Nailfold capillaroscopy in juvenile rheumatic diseases: known measures, patterns and indications

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ABSTRACT

Nailfold capillaroscopy has become an established method in adults for the evaluation of structural abnormalities of the microcirculation associated with rheumatic disease. It is a cornerstone for the diagnostic work-up of patients with Raynaud's phenomenon and the early diagnosis of systemic sclerosis. However, this non-invasive examination may also be valuable in children and adolescents with rheumatic diseases. Based on the scarce data available, this review focuses on capillaroscopic findings in healthy children and adolescents as well as in children with juvenile systemic sclerosis, juvenile dermatomyositis, juvenile idiopathic arthritis, and Raynaud's phenomenon. In addition, it outlines the potential benefits and limitations of nailfold capillaroscopy for routine care in paediatric rheumatology.

Introduction

Systemic inflammatory autoimmune diseases are often accompanied by microangiopathies manifested in early disease stage; their recognition may provide useful diagnostic and prognostic information. Whereas capillaries are not accessible through classical angiologic methods such as Doppler or duplex sonography, microangiopathies and the resulting impairment of microcirculation can be functionally detected by oxygen partial pressure measurements, or by imaging using an optical or stereo microscope with at least a 100x magnification or newer video-capillaroscopic devices with a 200x magnification. In a similarly reliable and valid way, both techniques of nailfold capillaroscopy allow for an evaluation of capillary density and morphology, the capillary blood flow and the extra-capillary tissue *in vivo* (1-4). For documentation purposes, a digital camera is needed for the stereo microscope to capture single images or image series; however, the newer digital video techniques provide an easier approach to record the capillary blood flow (5).

Nailfold capillaroscopy is a well standardised and routinely used diagnostic measure in adult patients with Raynaud's phenomenon (RP) or connective tissue diseases (5), especially in systemic sclerosis (SSc), where it recently has been included into new classification criteria (6). However, capillaroscopy is less commonly used in paediatric rheumatological practice so far. Results of the few studies available on age-specific normal values and disease-related findings are discussed in this article to highlight possibilities and limitations of nailfold capillaroscopy as a potentially non-invasive, quick and cost-effective tool in routine paediatric rheumatology care today.

Basic principles of nailfold capillaroscopy

Due to their relative proximity to the skin surface, nailfold capillaries are easily accessible for capillaroscopy: In the transition area between skin and nail, the strata of dermis and epidermis are directed in parallel, not vertically to the skin surface (7). Therefore, each hair-pin shaped dermal capillary, rising from the sub-papillary venous plexus, runs in parallel, not vertically, to the skin surface and finger axis, and can be illustrated microscopically in its full length up to its vertex. Each vertex is located in a dermal papilla, which appears as whitish "halo" demarcated from the epidermis, the perionyx, further distal (7) (Fig. 1A). In older studies, visibility of the sub-papillary venous plexus was preferably examined, which appeared later to be most likely dependent on the integrity and thickness of the perionyx (8). Today, the distal capillary loop row is usually investigated as it allows direct evaluation

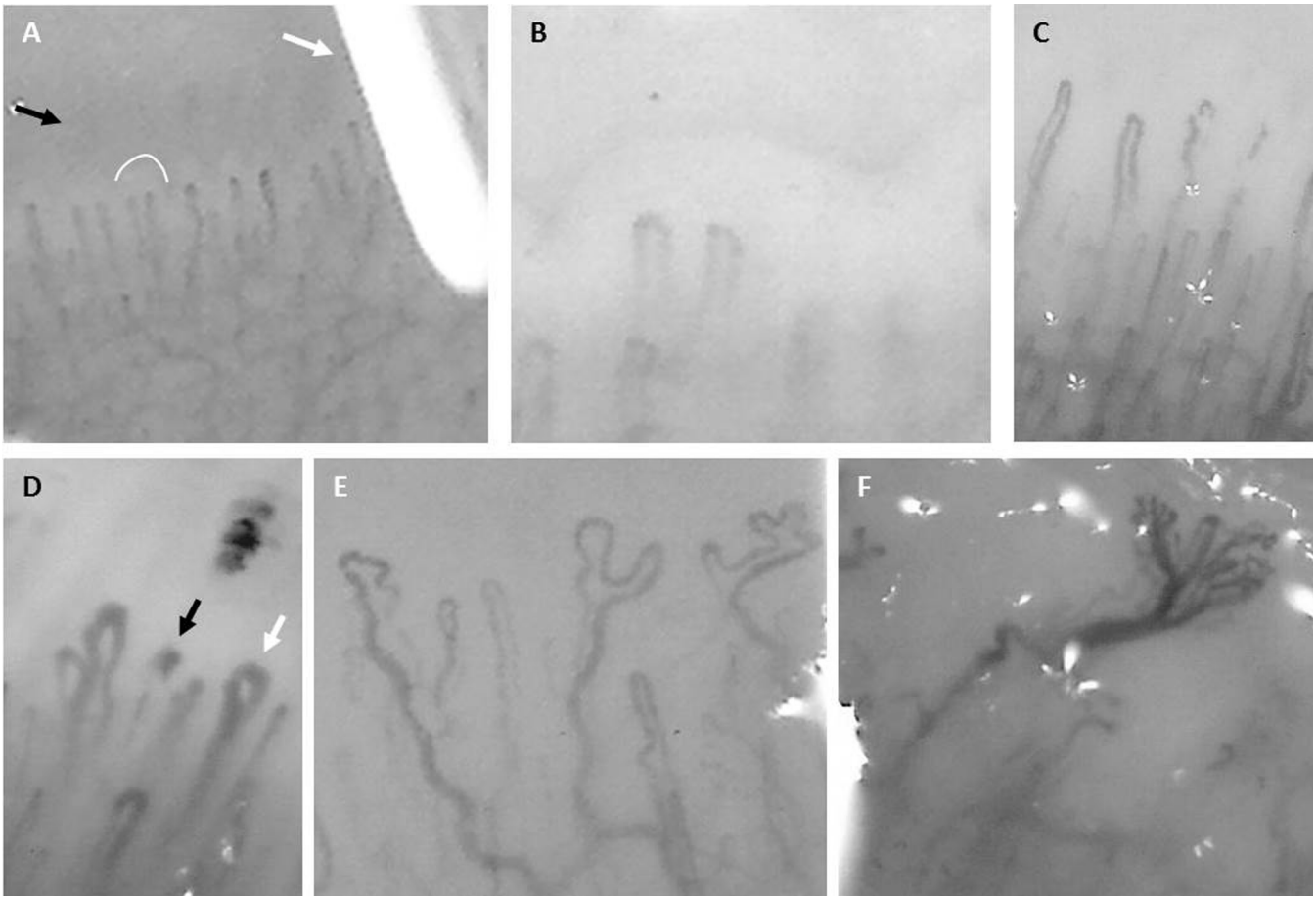

Fig. 1. Capillary patterns in children and adolescents. **A**) Normal pattern with presentation of the nail, the slightly darker perionyx (black arrow), and bright dermal papilla ("halo", marked) containing a longitudinal capillary loop each followed by the sub-papillary venous plexus (white arrow: light reflex by the immersion oil). **B**) Wide dermal papillae with blurred capillaries as signs of edema of the extra-capillary tissue as it appears in the early state of juvenile sclerosis. **C**) The physiological "clotting"-phenomenon occurs usually in capillaries when the laminar blood flow is decelerated and erythrocytes aggregate transiently to rouleaux. Rouleaux formation is promoted by thrombocytosis, elevated levels of immunoglobulins or acute phase proteins such as fibrinogen, and may be a common sign of inflammatory diseases such as connective tissue diseases. Capillaroscopy shows aggregated ("clotted") erythrocytes in turns with erythrocyte-free plasma, appearing as variations in capillary diameter up to reversible capillary occlusions ("sludge"). **D**) Irreversible capillary occlusions/thrombosis (black arrow) may also appear; loss of capillaries results in reduced capillary density or avascular areas. Reduced capillary blood flow leads to ecstatic or giant capillaries (white arrow), a classical sign of juvenile sclerosis. Stasis and enhanced capillary permeability cause hemorrhage, growing out here in an onion-like shape. **E**) Typical presentation of elongated capillaries. Elongation as well as contortion can develop in a compensatory way if capillary density is reduced. **F**) In adjacencies of reduced capillary density or avascular areas neovascularisation is accompanied by development of branching capillaries. Own images, light microscopy with a USB video light microscope, digital imaging by means of MicroCapture Software, oil immersion, magnification A) 10x, B-E) 200x.

of the microcirculatory situation (8, 9). Since normal values and pathologies were found to vary between fingers, more than one finger should be investigated. Due to the vulnerability of the capillaries, capillaroscopy can be impaired by manicure or physical injury of the perionyx and the nailfold; therefore, capillaroscopy of the third to the fifth finger was recommended (5). The informative value of the examination can be further limited due to a dry, thick and/or pigmented skin (7), and a reduced capillary flow attributable to vaso-active drugs or anaemia (5). Since patients should be able to sit quietly during the procedure, routine microscopy appeared to be practicable from the age of five years on (10).

Age-specific findings of nail-fold capillaroscopy in children and adolescents

To evaluate microcirculatory abnormalities, knowledge of the regular nailfold capillary pattern in healthy individuals is needed. Age-dependent development of nailfold capillaries has not been examined in a prospective study design with repeated measurements in a definite study population. Only a few data of single cross-sectional studies on capillary density and capillary morphologies in healthy children and adolescents between two and eighteen years of age are available, summarised here in Table I (8, 9, 11-15).

The normal capillary pattern in adolescents and adults was presumed to be characterised by hair-pin shaped capillaries arranged in rows parallel to the skin surface (5, 8). An overall age-dependent increase of capillary density was observed in infants, toddlers and young children up to the age of six years (9, 13, 16). Since capillary density varied intra- and inter-individually across all age groups, normal values

Table I. Capillary findings in children and adolescents between two and eighteen years of age.

Study	n.	Age (years)	Capillary density (mean [range]) (capillary/mm)	Capillary width arterial branch (mean [range]) (μm)	Capillary width venous branch (mean [range]) (μm)	Capillary length (mean [range]) (μm)
Scheja 1999 (38)	23	6–16	6.8[1] (5.3–8.0)			
Terreri 1999 (13)	329	2.1–16.7	7.1 (4.9–9.2)	– [2]		–
Herrick 2000 (14)	110	6–15	5.7–6.3[3,4]	16.1–20.6[3]	18.3–23.6[3]	–
Dolezalova 2003 (9)	17	2–18	6.7[1] (5.3–9.3)	47 (33–142)		–
Ingegnoli 2005 (8)	50	2–16	6.1 (5–8)	–	–	341.04 (159–500)
Górska 2008 (15)	20	4–17	16.2 (7–33)[5]	24.7 (12.9–46.3)	27.1 (14.8–46.7)	139.6 (64.1–287.0)

[1] Median; [2] relative measurement to the adjacent capillaries within one individual; [3] range of mean values of 5 age groups; [4]original values 17–18.9/3 mm; [5] per mm^2.

were assumed to range, according to present data most likely between six and eight capillaries per millimetre (8). The mean capillary diameter, measured by the maximum diameter of the three widest loops, was 47μm in healthy children between two and 18 years of age, declining with age down to 40μm in healthy adults (9). Capillary length was found to rise with age; the maximum normal value was assumed to be less than 500 μm across all age-groups (8).

Concerning capillary density, less than six capillaries per millimetre were considered to be clearly pathologic (8); avascular areas, defined as two or more capillaries missing in an area of the distal row compared to the density of capillaries in the remaining row, were present in only about 2% of healthy children and adolescents (13). Despite diverse definitions of the capillary diameter (8, 14, 15), respectively defined "giant capillaries" were consistently not described in healthy children. Elongated capillaries of more than 500μm of length and/or tortuous capillaries were found regularly in healthy children and adolescents (8, 15). Bizarre capillary forms or branched loops were seen with different frequencies in 0 up to 27% of healthy children and adolescents; associations to age and sex were discussed controversially (8, 9, 13). Impairment of the blood flow by erythrocyte clotting or thrombosis was not investigated in these studies. Extracapillary tissue pathologies such as haemorrhages located over the vertex or around the whole length of the capillary were found in up to 10% of healthy children and adolescents (8).

Due to varying methods of measurements, the studies are difficult to compare overall. For example, diameter measures comprised the width of the complete loop across the widest aspect, the lumen of the arterial or venous arm, or the loop vertex (8, 14, 15); but in two studies, the diameter was measured relatively to the adjacent capillaries within one individual (9, 13). Since distances measured directly at the microscope provide slightly higher values than distances measured in a digitally-based way, they were not comparable (17). Inter-observer reproducibility was better for qualitative capillaroscopic findings on capillary morphology than for metric parameters on capillary length or width (9). As well, classification of capillary patterns in four categories – 1) normal, 2) minor abnormalities, 3) major abnormalities, 4) scleroderma pattern – achieved good inter-observer agreement with a Cohen's kappa of 0.85 (8).

Disease-specific findings of nail-fold capillaroscopy children and adolescents

Primary and secondary Raynaud's phenomenon

In adulthood, nailfold capillary microscopy and auto-antibody detection, as simple diagnostic tools, are established to differentiate between primary and secondary RP in order to plan further diagnostic procedures and the follow-up of patients (18-20). Presence of giant capillaries and avascular areas are distinct major abnormalities in an attack-free patient, and predict later manifestation of a connective tissue disease (21, 22). In patients with RP, the risk to develop systemic sclerosis was about 65% within five years and 80% within ten years, if capillaroscopy showed major abnormalities and scleroderma-associated auto-antibodies were found (21).

In cross-sectional studies, there were no capillaroscopic differences between attack-free adult or pediatric patients with idiopathic or primary RP and respective healthy controls (8, 9, 23). In a retrospective cross-sectional study, capillaroscopic minor alterations were found in 23% of 85 children and adolescents under 19 years of age with primary RP, and in 68% of 34 respective patients with secondary RP; the type of alteration was not further differentiated (24). In a prospective study design, 250 adolescents between 10 and 20 years of age with RP were followed up for one to six years; the primary endpoint was the manifestation of a connective tissue disease. Mean follow-up time until this diagnosis was two years. Capillaroscopic findings from the visit six months before the diagnosis was made were considered in the analysis. Notably, 76% of the children and adolescents had primary RP and did not develop a connective tissue disease by the end of follow-up, of which 91% had normal capillarscopic findings, which were also observed in 81% of 27 patients who developed an undifferentiated connective tissue disease, in 70% of 10 patients with inflammatory arthritis, in 67% of 9 SLE patients (25). Unspecific abnormalities such as tortuous capillaries, focal haemorrhages or caliber variations were found in 18 patients with primary and in 11 patients with secondary RP. Of all patients, only 10 showed a scleroderma pattern; all of these patients were affected by a particular connective

tissue disease six months after capillaroscopy was performed (25). Secondary Raynaud's phenomenon in children and adolescents is, similarly to adults, most often associated with juvenile systemic sclerosis (JSS) and juvenile mixed connective tissue disease (>70% [26, 27]), and less often with juvenile SLE (10–15% [28]). Hence, capillaroscopy could be valuable in diagnostic routine for the differential diagnosis of children and adolescents with RP, too, and for most evidence has been collected in this setting.

Juvenile systemic sclerosis

In adults, capillary microscopic findings of SSc were presumed to be disease-specific. Maricq *et al*. (2) described the typical "scleroderma pattern" for the first time in 1980, as characterised by ecstatic or giant capillaries with a diameter of more than 50μm and a reduction of capillary density or by avascular areas; haemorrhages and areas of neovascularisation with branched or bushy capillaries may be additionally present (29). Capillaroscopy findings in adult SSc patients are moreover used for prediction of outcome measures. For example, the capillaroscopic skin ulcer risk index considering the total number of capillaries in the distal row (N), the maximum loop diameter (D), the number of megacapillaries (M), and the M:N ratio was introduced as a useful tool to predict the occurrence of new digital ulcers or the persistence of non-healing lesions within three months after nailfold capillaroscopy (30, 31). Kayser *et al*. showed very recently in 135 SSc patients that an avascular score of more than 1.5 based on the number of avascular areas per finger was an independent predictor of death (32).

Dolezalova *et al*. (9) investigated three patients with JSS; compared to 17 healthy control children (Table I) they found the capillary density to be reduced (median [range] 3.7/mm [2.5–7.6/mm]), while the maximal capillary width was increased (225.7μm [98.5–353 μm]). Ingegnoli *et al*. (8) showed for five of eight patients with JSS a so-called scleroderma pattern at diagnosis of the disease. Reduced capillary density of less than six capillaries per millimetre, avascular areas and giant loops were typical findings; additionally, elongated and tortuous capillaries as well as bushy loops and haemorrhages were present (8). In a small retrospective study, the scleroderma pattern was observed in 12 of 19 JSS patients; single components of this typical pattern were found in 17 of 19 patients with JSS, with widened loops or avascular areas found most frequently (33). Healthy controls were not investigated (33). If patients were examined repeatedly during the course of the disease, findings were progressive with increasing frequencies of ecstatic or giant capillaries, and of avascular areas. However, truly prospective studies evaluating capillaroscopy for the prediction of outcome parameters, as done for adults, are still lacking.

Juvenile dermatomyositis

An underlying inflammatory vasculopathy of mainly the skin and muscles is the cause for symptoms in dermatomyositis, wherein pathologic alterations of microcirculation can be demonstrated by histology but also by nailfold capillaroscopy. In adult patients, it is characteristic to find capillary ectasia up to giant capillaries and reduction of capillary density up to avascular areas as well as bushy capillaries similar to the scleroderma pattern (34-36). Overlapping syndromes are also common.

Pathologic capillary pattern as a sign of the systemic microangiopathy were seen as well in paediatric patients with juvenile dermatomyositis (JDM), particularly in cases of chronic and severe disease courses (37). In the majority of JDM patients, capillary density was reduced, and avascular areas, capillary ecstasy up to giant capillaries, and bushy capillaries were described as typical patterns (8, 9, 37, 38). Dolezalova *et al*. (9) found in eight JDM patients a reduced capillary density of 4.5 capillaries/mm (median; range 2.0–7.6 capillaries/mm) and an enlarged maximum diameter of 182 μm (median; range 41–420 μm), compared to age-matched healthy controls (Table I). Ingegnoli *et al*. (8) investigated eight patients with JDM compared to 50 healthy children. In 60% of these patients, but only in 4.3% of the healthy controls, major abnormalities were described (reduced capillary density ≤6–8 capillaries/mm, portion of elongated capillaries >10%, portion of tortuous and/or bushy capillaries >50%); in 20% of the patients, but not in control children, a scleroderma pattern was found (8). In an inception cohort of 28 JDM patients, median capillary density was 3.1 (range 0.7–5.6) capillaries/mm at the time of diagnosis, increasing significantly within the first 12 months of treatment (39). The initial (diminished) capillary density was described as a reliable parameter of the current inflammatory activity of the underlying disease without concomitantly predicting long-term outcome or the course of the disease (39). No control group was investigated. In a longitudinal study of 80 JDM patients, disease duration and activity of cutaneous inflammation prior to treatment was associated with a reduced capillary density at time point of diagnosis or with development of reduced capillary density during the first 2.5 years of disease (40). In this study, a normal minimal value of seven capillaries/mm was presumed in accordance to an abstract publication by Pachman *et al*. 1996 (41); no control group was used. In 61 JDM patients, microscopically visible regeneration of nailfold capillaries within 36 months after diagnosis were associated with a shorter disease duration prior to treatment start and with a rather monophasic disease course (42). In this study, controls, characteristics of drop outs, and treatment procedures were not considered. Accordingly, in a cohort of 86 JDM patients, persistent nailfold abnormalities six months after therapy start were described with longer duration until remission (43); however, these abnormalities were not further defined, and no control group was evaluated.

Other autoimmune diseases

The capillaroscopy pattern of mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), or rheumatoid arthritis was described to be more diverse and less specific than that of systemic sclerosis or dermatomyositis in adulthood as well

as in childhood and adolescence. Diminished capillary density, increased capillary width, higher frequency of elongated, tortuous, widened or bushy capillaries were reported for paediatric MCTD patients (9, 23). In adult as well as paediatric SLE patients, an assorted pattern with elongation, branching, sludge phenomena and caliber variations without any significant reduction of capillary density was described; normal findings were not seen in any SLE patient with active disease, but were found during remission (4, 8, 9, 30).

In a very recent uncontrolled study, signs of microangiopathy, such as elongated and dilated capillaries, as well as a prominent sub-papillary venous plexus, were described in patients with rheumatoid arthritis as well as in patients with juvenile idiopathic arthritis (JIA) (15, 44). However, in two controlled studies with 15 and 55 JIA patients and 17 and 50 sex- and age-matched healthy controls, respectively, significant differences of capillary density and morphology were not found; there were no signs of specific alterations such as a scleroderma pattern, giant capillaries or branched loops in patients or controls (8, 9, 33). Subgroups of JIA patients did not show any significant differences in their capillary pattern (8).

Possibilities and limits of nail-fold capillaroscopy in childhood and adolescence

Nail-fold capillaroscopy as a non-invasive and cost-effective measure is principally available for children and adolescents from about five years of age on with suspected or confirmed rheumatic diseases. At present, data on healthy children are based on few, only partly comparable cross-sectional studies; normal values for capillary density, diameter, and portions of distinct morphologies are limited, and measurements have not been standardised. However, giant capillaries and avascular areas, the specific changes of the so-called "scleroderma pattern", were described consistently as pathologic and mainly characteristic for JSS and JDM, independently of the method used for measurement. Treatment of the underlying disease was shown to go along with enhancing capillary density. Giant capillaries and avascular areas were also found to predict development of connective tissue disease in patients with RP. Capillary patterns in MCTD, SLE, and JIA were unspecific, and differences to healthy controls were not consistently found. Differential diagnostics of RP is the main indication of nailfold capillaroscopy in children and adolescents today, since the presence of a "scleroderma pattern" may provide diagnostic and prognostic information on the development of connective tissue diseases such as JSS and JDM. However, up to now there has been a lack of prospective longitudinal controlled studies for 1) definition of normal age-related capillary patterns, and 2) for associations between capillaroscopy findings and disease courses and outcomes.

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