Computerized Nailfold Video Capillaroscopy — A New Tool for Assessment of Raynaud's Phenomenon

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ABSTRACT. ***Objective.*** To develop a computer based nailfold video capillaroscopy system with enhanced image quality and to assess its disease-subgroup resolving power in patients with primary and secondary Raynaud's phenomenon (RP).

Methods. Using frame registration software, digitized video images from the microscope were combined to form a panoramic mosaic of the nailfold. Capillary dimensions (apex, arterial, venous, and total width) and density were measured onscreen. Significantly, the new system could guarantee analysis of the same set of capillaries by 2 observers. Forty-eight healthy control subjects, 21 patients with primary RP, 40 patients with limited cutaneous systemic sclerosis (lcSSc), and 11 patients with diffuse cutaneous SSc (dcSSc) were studied. Intra- and interobserver variability were calculated in a subset of 30 subjects.

Results. The number of loops/mm was significantly lower, and all 4 capillary dimensions significantly greater, in SSc patients versus controls plus primary RP patients ($p < 0.001$ for all measures). When comparing control (+ primary RP) patients with SSc patients (lcSSc + dcSSc) the most powerful discriminator was found to be the number of loops/mm. Results for intra- and interobserver reproducibility showed that the limits of agreement were closer when both observers measured the same capillaries.

Conclusion. The key feature of the newly developed system is that it improves reproducibility of nailfold capillary measurements by allowing reidentification of the same capillaries by different observers. By allowing access to previous measurements, the new system should improve reliability in longitudinal studies, and therefore has the potential of being a valuable outcome measure of microvessel disease/involvement in clinical trials of scleroderma spectrum disorders. (J Rheumatol 2005;32:841–8)

Key Indexing Terms:
NAILFOLD VIDEO CAPILLAROSCOPY
NAILFOLD MICROSCOPY
OUTCOME MEASUREMENT
MICROVASCULAR
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Widefield nailfold microscopy has been used for many years in the assessment of Raynaud's phenomenon (RP). Widened, dilated loops, with areas of avascularity, signify an underlying connective tissue disease such as systemic sclerosis (SSc)[1,2]. A key issue is whether these abnormalities in nailfold capillary structure are quantifiable. If so, then nailfold microscopy would offer the potential of monitoring microvascular disease progression and/or treatment response. This is especially relevant now that it is recognized that several vasoactive agents have effects on vascular remodeling, including prostanoids and endothelin-1 antagonists[3]. A method of quantifying microvascular remodeling would be a major advance in measuring treatment effect.

In recent years video capillaroscopy, an extension of the widefield technique, has allowed measurement of capillary density and dimensions from the stored image[4]. However, this method has limitations. First, it must be remembered that it is the column of red blood cells rather than the capillary wall that is seen. This means that at any one timepoint, some capillaries are very difficult to see, therefore any single video frame image is likely to include capillaries that cannot be measured. This increases subjectivity. Second, even if image quality was ideal, measurement of capillary dimensions using currently available software is time-con-

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suming, meaning that in practice only a small number of capillaries can be examined. This too leads to subjectivity, especially in patients with scleroderma spectrum disorders (the patient group in which we are most interested) because measurements from a set of (say) 5 sequential capillaries may be very different to those from an adjacent 5. Therefore ideally we should be confident that the same set of capillaries is measured at each visit. This is not possible using commercially available software.

Against this background, our aims were:

1. To develop a computer based nailfold video capillaroscopy system with enhanced image quality (obviating the problem of "ghost" capillaries) that would allow identification of the same set of capillaries for measurement at different timepoints. This data acquisition and measurement system will be described briefly in the Methods section, as reported fully elsewhere[5-7]. Figure 1 shows an example of how the new system enhances ghost capillaries.
2. To apply the technique to patients with primary RP, RP secondary to SSc, and healthy control subjects, and assess its disease-subgroup resolving power.
3. To assess the intraobserver and interobserver variability of the technique.

MATERIALS AND METHODS

Patients. Characteristics of patients and healthy controls are shown in Table 1. The following groups were studied: (1) Forty-eight healthy control subjects. None had diabetes or other condition affecting the microvasculature. (2) Twenty-one patients with primary RP, as defined by LeRoy and Medsger[8]. No patient with primary RP had any clinical or immunological evidence of underlying connective tissue disease. (3) Fifty-one patients with SSc, subdivided into 40 with limited cutaneous SSc (lcSSc) and 11 with diffuse cutaneous SSc (dcSSc) on the basis of the extent of skin involvement[9]. Patients with dcSSc had proximal limb or truncal involvement: patients with lcSSc had skin involvement confined to head, neck, and distal to elbows and knees.

Video capillaroscopy protocol. Patients and controls were acclimatized for 20 min at a room temperature of 23°C prior to video capillaroscopy. They were asked to refrain from smoking and drinks containing caffeine for 4 h prior to examination. The ring finger of the nondominant hand was examined.

Table 1. Clinical characteristics of control subjects, patients with primary RP, and patients with limited and diffuse cutaneous SSc.

	Healthy Controls, n = 48	Primary RP, n = 21	lcSSc, n = 40	dcSSc, n = 11
M/F	15/33	6/15	6/34	3/8
Age, yrs*	41 (20–81)	39 (17–70)	53 (27–81)	51 (28–69)
Duration of RP, yrs*	Not applicable	12 (1–50)	15 (2–60)	2 (0–29)

* Results are median (range).

Capillaroscopy equipment. The optical microscope was developed by KK Technologies (Holyford, Devon, UK) and incorporated a CCD video camera with ×300 magnification. A ring of green light-emitting diodes provides high contrast illumination of the nailfold blood vessels. The output from the camera is fed to a Snapper (www.datacell.co.uk) video digitizer board inside a standard PC (processor 200 MHz, memory 512 Mb).

Data acquisition. Figure 2 shows the user interface of the data acquisition system, which allows a panoramic mosaic of the nailfold to be constructed. The bottom left window displays a live image from the microscope. The user moves the microscope to one end of the nailfold. Once optimum focus is achieved he/she then presses the "capture" button — 16 video frames are captured at a rate of 5 Hz by the Snapper board and stored in the computer's hard disc. These 16 frames are then automatically registered to compensate for any small finger movements, and combined into a single image, which is then displayed in the bottom right window. The user then moves the microscope to the next area of interest, maintaining an overlap with the first area. The capture button is pressed again, and a second set of 16 video frames is digitized, only this time the composite image that results is registered with the first composite image and the resulting panoramic composite is displayed in the window in the middle of the interface. This process is repeated until the whole area of interest has been studied. This takes 10 to 15 min per nailfold studied.

If the patient has been examined before, then the previous panoramic mosaic can be displayed in the window at the top of the interface (Figure 2). This allows the user to ensure that the same region is recorded on each visit.

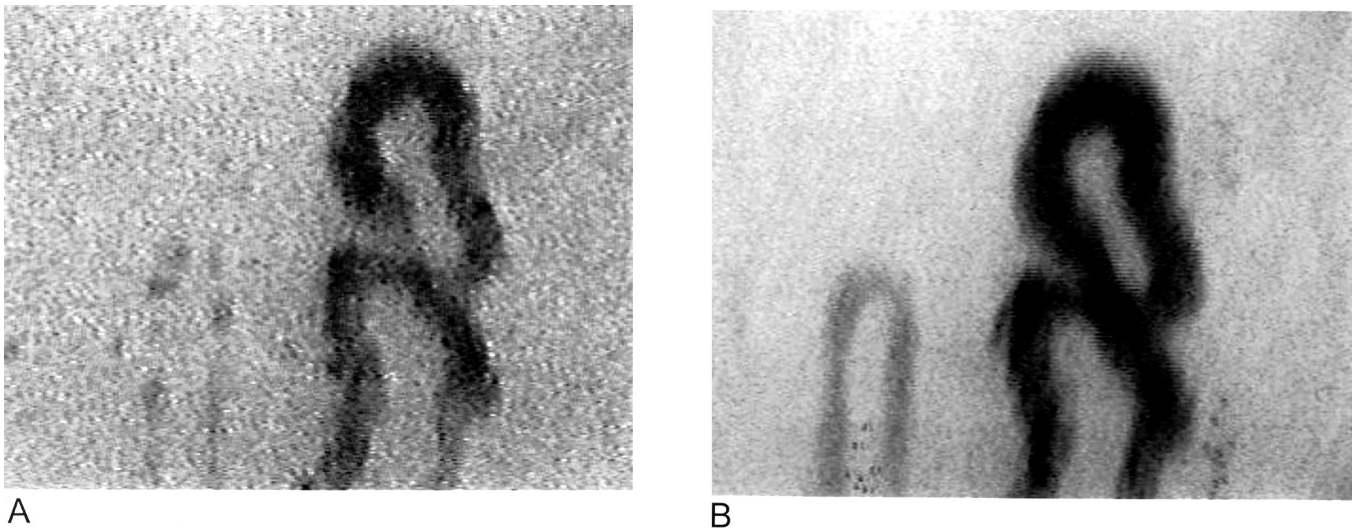

Figure 1. A "ghost" capillary on the left in (A) becomes easily visible in (B) in which the image quality has been enhanced with the new system.

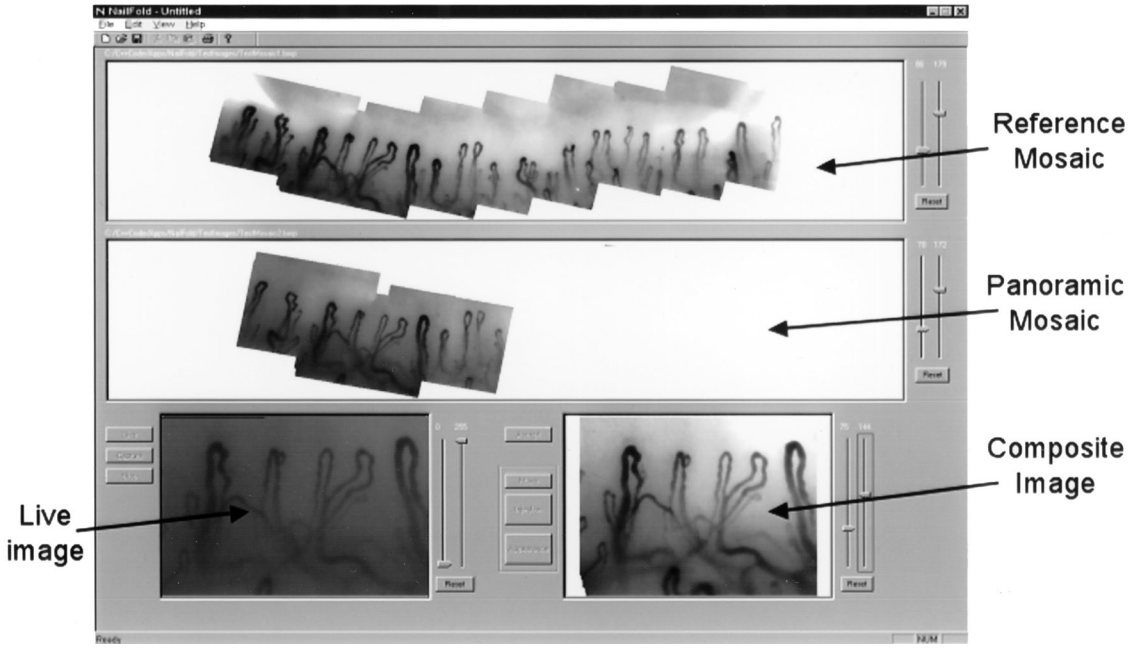

Figure 2. The user interface of the data acquisition system. The panoramic mosaic (middle panel) is currently under construction. The reference mosaic in the top panel is from a previous occasion, allowing comparison to the present study and ensuring that the same set of capillaries is being examined each time.

Capillary measurement

Capillary dimensions. Figure 3 shows the user interface for measurement of capillary dimensions. As in the data acquisition interface, the panoramic mosaic is displayed in the window in the middle of the interface. The user clicks on the first of the capillaries of interest and an enlarged view of this portion of the mosaic is displayed in the bottom left window. Apex, arterial, venous, and total capillary width (the width at the widest point) of each capillary are measured using the software, which involves clicking at each side of the capillary for each measurement. It may be difficult to distinguish which side of the loop is arterial and which is venous, and so the user must be able to see which way the blood is flowing. This is done by playing back the original 16 frames that made up the scene containing that particular capillary loop in a movie sequence at the bottom right of the interface (Figure 3). As in the data acquisition system, if a patient has been examined before, then the data from the previous visit can be displayed at the top of the interface.

We chose to study 5 consecutive capillaries in each patient — the mean across the 5 loops was calculated for each of apex, arterial, venous, and total capillary widths. The 5 capillary loops chosen were the first 5 capillaries from the right hand edge of the nailfold in which arterial, apex, and venous widths could all be discerned. This method of capillary measurement takes about 10 min.

Capillary density. This is calculated from the number of loops per mm. From the mosaic in the middle panel, the user marks the position of all the distal capillaries by clicking on the apex of each loop. This takes a few seconds only.

Intra- and interobserver variability/reliability. Images from a subset of 30 subjects (10 healthy controls, 10 patients with primary RP and 10 with SSc) were reexamined by Observer 1 (TM) and also by Observer 2 (MA). To assess the effect of being able to guarantee assessment of the same capillaries on each occasion (possible using our newly developed data acquisition system) for both intra- and interobserver variability these analyses of 30 images were performed in 2 ways: (1) "Blind": the observer had no access to previous measurements. This meant there was no guarantee of the same 5 capillaries being measured each time, nor of the same capillary positions being included for calculation of capillary density. (2) With the previous mosaic displayed in the top panel: this allowed the same capillaries/capillary positions to be examined by highlighting (as in Figure 3) the 5 capillaries previously measured.

Statistical analysis. Between-group comparisons. Data were log transformed to achieve normality, and compared using Student's t tests. Comparisons were made between controls and patients with primary RP, between lcSSc and dcSSc patients, and between control plus primary RP patients and all SSc patients. Discriminant analysis was performed to determine the degree to which the 5 measures differed.

Intra- and interobserver variability. All loop dimensions were log transformed to achieve normality. For all intra- and interobserver studies, we calculated the bias and limits of agreement[10]. If the differences between the 2 observers' measurements are normally distributed, that distribution will have a mean that represents the "bias" between the 2 observers. Because 95% of the differences will lie between 1.96 standard deviations (SD) of the mean, the mean ± 1.96 SD represent the upper and lower limits of agreement.

RESULTS

Between-group comparisons (Table 2, Figure 4). The number of loops/mm was significantly lower, and all 4 dimensions significantly greater, in SSc patients versus controls plus primary RP patients ($p < 0.001$ for all parameters). There were no significant differences between the 2 SSc subtypes. Apex and arterial width were greater in primary RP patients than in healthy controls ($p = 0.041$ and $p = 0.031$, respectively).

Comparing controls (+ primary RP) patients with SSc patients (lcSSc + dcSSc), the most powerful discriminator was found to be the number of loops/mm, correctly classifying 97% of the "control + PRP" group and 86% of the SSc group.

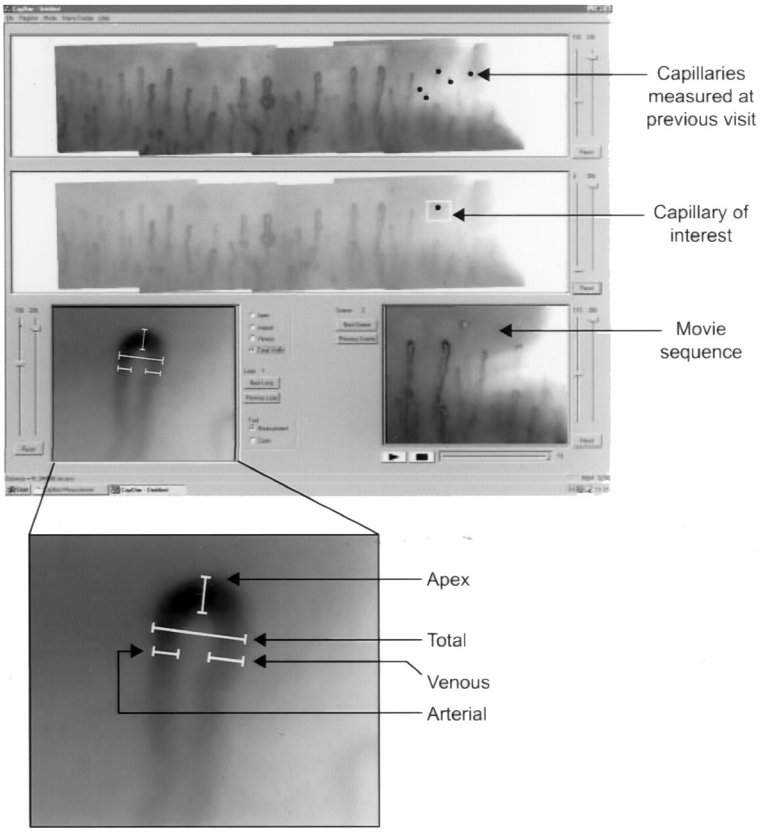

Figure 3. The user interface for measurement of capillary dimensions. As in Figure 2, the reference mosaic in the top panel allows comparison to a previous study. The inset shows the different dimensions measured.

Table 2. Mean capillary density and dimensions with between-group comparisons for log transformed data. Loops/mm is mean (with standard deviation). Dimensions are geometric mean in microns [with coefficient of variation, %].

	Control, n = 48	Primary RP, n = 21	lcSSc, n = 40	dcSSc, n = 11	Control vs Primary RP	lcSSc vs dcSSc	Control + Primary RP vs SSc
Loops/mm, mean (SD)	11.25 (1.31)	10.81 (1.43)	5.98 (2.17)	5.82 (2.51)	0.219	0.833	< 0.001
Apex width, µm [%]	14.06 [21]	15.71 [24]	26.84 [87]	20.43 [32]	0.041	0.440	< 0.001
Arterial width, µm [%]	10.73 [19]	11.98 [21]	20.28 [86]	15.80 [24]	0.031	0.164	< 0.001
Venous width, µm [%]	13.20 [23]	14.50 [19]	25.02 [83]	19.99 [26]	0.085	0.232	< 0.001
Total width, µm [%]	38.01 [16]	40.27 [14]	74.16 [73]	59.14 [24]	0.146	0.188	< 0.001

Intra- and interobserver variability. Table 3 shows bias and limits of agreement when images were examined "blind" (measurement of the same capillaries was not guaranteed). Table 4 shows these results when both observers measured the same capillaries. Figure 5 compares these results with and without measurement of the same capillaries being guaranteed. The limits of agreement were closer when both observers measured the same capillaries (Figure 5). For example, for arterial width, lower and upper limits of agreement improved from –35%/+43% to –19%/+13% for intraobserver measurements, and from –20%/+65% to –14%/+30% for interobserver measurements.

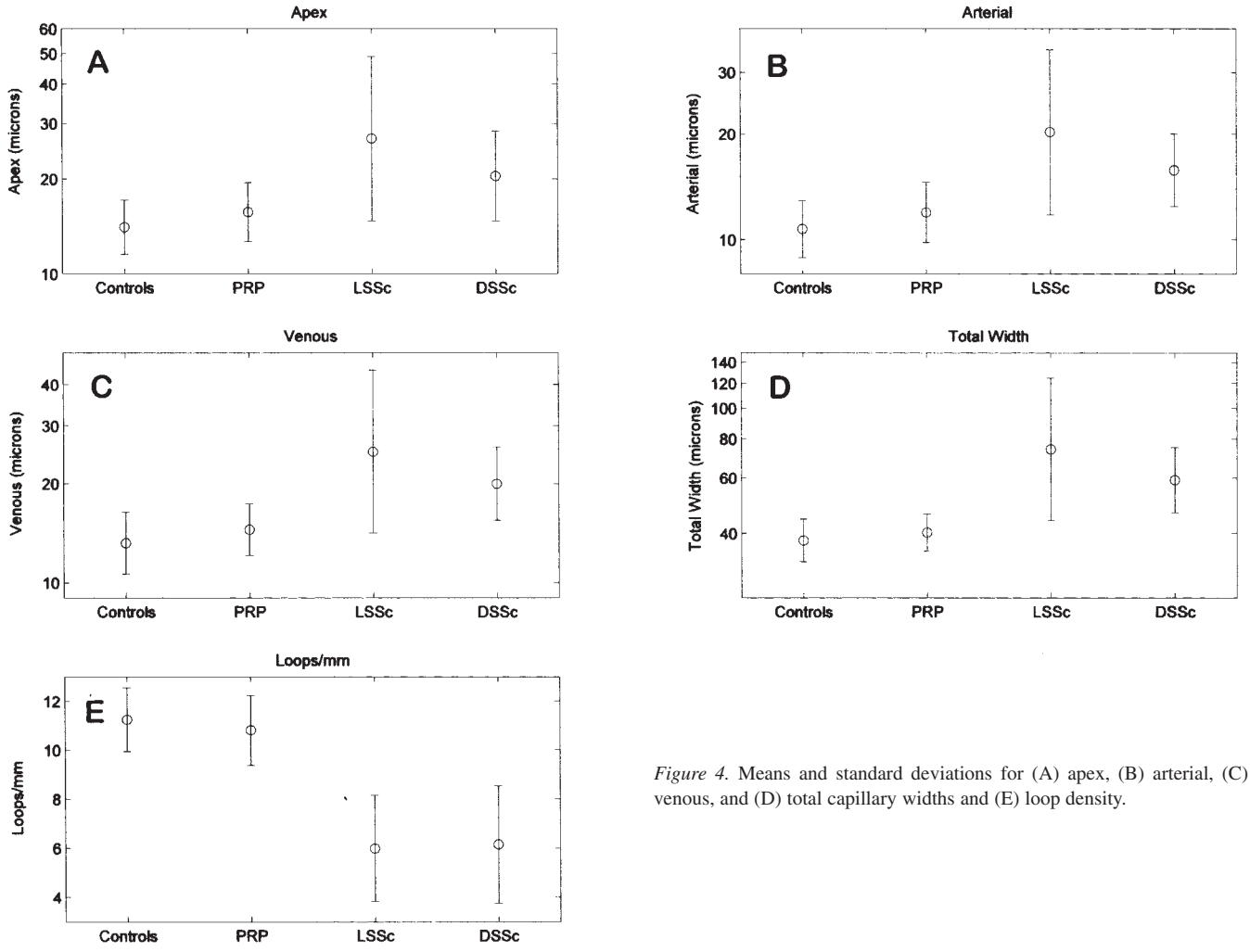

Figure 4. Means and standard deviations for (A) apex, (B) arterial, (C) venous, and (D) total capillary widths and (E) loop density.

DISCUSSION

The development of our new computer based capillaroscopy system provides interfaces for image acquisition and measurement. Having developed the system, we applied it in a cross-sectional study of primary and secondary RP, and assessed intra- and interobserver reproducibility. As anticipated, measurements were greater, and capillary density lower, in patients with SSc compared to control subjects and patients with primary RP. The findings in this cross-sectional study are consistent with those of our previous studies when measurements were made from single video frames[4,11]. In our first study[4], capillary measurements were derived from a single measurement from the distal row, and capillary density was calculated from loops/mm^2. Capillary dimensions in this 1996 study were greater in patients with primary RP than healthy controls, suggesting that structural microvascular change may occur in primary RP. In the present study, we found that the arterial and apex widths were significantly greater in patients with primary RP than in control subjects, and there was a trend toward greater venous and total widths. Thus the findings from the present study support the theory that subtle microvascular change may occur in patients with primary RP.

In our 2000 study, capillary dimensions and density were averaged across all measurable capillaries in two 3-mm lengths of nailfold — one from the left and one from the right ring finger[11]. We felt that this method was more likely to be representative of the whole nailfold than measuring only the most abnormal capillary, as in the 1996 study. This method, using the two 3-mm lengths, involved measuring dimensions from as many as 40 capillaries, and was extremely time-consuming. In the 2000 study, dimensions were significantly larger in patients with lcSSc than those with dcSSc[11]. In the present study there was a trend for dimensions to be larger in patients with lcSSc than in those with dcSSc. Our 2000 study also examined intra- and interobserver reproducibility: we found that although there was good correlation between observers, the limits of agreement were wide (±25%–50%), indicating lack of reproducibility[11].

Table 3. Bias and limits of agreement for intra- (TM1 and TM2) and interobserver (MA and TM1) variability when measurement of the same capillaries is not guaranteed. Venous results for TM1 vs TM2 represent an upper limit, due to a relationship existing between the difference in measurements and the size of the capillaries.

	TM1 vs TM2				MA vs TM1			
	Bias, %	Lower Limit, %	Upper Limit, %	p	Bias, %	Lower Limit, %	Upper Limit, %	p
Loops/mm	–1.63	–33.80	46.19	0.659	13.92	–24.81	72.60	0.002
Apex	–4.74	–24.78	20.63	0.035	15.32	–16.18	58.67	< 0.001
Arterial	–3.96	–35.47	42.94	0.285	14.76	–20.31	65.27	< 0.001
Venous	–9.25	–36.13	28.93	0.006	15.16	–19.69	65.14	< 0.001
Total width	–2.93	–20.30	18.23	0.117	6.82	–13.46	31.85	0.002

Table 4. Bias and limits of agreement for intra- (TM1 and TM2) and interobserver (MA and TM1) variability when both observers measured the same capillaries. Apex and venous results for TM1 vs TM2 represent an upper limit, due to a relationship existing between the difference in measurements and the size of the capillaries.

	TM1 vs TM2				MA vs TM1			
	Bias, %	Lower Limit, %	Upper Limit, %	p	Bias, %	Lower Limit, %	Upper Limit, %	p
Apex	–6.36	–17.99	6.92	< 0.001	4.21	–8.61	18.83	0.002
Arterial	–4.38	–18.81	12.63	0.006	5.88	–13.54	29.65	0.005
Venous	–3.49	–15.78	10.58	0.009	4.99	–9.26	21.49	0.001
Total width	–0.79	–7.34	6.23	0.225	0.47	–7.26	8.84	0.535

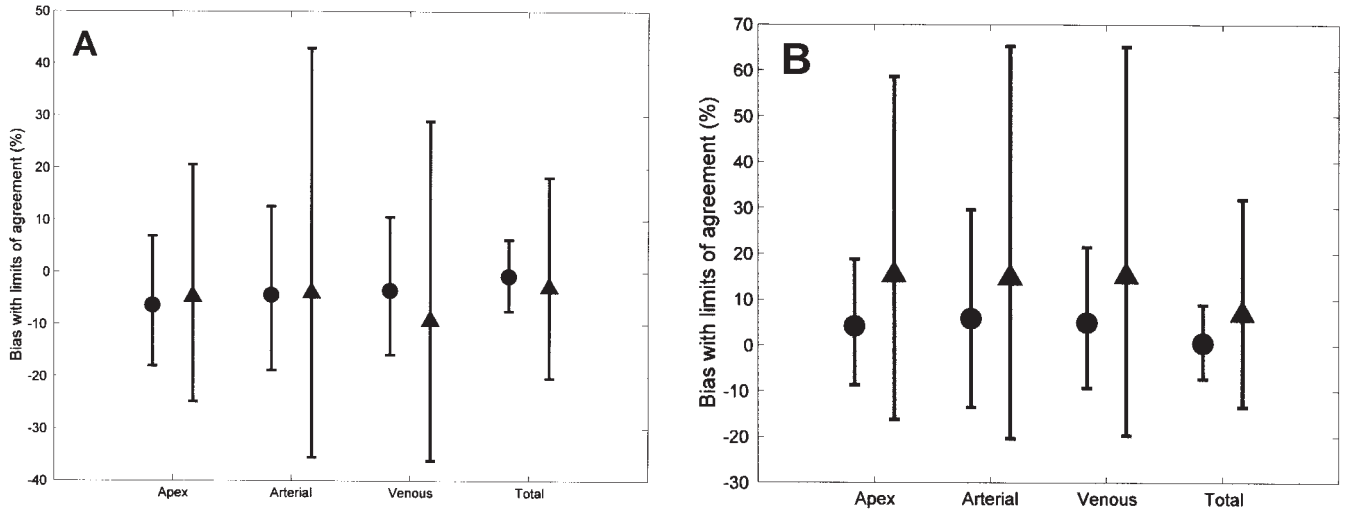

Figure 5. Bias with limits of agreement for (A) intraobserver and (B) interobserver reliability for apex, arterial, venous, and total capillary widths with (●) and without (▲) measurement of the same capillaries being guaranteed.

This lack of reproducibility was a major concern to us — the major clinical application of capillary dimension measurement is likely to be in following microvascular disease over time, either in studying the natural history of the disease, or in monitoring the response to drug treatment. Thus capillary dimensions and density measurement must be reliable, otherwise these are unlikely to be sufficiently sensitive to be applied to longitudinal studies.

It was against this background that we developed the new computer based system. The scientific background to the development of this system has been described[5-7], but the fundamental points are given in the Methods section. The key points are the following: (1) The improved image quality resulting from the frame registration process — the single image acquired from the 16 video frames averages out temporal variability. These improved images facilitate measurement of both dimensions and density. (2) The ability to differentiate between arterial and venous limbs with certainty, because of the playback facility on the measurement system (Figure 3). (3) The ability to study the same capillaries on repeat inspections. All these 3 features we felt were likely to improve reproducibility, especially the ability to guarantee examination of the same capillaries at each inspection. This indeed proved to be the case, as shown by

the much narrower limits of agreement when measurements were made with reference to previous mosaics (Figure 5). For intraobserver variability, the limits of agreement were in the order of +7% to 19%. Because to date we have not carried out longitudinal studies (and therefore do not know whether capillary dimensions are likely to change more or less than this), it is not known whether these limits of agreement are acceptable for clinical studies. As discussed below, we hope to improve on these by increasing the number of capillaries studied (currently only 5). However, the narrower limits of agreement achieved using the new system (even when only 5 capillaries are measured) increase the potential of the technique for measuring changes within an individual over time. We believe that this is the most important observation from the current study, and prospective studies are now in progress.

Regarding the ability of the new computerized system to differentiate between SSc patients and controls and patients with primary RP, the most powerful discriminator was found to be the number of loops per mm. Other investigators have found that capillary density may discriminate between secondary and primary RP (or control subjects)[12-15]. This observation has clinical implications because capillary density, as described above, can be very quickly calculated and so could be feasible even in a busy outpatient clinic. Thus if there are constraints on time, then this measure could be included in routine assessment even if calculation of dimensions was not practicable. However, at present the computerized system should be considered a research tool.

Other investigators have applied image analysis techniques to the interpretation of nailfold capillaries: Hu and Mahler[16] describe an image analysis system (CapiShape) that computes not only dimensions but also parameters related to surface area and capillary distribution. The CapiShape system digitizes the video signal (as does our own system). However, analysis is based on single video frames (unlike in our study). The CapiShape system rotates the image to facilitate calculation of area and characterization of capillary morphology. Another feature of the system is that for each capillary, individual diameters (e.g., arterial diameter) are averages of a number of local diameters rather than a "widest point" diameter. The authors reported that in studies of reproducibility, measured differences between operators were smaller than 1.5 µm (although data were not given). Capillary dimensions were significantly greater in 10 patients with SSc than in 49 control subjects. The CapiShape software allows derivation of a more complex set of parameters than our system, but we believe our system has the advantage of ease of identification of the same capillaries in longitudinal studies.

The complexity of the problem of analysis of nailfold images for clinicians is well summarized by Jones, *et al*[17]. These authors propose a taxonomy for nailfold capillaries incorporating 6 descriptive classes: cuticilis, open, tortuous, crossed, bushy, and bizarre, reflecting the heterogeneity of the nailfold abnormalities that can occur.

Our computerized system does not directly take into account these different capillary morphologies, and does not directly assess the pattern of architectural derangement of the capillary network. Our feeling is that the morphology of certain capillaries is too abnormal to allow reliable measurement of dimensions. That these capillaries exist, especially in patients with SSc, is indirectly taken into account in calculation of density. Fortunately, in our experience, these capillaries are a minority. Thus in most patients, 5 consecutive capillaries for measurement can readily be identified.

A limitation of nailfold microscopy (although one that applies to any microscopy system irrespective of the method of image analysis) is the inability of a substantial proportion of patients with diffuse cutaneous disease to extend their fingers sufficiently to allow nailfold measurements. This problem contributed to the relatively small number of patients in the dcSSc subgroup. Adaptations in microscope design may minimize this difficulty in future studies.

In summary, quantifying nailfold capillaries is complex. We have developed a computerized image analysis system for acquisition and analysis of these capillaries. At present, we propose this system as a research tool, rather than as a method for everyday clinical use. The key feature of this system is that it allows access to previous measurements from the same nailfold, and we have demonstrated how this improves intra- and interobserver reproducibility. Thus our new system should improve reliability in longitudinal studies, and therefore has the potential of being a valuable outcome measure of microvascular disease progression and of treatment response in scleroderma spectrum disorders. Longitudinal studies are now required.

This improvement in reproducibility probably reflects how 5 consecutive capillaries are not necessarily representative of the whole nailbed, especially in patients with SSc, in whom capillary morphology can vary widely across the nailbed, with widened capillaries and areas of avascularity with loop dropout. Thus, although our system will improve reliability of longitudinal studies examining change within an individual over time, a larger number of capillaries (preferably the whole nailbed) should be examined, as this may prove even more reliable by averaging over a larger number of measurements, and should improve the sensitivity and specificity of the technique to discriminate between patients with primary and secondary RP, and perhaps also within patient subgroups (for example early versus late disease). Measuring a greater number of capillary loops is not feasible using a manual measurement system (measurement of only 5 capillaries requires roughly 15 minutes): this must await a fully automated system, which is the subject of current research. The fully automated system being developed further enhances the visibility of capillaries. It measures capillary width using a technique called pseudo-granulome-

try, and capillary tortuosity from the dispersion and orientation of vessel pixels. This fully automated system should further improve objectivity.

Our study achieved its aims as follows:

1. A computer based nailfold microscopy system with enhanced image quality (Figure 1) has been developed. This system allows identification of the same set of capillaries for measurement at different timepoints by displaying the capillaries measured at the previous visit in the upper panel of the user interface (Figures 2 and 3).
2. The technique was applied in a cross-sectional study of patients with primary RP, lcSSc, and dcSSc and healthy controls. When comparing controls (+ primary RP) with SSc patients the most powerful discriminator was the number of loops per mm.
3. Intra- and interobserver variability were assessed, and both were improved by the ability of the system to reidentify the same capillaries (Figure 5).

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