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Review

Quantitative nailfold capillaroscopy—update and possible next steps

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Abstract

We review the exciting potential (and challenges) of quantitative nailfold capillaroscopy, focusing on its role in systemic sclerosis. Quantifying abnormality, including automated analysis of nailfold images, overcomes the subjectivity of qualitative/descriptive image interpretation. First we consider the rationale for quantitative analysis, including the potential for precise discrimination between normal and abnormal capillaries and for reliable measurement of disease progression and treatment response. We discuss nailfold image acquisition and interpretation, and describe how early work on semi-quantitative and quantitative analysis paved the way for semi-automated and automated analysis. Measurement of red blood cell velocity is described briefly. Finally we give a personal view on 'next steps'. From a clinical perspective, increased uptake of nailfold capillaroscopy by general rheumatologists could be achieved via low-cost hand-held devices with cloud-based automated analysis. From a research perspective, automated analysis could facilitate large-scale prospective studies using capillaroscopic parameters as possible biomarkers of systemic sclerosis-spectrum disorders.

Key words: nailfold capillaroscopy, videocapillaroscopy, USB microscope, quantitative, automated, systemic sclerosis, Raynaud's phenomenon

REVIEW

Rheumatology key messages

- Quantitative nailfold capillaroscopy, including automated analysis, may improve precision of capillaroscopy as a diagnostic tool.
- Automated analysis removes the subjectivity from the interpretation of nailfold capillaroscopy images.
- Automated analysis is likely to facilitate development of a nailfold capillaroscopy-based biomarker.

Introduction

Nailfold capillaroscopy allows direct, non-invasive assessment of the microcirculation. All rheumatologists need to have some working knowledge of the technique, because otherwise they may miss an early diagnosis of SSc: abnormal nailfold capillaries score two of the nine required points to fulfil the ACR/EULAR classification criteria [1, 2]. There are two main elements to nailfold capillaroscopy: image acquisition and image interpretation. Both of these can present challenges: we need to ensure that the best possible images are captured, and we need to define the 'Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold' referred to in the SSc classification criteria [1, 2].

Much of the work on nailfold capillaroscopy has been qualitative or semi-quantitative, relying on subjective assessments. We believe that for nailfold capillaroscopy to achieve its full potential, normality and abnormality have to be quantifiable, and that if we aim (as many have suggested) to expand the clinical application of nailfold capillaroscopy beyond early diagnosis to monitoring of disease and of treatment response, then we must be able to accurately track change over time. Since our first quantitative studies over 20 years ago [3, 4] much progress has been made [5], but still more remains to be done. In this review article we shall first outline the rationale for quantitative analysis and then discuss, in turn, image acquisition, the key features (and challenges) of image interpretation and of monitoring disease over time,

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TABLE 1 Nailfold capillaroscopic image concepts

Image concept	Definition and/or explanatory notes
Distal (capillary) row	The row of capillaries nearest the fingertip where individual capillaries can usually be easily identified, because here they run parallel (as opposed to perpendicular) to the skin surface
Capillary density	This is usually defined as the number of capillaries/mm of distal row. See text for discussion of how to select which capillaries should be included
Capillary width	The diameter of the capillary. Different investigators have measured this differently, and the literature refers to 'arterial', 'apical', and 'venous'. 'Total loop' width is different, and not a diameter. If not explicit, then 'capillary width' is often assumed to mean 'apical width'
Giant capillary	A homogeneously (very) enlarged capillary, with a diameter of $>50\,\mu m$
Angiogenic capillary	Also termed 'ramified' or 'bushy'. The capillary has more than one apex, although this can be difficult to gauge if the 'feeder' arteriole is not well seen. Angiogenic capillaries are very commonly seen in patients with myositis
Ghost capillary	A capillary that slips in and out of the field of view (during live imaging) because it is only intermittently perfused
Avascular area	Section of the nailfold where no capillaries can be seen. It can sometimes be difficult to decide whether this is 'true' avascularity or due to difficulties in visualising (sections of) the distal row. When using a contact probe, a section of the nailfold can appear avascular if too much pressure is applied
Evaluability	Whether or not an image is sufficiently clearly seen to allow judgements/measurements to be made. It is well recognized that it is not possible to obtain high quality images from every nailfold. Sometimes it can be difficult to decide if an image is not evaluable because of image quality, or because the nailfold is so abnormal (i.e. avascular) as to contain no visible capillaries

semi-quantitative analysis, then automated and semi-automated analysis. Measurement of capillary red blood cell velocity will be touched upon briefly. Finally we shall give a personal view on 'next steps'.

To aid the reader, in Table 1 we provide some explanatory notes on capillaroscopic image concepts. Progress has been made in standardizing the terminology/reporting of capillaroscopic analysis (as well as image acquisition and interpretation) as recently described by Smith *et al*. [6] and Ingegnoli *et al*. [7].

The rationale for quantitative analysis

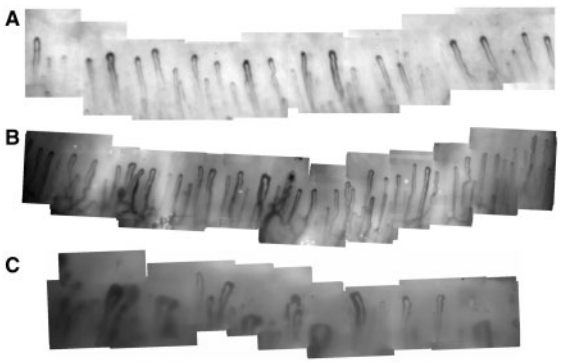
Early studies of nailfold capillaroscopy were mainly descriptive/qualitative, including the seminal work of Hildegard Maricq in the 1970s and 1980s that described the 'scleroderma pattern' of capillary abnormality, putting capillaroscopy 'on the map' as a predictor of connective tissue disease. Maricq used a wide-field microscope with magnification in the order of $\times$12–14 [8–10]. The development of high magnification nailfold videocapillaroscopy heralded a new surge of interest in capillaroscopy from the 1990s [6, 11]. An advantage of videocapillaroscopy is the ability to see individual capillaries in great detail and to measure them [3, 4, 6, 12, 13], although at the expense (with most systems) of no longer having the wide-field view 'at a glance'.

There are several reasons why quantitative nailfold capillaroscopy analysis, for which videocapillaroscopy paved the way, is important, including the following.

First, the wide spectrum of nailfold capillary 'normality' [14–16] often makes it difficult to separate out normal and abnormal (Fig. 1). While a grey area of uncertainty is to be expected in a real-world scenario, the number of 'non-specific' appearances recorded, even by experts, is of concern [17]. For a given patient, it would be good to give the clinician positive and negative predictive values for an underlying SSc-spectrum disorder from a nailfold image or set of nailfold images. For this to be achievable a numerical (i.e. quantitative) rating of abnormality (on a continuous scale) is required.

Second, a key question is whether we can track microvascular disease severity over time in patients with

FIG. 1 The challenges of nailfold capillary appearances



(**A**) Normal, evenly spaced loops from a healthy control subject. (**B**) Mainly normal capillaries but one slightly widened capillary and an area of haemorrhage. (**C**) Marked abnormality in a patient with SSc, with several widened capillaries (including giant capillaries) and areas of avascularity. The challenge is deciding whether the appearances in (**B**) are normal or abnormal.

SSc-spectrum disorders. If so, this would allow examination of (i) SSc pathophysiology and (ii) responses to treatments that have the potential of remodelling the abnormal microvascular architecture that characterizes the SSc disease process. Only quantitative assessment will allow precise measurement of abnormality in a way that is likely to be sensitive to change, i.e. to have potential as a biomarker. Capillaroscopic parameters have already been proposed as primary outcome measures in clinical trials [18], but for these to be meaningful they must be reliable. Quantitative parameters have been found to be highly reliable (subject to evaluability) [17, 19].

Third, many studies have examined associates of abnormal capillaroscopy in patients with SSc and with dermatomyositis (recent examples include [20, 21]). Future studies of associates, and also studies examining the degree of nailfold capillary abnormality as a predictor of (for example) digital ulceration (reviewed in [22]) would benefit from reliable and fast quantitative assessments.

Acquiring capillaroscopic images

Factors to be taken into account when acquiring images and making measurements for quantitative analysis include:

i. What equipment (microscope) and software should be used, and how image quality can be maximized. Although gross abnormalities may be identifiable in low-quality images, high-quality images are fundamental for meaningful quantitative analysis.
ii. Which section(s) of the nailbed should be examined.
iii. How many fingers should be examined.

Equipment

It is outwith the scope of this review to discuss in detail the different microscope systems available [6, 23]. Videocapillaroscopy is currently considered the gold standard and is the technique most used by European clinicians with an interest in SSc [24]. Different videocapillaroscopy systems (incorporating measurement software) are commercially available, some using a fixed microscope, others a hand-held probe. Low cost hand-held systems (e.g. USB microscopy, dermoscopy) are likely to increase in popularity: a survey of 42 United States SSc specialists suggested these low cost systems are favoured by US clinicans [25]. Using green light illumination provides high contrast images of the blood vessels and may be preferable to white light [26]. The hands to be examined should be clean, and the examination performed after acclimatization at a standard temperature [7].

At present, commercially available software tends to be restricted to videocapillaroscopy, but research is ongoing into deriving measurements from low-cost systems [27]. Most current software captures individual video frames for analysis/interpretation. There is an inherent problem with this approach, because at any one time some capillaries are difficult to visualize ('ghost' capillaries) because they are not perfused (capillary walls are invisible, what is seen is the column of red blood cells within the capillary). This has implications for quantitative analysis including capillary density. Our approach to this problem was to develop software that enhances image quality by combining a sequence of 16 video frames, captured at a rate of 5 Hz by a Snapper board and then registered [12, 28] (Fig. 2). Capillary density was higher in patients with SSc when assessed using this software than with stereomicroscope measurement [29], and the authors suggested that this might be due to inclusion of ghost capillaries.

Experience during nailfold capillaroscopy 'hands-on' courses suggests that image acquisition is a rapidly learnt skill, although the learning curve will be longer for acquisition of images of sufficiently high quality for accurate quantitative assessment. The reliability of image acquisition has been less studied than reliability of image interpretation [6] although we reported that image acquisition was reproducible, at least with a single skilled operator [30].

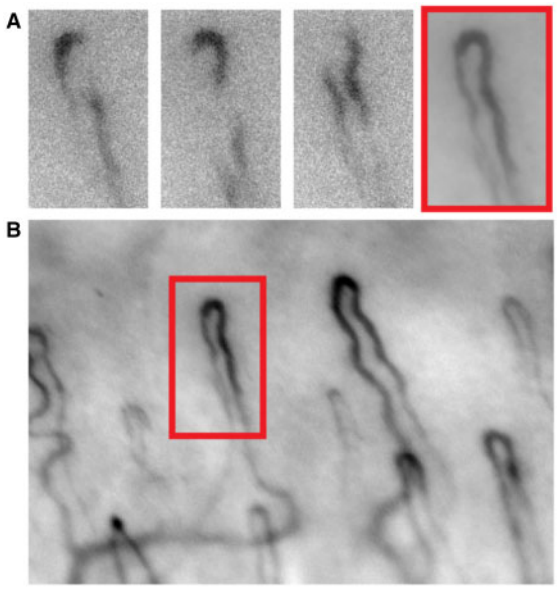
Which section(s) of the nailbed should be examined?

For quantitative measurements, ideally the whole nailfold should be examined. This is because there can be considerable heterogeneity in capillary appearances across a nailfold, as demonstrated in Fig. 3, and so selecting only (say) a 1 mm section may be unrepresentative. In longitudinal studies, looking for change over time, it is imperative that the same set of capillaries is examined each time as discussed in the next section. The importance of viewing the whole nailfold 'at a glance' was recognized by Maricq who was very aware that the wide-field is crucial for pattern recognition [9]. Our approach to combining the advantages of high magnification with being able to view the whole nailfold is to construct a panoramic mosaic of the nailfold [12, 28, 31] with examples of mosaics demonstrated in Figs 1 and 3.

How many fingers should be examined?

How many fingers should be examined will depend on the question being asked. For diagnostic purposes, ideally all eight fingers should be examined to capture the hetereogeneity in appearances that commonly occurs across as well as within nailfolds [32] as demonstrated in Fig. 3. The thumb nailfold is often difficult to visualize and so thumbs are usually excluded. Examining only four fingers (both ring and both middle) had a sensitivity against the diagnostic criteria of SSc of 66.7%, *vs* 74.6% when eight fingers were examined [33], based not on quantitative analysis but on the presence of either giant capillaries or an 'early, 'active' or 'late' SSc pattern [11]. Of course for purely diagnostic purposes, a busy clinician may stop after one nailfold if this shows obvious anormality, e.g. a giant capillary or

Fig. 2 Ghost capillaries



(**A**) A 'ghost' capillary in three sequential video frames becomes easily visible when multiple frames are co-registered and averaged into a composite with greatly increased image quality. (**B**) The full composite frame (red box shows location of featured capillary). A series of such composite frames are stitched together to form a panoramic mosaic of the whole nailfold (see Fig. 1 for examples).

marked avascularity [34]. Quantitative analysis is less relevant for diagnosis when abnormality is unequivocal.

The key features (and challenges) of image interpretation and of monitoring disease over time

Image interpretation is challenging, as exemplified by Fig. 1. Key issues that we need to consider as a background to quantitative analysis include: how to separate normal from abnormal; how to decide which capillaries should be considered as belonging to the distal row; how to decide if an image is evaluable; and how to monitor disease progression/track change over time.

Normal *vs* abnormal

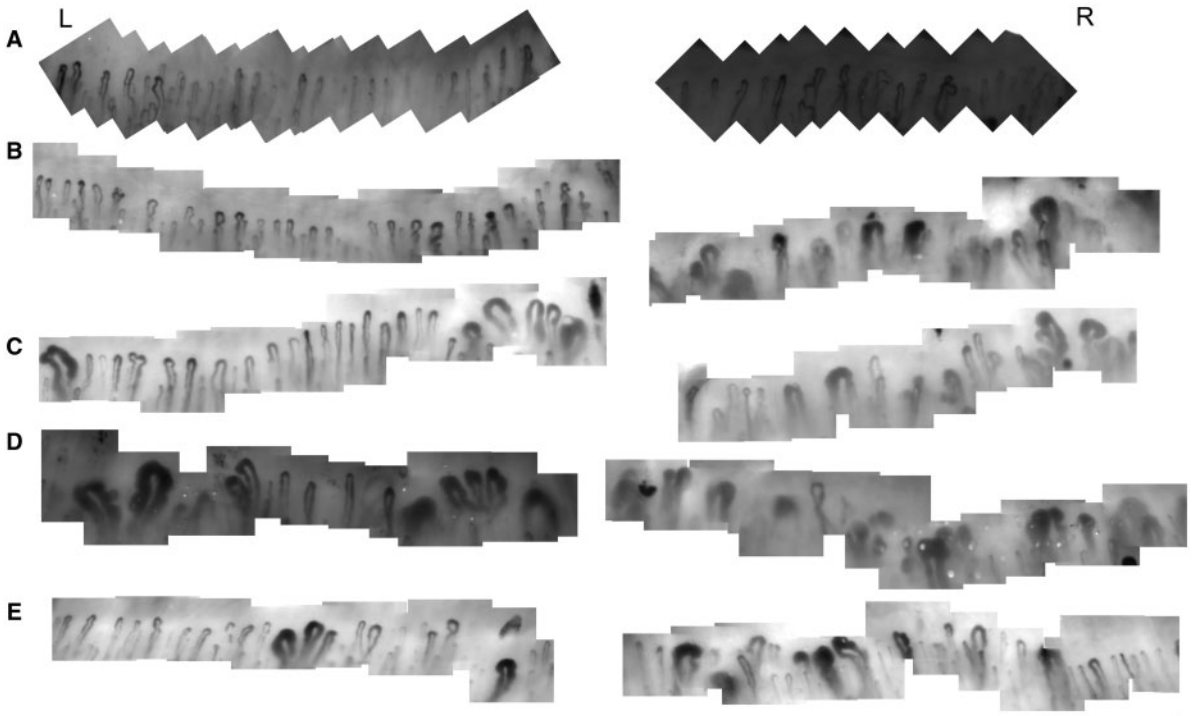
The two key abnormalities that define a 'scleroderma-pattern' are enlarged capillaries and capillary loss (avascularity). Capillary enlargement can be quantified by measuring capillary width, and avascularity by measuring density. Smith *et al*. [34] have recently suggested that to be definite about a scleroderma pattern, either a giant capillary (diameter $>50\,\mu m$) must be present, or density over a 1 mm section of nailfold should be ≤ 3 capillaries/mm. This definition/algorithm (which had high reliability when raters were asked to grade 1 mm images [34]) is likely to be specific but insensitive, given that other investigators have reported densities higher than 3/mm in most patients with SSc [4, 35–37] and patients with an 'early scleroderma pattern' are generally considered as having densities higher than 7/mm [6]. Emrani [38] *et al.* reviewed the literature on capillary density in healthy controls and found a wide range of reported densities, which tended to be in the range of 7–10/mm. Regarding what is a 'normal' capillary size, Trombetta *et al*. [13] suggested a threshhold value of $30\,\mu m$ for 'average' capillary diameter (average of the largest arterial, apical and venous diameters in each image, across at least 16 images), as a predictor of development of SSc in patients with Raynaud's phenomenon (RP).

Capillary shape and distortion of the normal nailfold architecture also help to define abnormality. These are complex constructs about which opinion varies. On the one hand, different investigators have reported that tortuous, even 'bushy' capillaries are seen in healthy controls [14–16]. On the other, it has been suggested that an otherwise normal capillary but with a concave apex is abnormal [39]. The ideal would be for a quantitative image analysis approach to resolve this issue.

Defining distal row capillaries

Capillary density (usually taken to be the number of capillaries/mm of distal row) is one of the most commonly reported capillaroscopic parameters and is integral to some of the suggested algorithms for assessing risk of developing SSc [40, 41] or, in patients with SSc, of digital ulceration [42–44]. But counting capillaries is more complex than it might seem. Which capillaries should be included in the distal row? The 90 degree rule has been suggested and adopted by several investigators: a capillary is only counted if the angle formed between its apex and the apices of the two adjacent capillaries (i.e. to right and left) is $>90^\circ$ [19, 20, 29, 38]. At present, there is no universal agreement as to which capillaries to include. For example, when calculating the Capillaroscopic Skin Ulcer Index (CSURI), which includes density, Sebastiani *et al*. [42, 43] included capillaries at 'different levels' in the distal row, i.e. including those which would not have complied with the 90 degree rule. Another challenge is how to count 'angiogenic' ('ramified', 'bushy') capillaries. If there are multiple apical loops fed by a single arteriole (which might be difficult to see) is this counted as one capillary, or as more? Barth *et al.* excluded angiogenic capillaries from density assessment [45]. Karbalaie *et al*. addressed this issue by developing an 'elliptical broken line method' used in conjunction with the 90 degree rule [46]. This method localized the 'apex' of abnormal capillaries (e.g. 'ramified', 'bushy' or 'bizarre' capillaries) by fitting an ellipse around the capillary, defining the apex as the most distant vertex from the centre of the ellipse. The authors compared results for manual annotation with and without automatic correction using their

Fig. 3 Nailfold images from a patient presenting with Raynaud's phenomenon



Right (R) and left (L) hand thumb (**A**), index (**B**), middle (**C**), ring (**D**) and little (**E**) fingers, showing heterogeneity within and between fingers. For example (within-finger heterogeneity) in the left little finger, capillaries on the left side of the image are within normal limits whereas those in the middle are very abnormal. And (between-finger heterogeneity), appearances in the left index finger are very different from in the right ring finger.

elliptical broken line method and found improved inter- and intra-observer reliability with automatic correction [46].

Evaluability

It is not always possible to visualize the distal row of capillaries. Different observers vary in their opinions of 'evaluability', and this depends also on the nailfold capillary parameter being evaluated [17]. Some capillaroscopy studies state that only clearly seen capillaries or images were included, and so this will influence results.

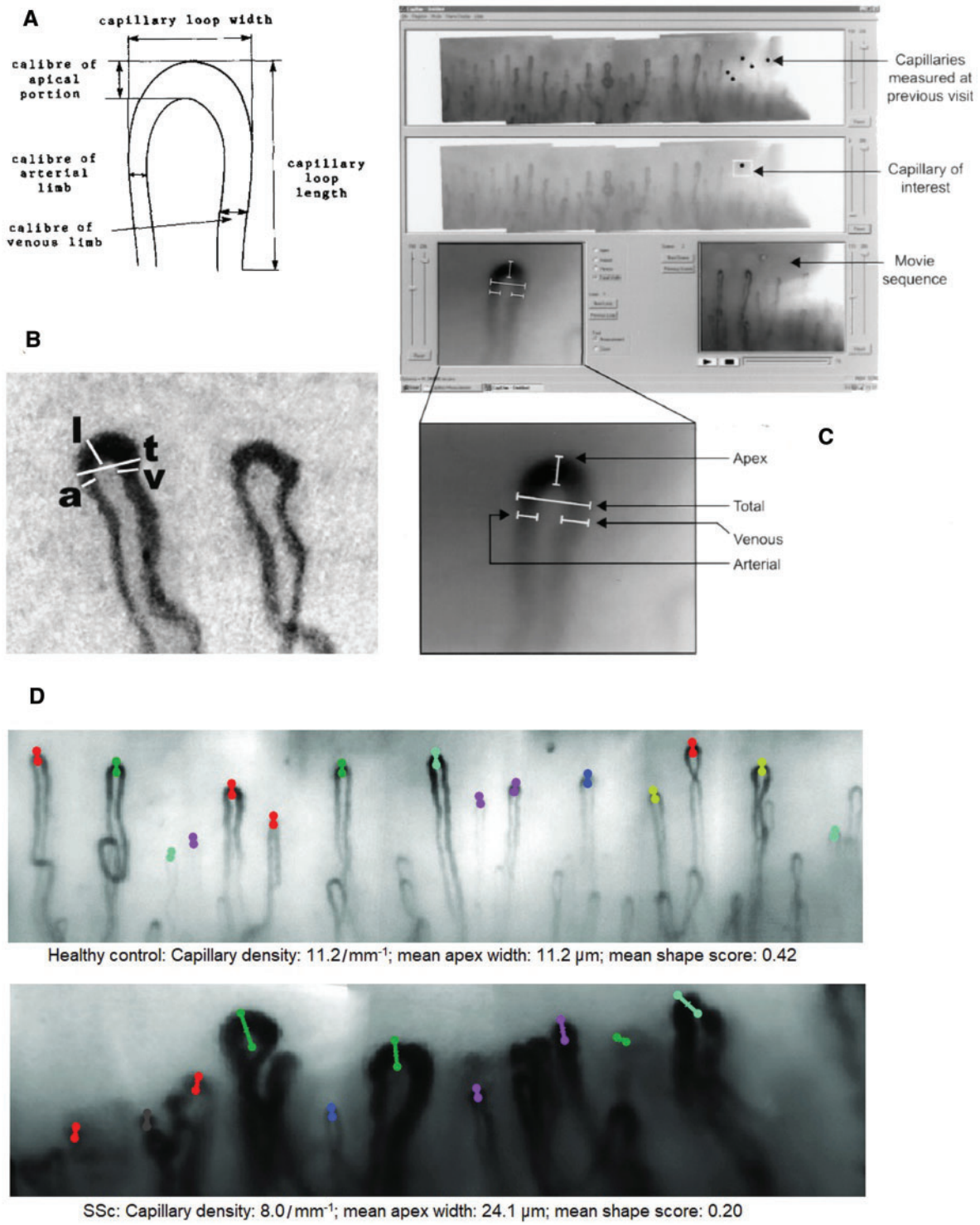
Monitoring of disease progression and of treatment response

The ability to study microvascular change over time non-invasively is perhaps the most exciting aspect of quantitative capillaroscopy. Recently Avouac *et al*. [37] suggested that in a study of 140 patients with SSc, capillary loss over a 3-year period was a marker of disease/organ progression. Nailfold capillary changes over time have also been examined in dermatomyositis [47]. In longitudinal studies, it is imperative that the same section of the nailfold is examined each time, otherwise different results may be obtained irrespective of any change in the clinical status of the patient [12, 48]. It is not clear that published examples demonstrating changes in capillary structure over time (for example in response to drug treatment) always control for this (for example in [49]), and we are not aware of any commercially available software that does so. Sampling errors can, however, be minimized by obtaining measurements from as much of the nailfold as possible [50].

Semi-quantitative (and early quantitative) analysis

In the early 'lead-up' to quantitative analysis, initial semi-quantitative approaches [9, 51] included subjective scales based on capillary size and the degree of avascularity. For example Maricq's 'size' scale was I (same range as healthy subjects), II (definitely enlarged) and III (extremely enlarged) with avascularity rated as 'none', 'slight', 'moderate' or 'extensive' [9]. Later she went on to measure dimensions: arterial and venous limbs, apical portion, loop width and loop length [10] (Fig. 4A). There followed a number of studies using wide-field techniques which consolidated the concept that capillary size and/or density were measurable and could help to discriminate between patients with SSc-spectrum disorders and patients with primary RP and healthy controls [52–54].

FIG. 4 Advances in quantification



(**A**) Schematic representation of capillary measurement (Maricq [10]). (**B**) Manually measuring arterial (a), venous (v), apical loop (l) diameters and total loop width (t) using Capiflow software (Bukhari *et al.* [4]). (**C**) Manual measurements from enhanced panoramic mosaics images, allowing comparison to previous images (Anderson *et al.* [12]). (**D**) Fully automated measurements across the whole nailfold (Berks *et al.* [63]). Figure parts (**A**), (**B**) and (**C**) reproduced with permission from the relevant publishers.

High magnification videocapillaroscopy, using a video camera and digitizing system, lends itself much more easily than the earlier imaging techniques to semi-quantitative and quantitative methods. We and others [3, 4, 15, 55] in the 1990s described differences in capillary density and dimensions between subject groups. Many subsequent videocapillaroscopy studies, including some of those mentioned above, have included interactive measurement of capillary density and dimensions. These measurements, which were made using the software available at the time, were extremely time-consuming, especially when results were averaged over multiple capillary loops to improve precision [4] (Fig. 4B). In early and later studies, this issue has been tackled in different ways, for example selecting only the most abnormal capillary for measurements [3], selecting a given number (e.g. five) of consecutive capillaries [56], or a given number (e.g. five) of the widest capillaries [19]. However, any approach that involves selection of capillaries introduces subjectivity.

Semi-quantitative and early quantitative approaches, reviewed by Mihai *et al*. [5], have been used to predict development of a SSc-spectrum disorder in patients with RP [40, 41, 57] and digital trophic lesions in patients with SSc [58]. For example, in the widely cited study by Koenig *et al*. [57], which showed abnormal nailfold capillaries to be an independent predictor of SSc in patients presenting with RP, capillary enlargement was graded 0–4 (5 point scale) and capillary loss A–D (4 point scale).

Semi-quantitative methods have also been used to track change over time. In 2008, Sulli *et al*. [59] described the semi-quantitative 'microangiopathy evolution score' and applied this in a prospective study of 90 patients with SSc. Eight fingers (thumbs excluded) were examined in each patient. For each finger, four 1 mm images were scored for six parameters (enlarged capillaries, giant capillaries, haemorrhages, loss of capillaries, 'disorganisation of the vascular array', capillary ramifications) on a 0–3 scale (0: no changes; 1: '<33% of capillary alterations/reduction per millimetre'; 2: '33–66%'; 3: '>66%'). An abnormality score was obtained for each finger by summing the mean values of three of the parameters (loss of capillaries, disorganization, ramifications), and a patient 'microangiopathy evolution score' (score 0–9) score was obtained by taking the mean of this score over the eight fingers. Advantages of this method are that by assessing 4 mm of each of eight nailbeds, much of the nailfold area of each patient is included. Disadvantages are that the scoring is subjective and time-consuming.

These semi-quantitative and early quantitative studies made clear the need for a fast quantitative approach, as recognized by Maricq 34 years ago ('The quantitative approach, although the most precise, is time consuming and difficult to use in clinical practice' [10]). This led to development of automated and semi-automated analysis.

Automated and semi-automated analysis

Automation of measurement should remove subjectivity and allow almost instantaneous image analysis (although there is still time involved in acquiring the images). We have taken the liberty of first describing our own work on automation, and then summarizing that of other groups.

'Manchester system'

Our current system has evolved from our early work on computerized imaging [28], in which we built up high-magnification whole-nailfold mosaics from multiple microscope fields of view, allowing the same capillaries to be identified on repeat visits [12] (Fig. 4C), thus creating the ability to track change over time [60, 61]. Our initial follow-on studies were semi-automated [56]. We subsequently developed a fully automated system described in detail elsewhere [31, 62, 63]. In summary, this 'Manchester system' comprises a video-microscope mounted on a software-controlled three-axis motorized stage, together with image acquisition and analysis software. This allows a series of high-magnification images to be captured rapidly as the microscope is moved under software control across the nailfold (~1 min per finger). These images are stitched together automatically to generate a high-quality static whole-nailfold capillary image mosaic, from which fully automated measurements of capillary structure and (as described in the next section) flow are derived (Fig. 4D). The structural measurements are as follows: capillary density, mean capillary width (the mean of the individual capillary widths), maximum capillary width (the largest of the individual capillary widths), shape score (the mean vessel tortuosity) and derangement score (the angular dispersion of the capillaries). These structural measurements are combined to give an abnormality score, which allows patients with SSc to be distinguished from those without (healthy controls and patients with primary RP), with an area under the receiver operating characteristic (ROC) curve of 0.919 (S.E. 0.026) [63].

Other studies on automation

Over the past 20 years various investigators have reported studies aiming to automate or semi-automate the analysis of nailfold capillaroscopic images in patients with different diseases including diabetes, hypertension and SSc. At the most basic level is work to enhance the visibility of capillaries, sometimes as a prequel to automated analysis, using colour, spatial pattern or temporal pattern filtering [28, 64–68]. Vessel detection has been extensively studied with methods aiming either to extract whole vessels/centrelines [69–72] or apices [68, 73–75]. Few of these systems have been clinically evaluated at scale, with the notable exception of the AUTOCAPI system [75], which gives vessel density results in good agreement with experts, for a manually selected region. Both fully automated [65, 68] and semi-automated [76]

measurement of vessel width and shape have been described but, again, with very limited clinical validation. There has also been work to explore the potential for texture analysis to detect disease in whole nailfold images [66, 77], but only very preliminary results are presented. To the best of our knowledge, the Manchester system (described above) is the only fully automated and systematically evaluated system to measure all capillaroscopic features of clinical interest (density, vessel width, vessel shape and vessel organization).

Measuring red blood cell velocity

Everything discussed above relates to measuring nailfold capillary *structure*, but capillaroscopy can also yield functional information. In high-magnification videocapillaroscopy, individual red blood cells (RBCs) are visible allowing RBC velocity to be estimated from video sequences. Methods include manual frame-by-frame analysis measuring displacement of plasma gaps [78], cross-correlation between manually selected windows on the same capillary [78, 79], oblique trace extraction from spatio-temporal images formed by taking image intensity along the vessel at successive time points [80, 81], and optical flow [82].

Initial studies of RBC velocity in patients with SSc-spectrum disorders assessed the 'stop-flow' time in response to a cooling stimulus [83]. Mugii *et al.* reported that RBC velocity was reduced in patients with SSc and dermatomyositis compared with healthy controls, although in dermatomyositis differences were not significant [84, 85]. In seven patients with SSc, RBC velocity increased after treatment with alprostadil [84]. Increased RBC velocity has been reported in response to vasoactive treatment in other conditions [86, 87]. More recently, we measured RBC velocity averaged across all capillaries in a nailfold using an optical flow method [31, 63] and found that adding flow to structural measurements improved discrimination between patients with SSc and those with primary RP or healthy controls [63] [the area under the ROC curve when flow was added to the five structural measurements improved from 0.919 (S.E. 0.026) to 0.930 (S.E. 0.024)].

Measuring nailfold capillary RBC velocity is potentially very exciting because (unlike structure measurement) velocity is likely to be sensitive to short-term changes (e.g. in the context of early phase clinical trials examining acute dosing or short-term treatments). Thus RBC velocity measurement could expand the potential of nailfold capillaroscopy as a tool to examine pathophysiology and treatment response. However, measuring RBC velocity is complex and work remains to be done. If 'easy to use', reliable methods of measuring RBC velocity can be developed, these could complement other methods of measuring finger blood flow (for example laser Doppler techniques) [23, 88].

Next steps

The advances in quantitative capillaroscopy described above, including automation, have the potential to improve patient care and to facilitate research into the pathophysiology, measurement and treatment of SSc-spectrum disorders. What follows is a personal view on what we believe is achievable over the next 5–10 years.

Facilitating early diagnosis

To make a real impact on early diagnosis of SSc, all patients presenting with RP, and especially those with any 'red flag' (e.g. ANA positivity, older age of onset) should have nailfold capillaroscopy [89, 90]. Globally, this is not currently happening. Most patients seeking medical advice for Raynaud's are seen by general rheumatologists, most of whom are unfamiliar and/or uncomfortable with capillaroscopy image acquisition and/or interpretation. It is unlikely that more than a minority of general rheumatologists are ever likely to have access to videocapillaroscopy. We believe that the way forward is to promote the use of low-cost hand-held devices, for example, USB microscopy, advocated by Bhakuni *et al*. [91], or dermoscopy, which has been previously found to be less sensitive but more specific in detecting abnormality than videocapillaroscopy [92, 93] and has recently been suggested as a screening tool [94]. But ease and feasibility of image acquisition does not get around the problem of many rheumatologists being uncomfortable with image interpretation. Although both 'hands on' and online training courses can help here, this concern could be addressed by providing cloud-based automated analysis with near instantaneous 'results', for example positive and negative predictive values for the patient having an underlying SSc-spectrum disorder.

Facilitating research

In our opinion, automation will be the way forward to facilitating multicentre randomized controlled trials (which include capillaroscopic parameters as outcome measures) and 'big data' cross-sectional and longitudinal studies. Although many studies have reported changes in capillaroscopy in response to drug treatment, limitations of these studies have often been small patient numbers, the subjectivity of the qualitative and semi-quantitative capillaroscopic parameters used, and the frequent inability to be sure that the same section of nailfold has been compared at each visit. Automated analysis should circumvent these problems. Although automated analysis systems are not currently perfect, progress is very encouraging.

In conclusion, quantitative capillaroscopy has made enormous strides in the past 25 years. Quantitative analysis will never completely 'take over' from qualitative analysis, which may be all that is required when abnormalities are clearly diagnostic, and because some parameters, e.g. haemorrhage, do not lend themselves

to the quantitative approach. However, quantitative analysis complements and augments qualitative analysis, and is the way forwards to improve diagnostic accuracy and for capillaroscopy to become a long-awaited, non-invasive biomarker of disease progression and of treatment response.

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Data availability statement

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