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Original article

An EULAR study group pilot study on reliability of simple capillaroscopic definitions to describe capillary morphology in rheumatic diseases

Vanessa Smith[1,2,*], Sam Beeckman[1,2,*], Ariane L. Herrick[3], Saskia Decuman[1,2], Ellen Deschepper[4], Filip De Keyser[1,2], Oliver Distler[5], Ivan Foeldvari[6], Francesca Ingegnoli[7], Ulf Müller-Ladner[8], Valeria Riccieri[9], Gabriela Riemekasten[10], Alberto Sulli[11], Alexandre Voskuyl[12] and Maurizio Cutolo[11]on behalf of the EULAR study group on microcirculation

Abstract

Objective. To propose simple capillaroscopic definitions for interpretation of capillaroscopic morphologies and to assess inter-rater reliability.

Methods. The simple definitions proposed were: normal—hairpin, tortuous or crossing; abnormal—not hairpin, not tortuous and not crossing; not evaluable—whenever rater undecided between normal and abnormal. Based upon an aimed kappa of 0.80 and default prevalences of normal (0.4), abnormal (0.4) and not evaluable (0.2) capillaries, 90 single capillaries were presented to three groups of raters: experienced independent raters, n = 5; attendees of the sixth EULAR capillaroscopy course, n = 34; novices after a 1-h course, n = 11. Inter-rater agreement was assessed by calculation of proportion of agreement and by kappa coefficients.

Results. Mean kappa based on 90 capillaries was 0.47 (95% CI: 0.39, 0.54) for expert raters, 0.40 (95% CI: 0.36, 0.44) for attendees and 0.46 (95% CI: 0.41, 0.52) for novices, with overall agreements of 67% (95% CI: 63, 71), 63% (95% CI: 60, 65) and 67% (95% CI: 63, 70), respectively. Comparing only normal *vs* the combined groups of abnormal and not evaluable capillaries did increase the kappa: 0.51 (95% CI: 0.37, 0.65), 0.53 (95% CI: 0.49, 0.58) and 0.55 (95% CI: 0.49, 0.62). On the condition that the capillaries were classifiable, the mean kappa was 0.62 (95% CI: 0.50, 0.74) for expert raters (n = 65), 0.76 (95% CI: 0.69, 0.83) for attendees (n = 20) and 0.81 (95% CI: 0.74, 0.89) for novices (n = 44).

Conclusion. This multicentre, international study showed moderate reliability of simple capillaroscopic definitions for describing morphology of capillaries by rheumatologists with varying levels of expertise. Novices were capable of distinguishing normal from abnormal capillaries by means of a 1-h training session. In future studies, the class not evaluable may be obsolete.

Key words: EULAR study group on microcirculation, capillaroscopy, morphology, reliability, novices, trainees, experts, definitions

[1]Department of Rheumatology, Ghent University Hospital, [2]Department of Internal Medicine, Ghent University, Ghent, Belgium, [3]Centre for Musculoskeletal Research, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK, [4]Biostatistics Unit, Department of Public Health, Ghent University, Ghent, Belgium, [5]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [6]Hamburg Centre for Pediatric and Adolescent Rheumatology, Centre for Treatment of Scleroderma and Uveitis in Childhood and Adolescence, Teaching Unit of the Asklepios Campus of the Semmelweis Medical School, Budapest, An der Schön Klinik Hamburg Eilbek, Hamburg, Germany, [7]Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical Sciences & Community Health, University of Milano, Milano, Italy, [8]Rheumatology and Clinical Immunology, University of Giessen/ Kerckhoff-Klinik, Bad Nauheim, Germany, [9]Department of Internal Medicine and Medical Specialities, University Sapienza Rome, Rome, Italy, [10]Clinic of Rheumatology, University of Luebeck, Luebeck, Germany, [11]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy and [12]Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands

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Correspondence to: Vanessa Smith, Department of Rheumatology, Ghent University Hospital 0K12-IB, De Pintelaan 185, B-9000, Ghent, Belgium. E-mail: Vanessa.Smith@UGent.be

*Vanessa Smith and Sam Beeckman contributed equally to this study.

CLINICAL SCIENCE

Rheumatology key messages

- The EULAR study group on microcirculation aims to standardize morphological interpretation of individual capillaries.
- Novices in capillaroscopic evaluation can distinguish normal from abnormal capillaries by means of a 1-h training session.
- Multicentre, international evaluation of proposed simple capillaroscopic definitions shows moderate reliability for describing capillary morphology in rheumatic diseases.

Introduction

The EULAR study group on microcirculation in rheumatic diseases (RDs), established in 2014, aims to build an international network of centres of excellence to facilitate collaboration and the exchange of knowledge within Europe. Its aims are, among others: to study microvascular mechanisms involved in the progression of RD, to develop natural history investigations operating across existing cohorts of European centres and to identify models based on microvascular assessment tools to predict disease progression and outcome of RD. At present, the current literature contains a variety of definitions concerning the morphology of individual capillaries [1–3]. Additionally, not all single capillaroscopic morphologies have been credited with the same inter-rater reliability [4]. Owing to this shortcoming, standardization of morphological interpretation and simplification of morphological nomenclature seems necessary. Subsequently, one of the first tasks of the EULAR study group on microcirculation was to propose simple capillaroscopic definitions for interpretation of single capillaroscopic morphologies and assess their inter-rater reliability, as described in the present report.

Patients and methods

Collecting of capillaroscopic images

The first step was to gather a set of images that would include a broad spectrum of nailfold capillary abnormalities. Images were, therefore, acquired from 12 subjects, judged by one observer expert in nailfold videocapillaroscopy (V.S., Ghent): seven patients with a scleroderma pattern (three patients with the limited cutaneous form of systemic sclerosis, two patients with the diffuse cutaneous form of systemic sclerosis and two patients with a limited systemic sclerosis, according to LeRoy and Medsger's classification), two patients with SLE, one patient with MCTD, one patient with UCTD and one healthy control, according to currently used classification criteria [2, 5–10]. The nailfolds of the second, third, fourth and fifth fingers had been examined bilaterally in each patient using an optical probe videocapillaroscope equipped with a $\times 200$ magnification contact lens and connected to image analysis software (Videocap; DS MediGroup). Four adjacent fields, extending over 1 mm in the middle of the nailfold, had been stored per finger [4]. The images were made anonymous before being assessed by the raters.

Marking of single capillaries to be evaluated morphologically

In the distal row, each single capillary of the capillaroscopic images was marked with arrows by a novice (S.B., Ghent), who was trained by the supervisor (V.S.) (Fig. 1 and supplementary Fig. S1, available at *Rheumatology* Online). This marking with arrows was double-checked by the supervisor. In total, 319 capillaries were marked. As no information on the prevalence of the three types of capillaries (normal, abnormal or not evaluable) in the general RD microcirculation evaluable population was available, per default estimations of prevalence were used to calculate the number of single capillaries to be presented to the raters. This resulted in a total of 90 randomly sampled capillaries out of the pool of 319 capillaries being presented to each rater (see Statistical methods). These 90 single capillaries were presented in two batches of 45 capillaries each. The reason for having two presentations was to reduce the risk of observer fatigue from a longer single presentation. To assess inter-rater reliability, the raters read and scored all images once.

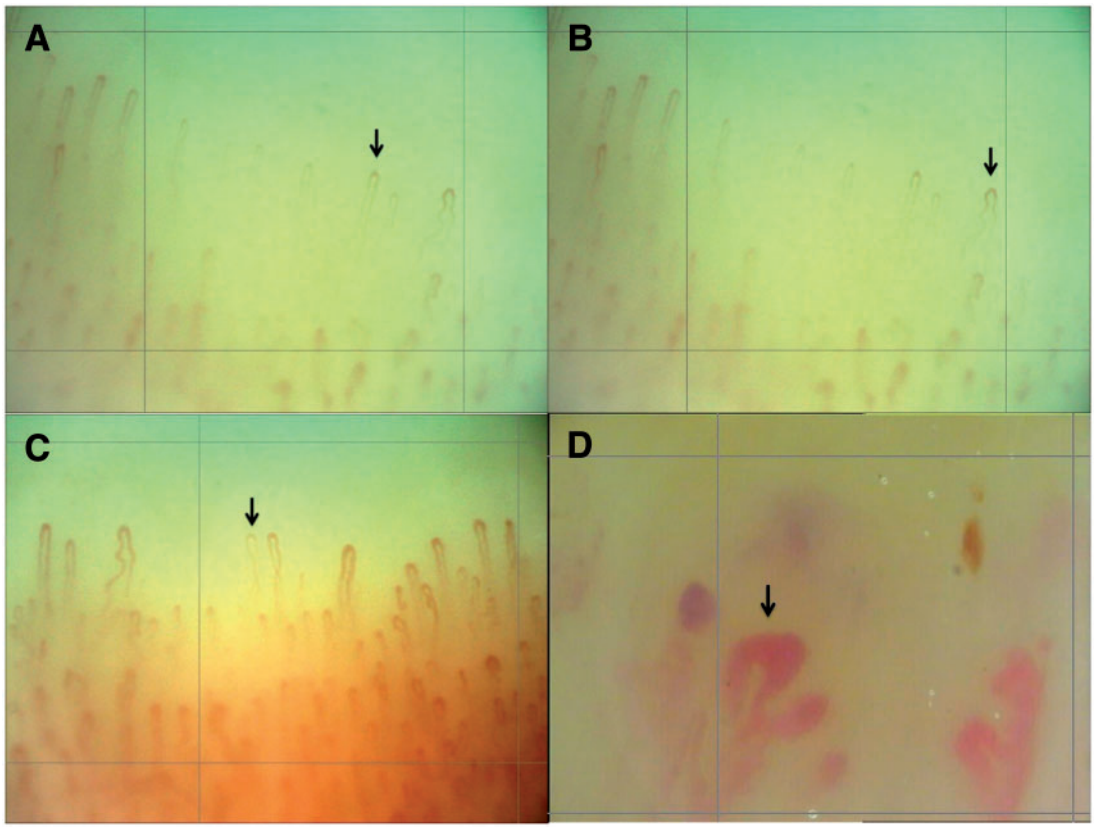
Presentation of simple morphological definitions

Simple morphological definitions were presented as drawings in a PowerPoint slide with minimal verbal descriptions (Fig. 2): Definition 0—normal or non-specific (defined as hairpin, crossing or tortuous); Definition 1—abnormal (not hairpin, not tortuous and not crossing); Definition 2—not evaluable (whenever rater undecided in classifying between normal and abnormal) [3, 11]. Raters were instructed not to assess dimension (apical diameter of capillaries). Consequently, if a dimension was abnormal, but the shape (morphology) was normal, the capillary was to be assessed as normal. Fig. 1 gives examples of nailfold videocapillaroscopy images. The gold standard was set upon the judgement of one expert rater, V.S.

Presentation of the capillaries to be evaluated by the raters

The set of 90 single capillary morphologies to be evaluated were presented in three settings to the different groups of raters: independent experienced raters; attendees of the sixth EULAR course on capillaroscopy, Genova 2014; and novices after a 1-h course at the Ghent University Hospital, November 2014. The previously mentioned definitions and instructions were sent by instructional email to the expert raters (setting 1) and shown to the raters of settings 2 and 3 by means of a PowerPoint slide during a lecture on

FIG. 1 Examples of nailfold videocapillaroscopy images, with marked individual capillaries



(**A**) is an example of a normal—hairpin capillary; (**B**) of a normal—tortuous capillary; (**C**) of a normal—crossing capillary; (**D**) of an abnormal capillary. (For minimal verbal descriptions, see Fig. 2.).

capillaroscopic definitions. When evaluating a single capillary morphology, the rater had to click one of the three options from a web-based system (supplementary Fig. S2, available at *Rheumatology* Online). This web-based system was secure and custom-constructed. The study was approved by the local ethics committee (Ghent University Hospital, Belgium), and all subjects participating in the study signed written informed consent.

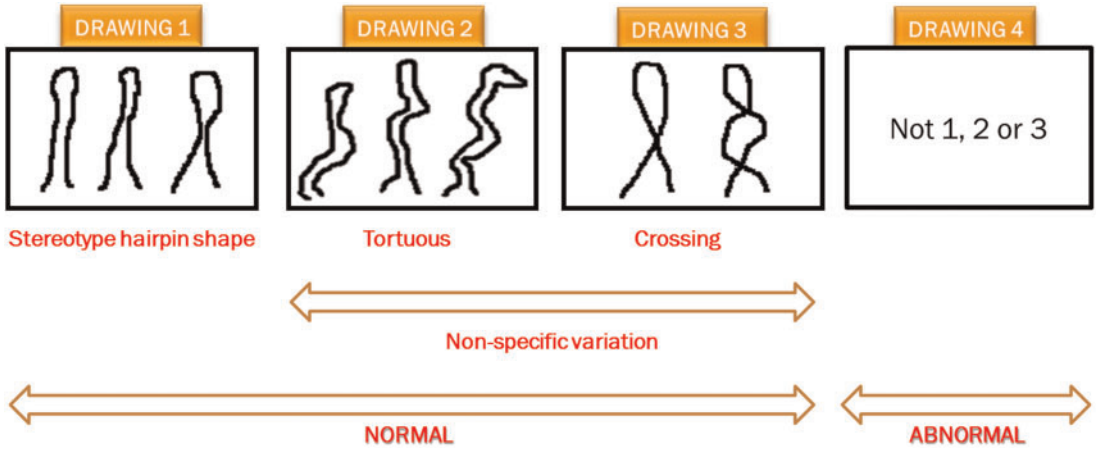
Statistical analysis and sample size

Based upon an aimed kappa of 0.80 and equal default estimated prevalences, in the general RD microcirculatory evaluable population, of normal (0.4) and abnormal (0.4) capillary morphology and a smaller proportion of not evaluable (0.2) capillaries, 87 capillaries evaluated by two raters were necessary to obtain a half width of the 95% CI of no larger than 0.2 (80% power, 5% significance level). Consequently, 90 randomly selected single capillaries (36 normal, 36 abnormal and 18 not evaluable) were presented in two batches of 45 single capillaries to the three groups of raters.

Inter-rater agreement of nominal data was assessed by calculation of the proportion of agreement and by kappa coefficients [mean kappa-values for each rater *vs* gold standard (V.S.)]. Light's kappa was also assessed for the experienced raters by computing the kappa for all coder pairs (V.S.–A.L.H., V.S.–F.I., V.S.–V.R., V.S.–A.S., A.H.–F.I., A.L.H.–F.R., A.L.H.–A.S., F.I.–V.R., F.I.–A.S., V.R.–A.S.) and then computing the arithmetic mean [12]. Landis and Koch [13] guidelines were used for interpreting kappa values, with values from 0.0 to 0.2 indicating slight agreement, 0.21 to 0.40 indicating fair agreement, 0.41 to 0.60 indicating moderate agreement, 0.61 to 0.80 indicating substantial agreement and 0.81 to 1.0 indicating almost perfect or perfect agreement. Two *post hoc* analyses were performed. In the first one, two categories (normal or non-specific *vs* abnormal or not evaluable) were taken into account instead of three. The second *post hoc* analysis was performed with capillaries assigned to either normal or abnormal, while those that could not be classified were excluded.

Overall and partial (abnormal, normal or non-specific, not evaluable) proportions of agreement were calculated for the three groups of raters. Values are represented as mean percentages (over all raters). Statistical analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, 2011, Vienna, Austria).

FIG. 2 Information given to the raters concerning the definitions of normal and abnormal capillaries



Normal had been defined as hairpin shaped (drawing 1) or non-specific variation (drawing 2 or 3): tortuous (the limbs bend but do not cross) or crossing (the limbs cross once or twice). Abnormal (drawing 4) had been defined as not 1, nor 2 or 3 [11, 16]. Of note, the raters had been asked not to assess the dimension of the capillaries in judging whether the capillary had an abnormal morphology or not.

TABLE 1 Mean kappa (95% CI) for the three groups of raters and Light's kappa (95% CI) for the expert raters

Group of raters	Mean kappa (95% CI)	Light's kappa (95% CI)
Expert raters after email instruction (n = 5)	0.47 (0.39, 0.54)	0.49 (0.44, 0.54)
Attendees of sixth EULAR course on capillaroscopy after short oral instruction (n = 34)	0.40 (0.36, 0.44)	NA
Novices after a 1-h institutional course (n = 11)	0.46 (0.41, 0.52)	NA

NA: not applicable.

Results

Participants

Five experienced independent raters [A.L.H., F.I., V.R., A.S., V.S. (gold standard)], 34 attendees at the sixth EULAR course on capillaroscopy (Genova 2014) and 11 novices after a 1-h course at the Ghent University hospital (autumn 2014) participated in the study (see list of collaborators).

Inter-rater repeatability

Mean kappa based on 90 capillaries was 0.47 (95% CI: 0.39, 0.54) for expert raters, 0.40 (95% CI: 0.36, 0.44) for attendees and 0.46 (95% CI: 0.41, 0.52) for novices (Table 1), with overall agreements of 67% (95% CI: 63, 71), 63% (95% CI: 60, 65) and 67% (95% CI: 63, 70), respectively (Table 2). Light's kappa for the expert raters was 0.49 (95% CI: 0.44, 0.54). Comparing only normal *vs* the combined groups of [AQ5]abnormal and not evaluable capillaries did increase the kappa: 0.51 (95% CI: 0.37, 0.65), 0.53 (95% CI: 0.49, 0.58) and 0.55 (0.49, 0.62), with a Light's kappa for the experts of 0.53 (95% CI: 0.47, 0.60) (Table 3).

Evaluation of kappa of images, on the condition they could be classified as performed elsewhere in literature [14, 15], resulted in the following values: 0.62 (95% CI: 0.50, 0.74) for expert raters (evaluable only, n = 65), 0.76 (95% CI: 0.69, 0.83) for attendees (evaluable only, n = 20) and 0.81 (95% CI: 0.74, 0.89) for novices (evaluable only, n = 44) (supplementary Table S1, available at *Rheumatology* Online).

Discussion

In order to facilitate interpretability of studies on microcirculation across RD, a standardisation of definitions on morphology is paramount. To this end, the EULAR study group on microcirculation in RD, established in June 2014, conducted a pilot study of simple capillaroscopic morphological definitions. The key findings of this multicentre, international study were the following: first, just after seeing the simple definitions (normal, abnormal, not evaluable) in a PowerPoint presentation during a lecture on capillaroscopy, attendees and novices had a moderate reliability in evaluating individual capillaries [respectively, mean kappa of 0.40 (95% CI: 0.36, 0.44) and 0.46 (95% CI: 0.41, 0.52)]. Assessing their reliability, on the condition

Table 2 Overall and partial proportion of agreement (95% CI)

Group of raters	Overall agreement % (95% CI)	Partial agreement % (95% CI)		
		Abnormal	Normal	Not evaluable
Expert raters after email instruction (n = 5)	67 (63, 71)	69 (64, 74)	75 (70, 80)	32 (2, 62)
Attendees of sixth EULAR course on capillaroscopy after short oral instruction(n = 34)	63 (60, 65)	64 (61, 67)	73 (71, 76)	24 (18, 30)
Novices after a 1-h institutional course (n = 11)	67 (63, 70)	71 (66, 76)	75 (72, 78)	26 (18, 35)

Table 3 Mean kappa (95% CI) and Light's kappa (95% CI): comparison between two categories

Group of raters	Mean kappa (95% CI)	Light's kappa (95% CI)
Expert raters after email instruction (n = 5)	0.51 (0.37, 0.65)	0.53 (0.47, 0.60)
Attendees of sixth EULAR course on capillaroscopy after short oral instruction (n = 34)	0.53 (0.49, 0.58)	NA
Novices after a 1-h institutional course (n = 11)	0.55 (0.49, 0.62)	NA

Mean kappa (95% CI) for the three groups of raters and Light's kappa (95% CI) for the expert raters [comparison between two categories (normal *vs* the combined groups of abnormal and not evaluable) instead of three (normal *vs* abnormal *vs* not evaluable)]. NA: not applicable.

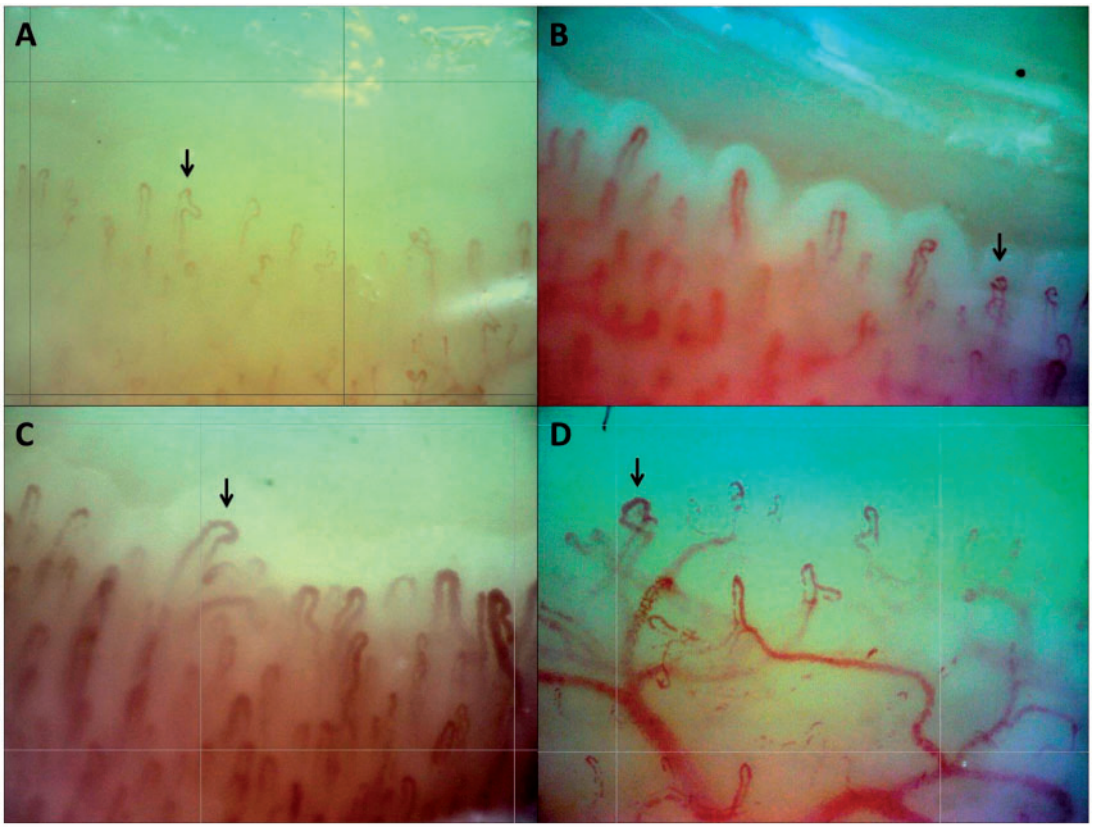
they were able to classify the images (= extracting the not evaluables from the analysis) augmented their reliability [mean kappa of 0.76 (95% CI: 0.69, 0.83) and 0.81 (95% CI: 0.74, 0.89)], but greatly diminished the number of images being evaluated. Second, experts, who had only received instructions via mail had a moderate reliability [mean kappa of 0.47 (95% CI: 0.39, 0.54)]—in line with the moderate reliability of the novices. This equal reliability between experts and non-experts may simply be a matter of training and instructions on the use of uniform definitions. Further optimization based on consensus meetings will be performed. Third, novices are capable of distinguishing normal from abnormal capillaries by means of a 1-h training session. Consequently, when encountering an abnormal capillary, they may refer the patient to an expert centre in nailfold videocapillaroscopy.

Looking at the capillaries where experts did not have consistent evaluation of the individual morphology, Fig. 3 reveals that the proposed simple definitions still leave the rater with difficulties when rating real-life capillaries. One of the pitfalls might be the fact that experts, in judging a single capillary, also took the characteristic dimension into consideration, whereas in this study the raters were asked only to judge morphology. In this way, consequently, some of the experts had evaluated a giant capillary (normal morphology but dimension of apical diameter >50) as an abnormal capillary, even though the shape (morphology) was normal. Consequently, further instructional refinement of the simple definitions would be a primary goal for future studies of the EULAR study group on microcirculation. It will clearly need to be stressed that only morphology (shape) is to be taken into consideration and not the dimension. One way to do this will be to speak of normal or abnormal shapes, rather than of normal or abnormal capillaries. Of note, the expert raters, even though from different European centres, all performed similarly in evaluating the individual capillary morphologies. This is attested by the fact that the Light's kappa (which is an arithmetic mean of all coder pairs of experts) equals the plain kappa (which reflects the concordance of each individual expert rater *vs* the gold standard).

Fourth, grouping together the not evaluable with the abnormal category renders a higher reliability, which may suggest that in future studies the class not evaluable may be obsolete. Since the partial agreement for the not evaluable capillaries was manifest lower in comparison with the two other groups, the definition of not evaluable can be questioned. Due to the fact that the kappa increases when taking the not evaluable capillaries together with the abnormal capillaries, one could propose that, whenever a rater is undecided in classifying a capillary as normal or abnormal, he should select the abnormal category. The definition of normal *vs* abnormal could be biased due to adjacent capillaries in the image. The idea was to provide the images as they would present themselves in a real-life setting. It is likely that when a normal capillary is presented in a setting of loss of capillaries and abnormal distribution, the rater would score the normal capillary as abnormal.

In conclusion, this multicentre, international pilot study has, first, demonstrated the moderate reliability of simple

Fig. 3 Four examples of nailfold videocapillaroscopy images with discrepancy between experts



(**A**) One expert: abnormal; one expert: not evaluable; three experts: normal. (**B**) Two experts: abnormal; three experts: normal. (**C**) One expert: abnormal; four experts: normal. (**D**) One expert: not evaluable; two experts: abnormal; two experts: normal.

definitions for use in describing capillaroscopic morphology by rheumatologists with varying levels of expertise in the technique. Second, novices were found to be capable of distinguishing normal from abnormal capillaries by means of a 1-h training session. In future studies, the class not evaluable may be obsolete.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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