with Sjögren's syndrome do not show typical abnormalities, a capillaroscopic examination should be systematically carried out in order to look for scleroderma pattern-related abnormalities [18]. A scleroderma pattern may be considered as a finding suggesting a possible evolution towards an overlap syndrome with subclinical SSc characterised by limited skin involvement.

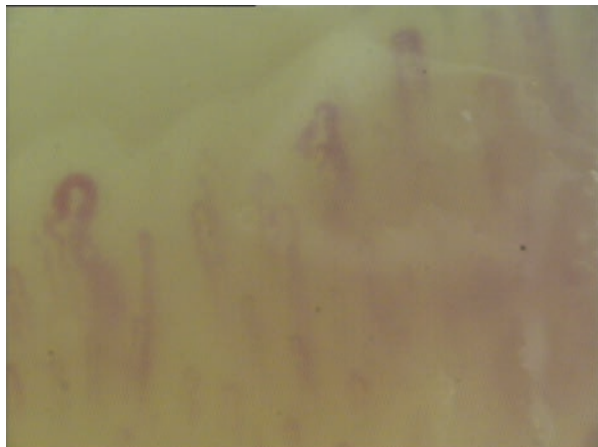
NVC examination is frequently normal in systemic lupus erythematosus; in some patients capillaroscopic abnormalities of uncertain diagnostic value such as increased tortuosity, loop elongation, enlarged loop capillaries and branching loops have been described [19].

Patients affected by antiphospholipid antibody syndrome may exhibit linear haemorrhages with parallel disposition to the nailfold, along with normal capillary morphology. However, these abnormalities may also be found in vasculitis and other connective tissue diseases [20].

A rheumatoid capillaroscopic pattern has been proposed by some authors [21]. However, there is no convincing evidence that specific nailfold capillaroscopic abnormalities can be detected in patients with rheumatoid arthritis. Aspecific elongated loops are often detectable. Other authors [22,23] have suggested a NVC pattern capable of distinguishing psoriatic arthritis (reduction in loop length) from rheumatoid arthritis (elongated loops).

Changes in the microvasculature are also deemed to play an important role in the pathogenesis of psoriasis and its associated arthritis. Psoriasis is a disorder affecting the skin and joints and is thought to be immune-mediated [24,25]. Psoriatic arthritis is a type of inflammatory arthritis affecting some 5-7 % of people suffering from the chronic skin condition psoriasis. It is said to be a seronegative spondyloarthropathy and involves the joints of the fingers and toes. Some authors performed studies to evaluate the microcirculation through NVC in patients suffering from psoriatic arthritis. Salli and coworkers found a reduction in ansa density and in capillary length and calibre as well as interstitial oedema and expansion of the ansa venular portion with coiling and kinking; avascular areas and microaneurysms have been found only in the "mutilans" form [26]. In the "rheumatoid-like" form, ansa reduced in length and calibre have been observed, the characteristic NVC pattern of psoriasis. Another interesting study has been performed to test the hypothesis that any abnormalities in nailfold capillaries of either a quantitative or qualitative nature might be observed



**Figure 5. Raynaud's phenomenon.**

more readily in subjects with a pathology adjacent to the nailfold, i.e. distal interphalangeal joint changes and/or nail dystrophy. In patients with psoriasis there was a significant diminution in both nailfold capillary bed density and a decrease in arterial and venous capillary limb diameters [27].

NVC appears to be extremely useful in patients suffering from Raynaud's phenomenon. Capillaroscopic pattern in these patients can range from features within the normal pattern to aspects classifiable as a so-called "acrocyanotic pattern" or abnormalities that show up like the ones observed in SSc [28,29] (Fig. 5).

Nowadays, NVC represents a standard investigation in patients with isolated Raynaud's phenomenon because it is possible to distinguish between patients with uncomplicated, or primary Raynaud's phenomenon, from those with secondary, connective tissue disease-associated. Furthermore, it is used to

classify and monitor microvascular disease progression and/or treatment response to several vasoactive agents, including prostanoids and endothelin-1 antagonists [12,30].

The "acrocyanotic pattern" is characterised by the prevalence of markedly enlarged loops. The increase in diameter is homogeneous and prevails at the venous limb. In some patients the presence of homogeneously enlarged loops may coexist with features of marked architectural derangement also involving the sub-papillary venular plexus.

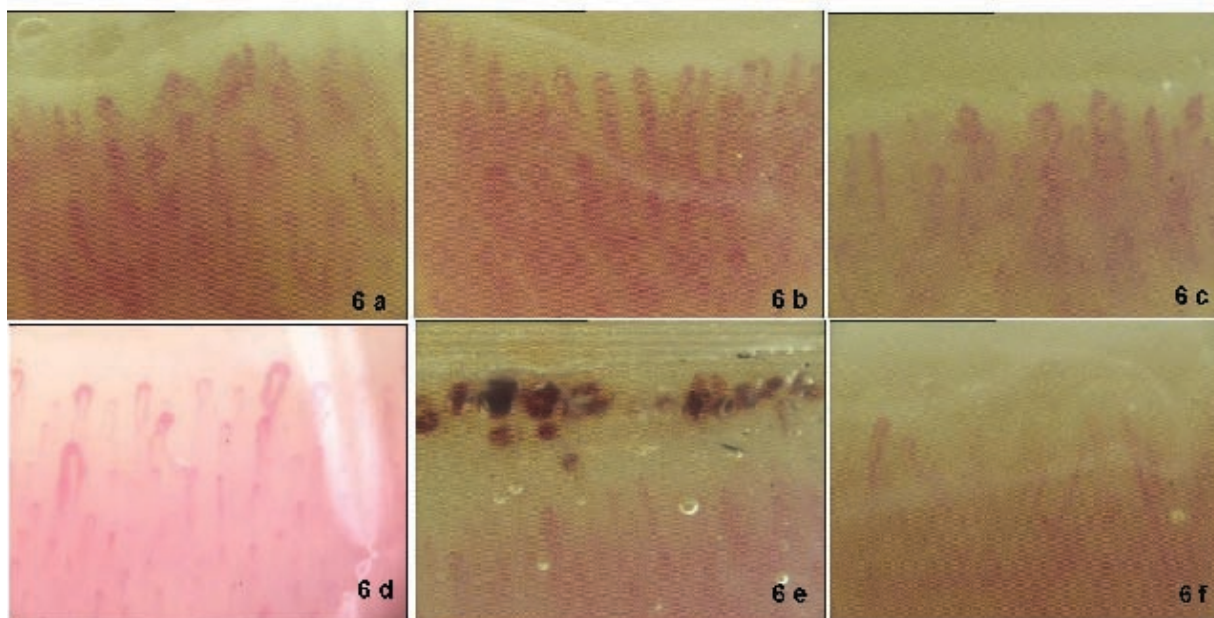
Patients suffering from mixed cryoglobulinaemia show a variety of microcirculatory changes, often clustered in a characteristic pattern of abnormally oriented, short capillaries and neoangiogenetic phenomena, including tortuosity and apical enlargement. Less common alterations included haemorrhages, enlarged and giant capillaries and avascular areas. Capillary changes are more numerous in nephritic patients [31].

## NAILFOLD VIDEOCAPILLAROSCOPY IN NON-RHEUMATIC DISEASES

NVC, traditionally used to evaluate microcirculation involvement in rheumatic diseases, recently showed an increasing relevance also in the evaluation of microangiopathies complicating various non-rheumatic disorders [1].

In arterial hypertension the most common alterations found in capillary organization may be approximately classified as follows: a) quantitative (mean capillary density is significantly reduced, from capillary loss to avascular areas); b) qualitative (neoangiogenesis: tortuosity, branching, enlarged loops, microaneurysms and microbleeding) [32,33]

**Figure 6. The most common alterations found in arterial hypertension: Tortuosity and branching (a, b, c); enlarged loops and microaneurysms (d); microbleeding (e); capillary loss (f).**



(Fig. 6). Some tortuosity is relatively frequent in healthy subjects (especially in the elderly) and should not necessarily be regarded as a feature of microangiopathy. In some clinical studies performed in hypertensive patients, authors observed disorders in peripheral microcirculation with a significant reduction in capillary density compared with normotensive subjects; furthermore, there was a correlation between capillary density and mean diastolic blood pressure. Other authors found that these findings may be improved by anti-hypertensive treatment [34]. After local cooling the frequency of blood flow stop was significantly higher in hypertensive patients. The NVC finding of abnormal vasoconstriction in finger microcirculation in essential hypertension suggests a vasospastic tendency in the disease. By means of this technique it is also possible to evaluate the effects of pharmacological compounds on microcirculation. In an interesting study, changes in the microvasculature were found in subjects with early and subtle elevations in blood pressure [35].

Recently, we observed that NVC demonstrated a higher percentage of microvascular abnormalities in hypertensive patients with nuclear magnetic resonance evidence of cerebral gliosis [36]. We also evaluated this procedure in hypertensives with and without secondary impairment of renal microcirculation. Considering the two groups of hypertensives (resistance index of renal artery higher or lower than 0.68), we found a significant percentage of nailfold NVC alterations in patients with high values of resistance index [37,38]. Our data suggest that NVC can be considered a useful procedure to evaluate impairment of microvascular bed in arterial hypertension, but it is likely that its diagnostic efficacy has to be improved through a numeric score able to quantify the capillaroscopic alterations and then to best discriminate the hypertensives with a higher resistance index.

A typical NVC “diabetic pattern” has not yet been described. However, NVC allows the detection of some possible features of diabetic microangiopathy such as homogeneous increase in capillary diameter (especially at the venous limb level) and convoluted loops. Indeed, differences in morphologic capillary diameters and capillary density were found between diabetics and healthy control subjects [39]. Such abnormalities, although of limited diagnostic value, could play a part in the characterization of diabetic microangiopathy. In diabetic patients microangiopathy is a frequent and often early complication, involving mainly retinal and renal microcirculation. Several studies have evaluated the morphology and density of nailfold capillaries in patients with type I and type II diabetes mellitus and in healthy controls by means of videocapillaroscopy [40-42]. Diabetic patients presented more tortuous and enlarged capillaries than controls; nodular apical elongation was found only in diabetics and was more frequent in patients with a longer history of disease. Type II diabetic patients with chronic clinical complications had a higher frequency of enlarged capillaries and nodular apical elongation [43]. An arrangement called “shoal of fish” has also been observed. Another interesting videocapillaroscopic

finding is a progressive loop enlargement of the efferent limb; it is homogeneous and centripetal, so that the capillary takes on the classic “elephant nose” image, in which the diameter is more than five times higher than normal values. In addition, changes of capillary response to ischemia may be observed among patients with diabetes through bidimensional measures of a projected area of capillary loop transverse segment in NVC using a computerized system of image analysis. Patients with diabetes mellitus have no significantly different maximum area increments compared with controls, but take more time to reach it during reperfusion [44].

In acromegaly wide range investigations on the heart and great vessels have been reported but the field of microcirculation is still largely lacking. The nailfold is a window through which it is possible to observe in vivo the vascular bed. In an elegant study, by means of nailfold NVC authors investigated the morphology of cutaneous microcirculation in acromegaly in relationship with the usual hormonal parameters of disease activity [45]. The following morphological parameters were calculated: the number of tortuous loops, meandering capillaries and capillaries per millimetre; avascular areas; visibility of subpapillary plexus; capillary length and intercapillary distance. In acromegalics the number of tortuous loops and meandering capillaries were significantly increased; the capillary number and length were reduced compared to controls. In some acromegalic patients branch-like capillaries were found. Finally, a significantly different and ameliorated capillaroscopic morphology was observed in acromegalic patients in stable remission compared to active disease patients as far as the total number (density) and meandering capillaries were concerned.

In patients with hyperthyroidism only minor changes in capillary blood flow velocity could be detected. In patients with hypothyroidism, skin microvascular autoregulatory mechanisms are disturbed and the impairment of the reactive hyperaemia response could be correlated with the control of the disease [46].

In Cardiac Syndrome X (CSX) (chest pain, exercise-induced ischemic ST-segment changes and angiographically normal coronary arteries) microvascular damage of the coronary bed has been considered the main pathogenetic factor. Patients with CSX exhibited some structural and functional alterations of systemic microvasculature [47]. NVC showed several morphologic changes and significant quantitative alterations (capillary density, granular flow score, alterations of vessel profile, length of capillary loop branches and arterial/venous diameter) which indicated a severe alteration of the whole vessel structure and an important rearrangement of microvascular disposition. The pattern is similar to the one detected in systemic inflammatory disease and suggests a vascular lesion of an inflammatory type. The same changes could also be operating in coronary microvessels of patients with CSX. In another study, Antonios and coworkers found that mean capillary density was significantly lower in patients with chest pain and normal coronary arteriograms [48].

Many authors suggest that mitral valve prolapse may, in most cases, be only a clinical sign of a primitive and systemic disorder of the connective tissue, as in Marfan syndrome. NVC features showed an architecturally disorganized microvasculature with aspects related to a reduced compactness of the microvascular unit. These results appeared to be correlated with stage pathology as severe microvascular disorders were observed in mitral valve prolapse syndrome [49].

Experimental and clinical observation suggests that patients with primary biliary cirrhosis (PBC) have endothelial dysfunction. PBC is a chronic disease that slowly destroys the liver. For reasons unknown these ducts sometimes become irritated and inflamed. As the inflammation spreads, the disease destroys the bile ducts and replaces them with scar tissue. PBC is thought to be an autoimmune disease, in which the cells attacked are those that line the bile ducts of the liver. It is liver disorder that is the most frequently encountered in SSc patients [50-52]. Many authors demonstrated that clinical manifestations of SSc were common in PBC, occurring in as many as 3-18 % of patients [53,54]. In an interesting study, NVC abnormalities were found in 91 % of patients studied with primary biliary cirrhosis and capillary alterations characteristic of SSc were found in 54 % of these. Eleven out of the 22 PBC patients (50%) had extrahepatic signs of connective tissue disease and most of them were related to SSc, while patients with other chronic liver disease did not present rheumatic manifestations. In PBC patients there was a significant association between SSc capillary pattern and rheumatic manifestations. The high prevalence of nailfold capillary abnormalities characteristic of systemic sclerosis in patients with PBC and correlation with scleroderma manifestations suggests that this capillaroscopic finding could be a useful indicator to investigate rheumatic manifestations in these patients [55,56].

It has been suggested that chronic mesenteric vasculitis is a pathogenetic mechanism in Crohn's disease. In a study of several years ago, minor nail bed abnormalities were frequently observed and three/seven patients presented with major capillary dystrophy. These features are similar to those observed in some systemic vasculitis [57].

There are changes in capillary morphology in continuous ambulatory peritoneal dialysis patients, correlated to clearance of urea and uric acid. Peritoneal dialysis treatment results in lipid abnormalities and high fibrinogen levels that may cause microvascular damage and poor perfusion [58].

NVC also showed morphologic capillary changes such as increased tortuosity, enlargement of capillary loops (but not microhaemorrhages) in familial Mediterranean fever [59].

Thus, capillaroscopic study may be indicated in all patients where microcirculation involvement is expected as capillaroscopic findings can supply useful information as to pathophysiology, differential diagnosis and therapy monitoring. However, whereas this technique plays a prominent role in the diagnostic approach to "scleroderma spectrum disorders" and is considered a standard investigation

in patients with isolated Raynaud's phenomenon, more studies including a greater number of patients are needed to evaluate the clinical usefulness and specificity of NVC abnormalities in non-rheumatic diseases.

## CONCLUSIONS

NVC represents a simple, non invasive and repeatable imaging technique, with low costs and high sensitivity. In addition, the technique is easy to learn with fine, well-defined images. The possibility of managing the imaging by means of dedicated software capable of characterizing quantitative and qualitative data represents another relevant property of NVC. In the clinical practice of rheumatology, this technique acquired a well-defined diagnostic and prognostic role.

Its usefulness in other fields of internal medicine is currently under extensive investigation.

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