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INCREASED NAILFOLD CAPILLARY DIMENSIONS IN PRIMARY RAYNAUD'S PHENOMENON AND SYSTEMIC SCLEROSIS

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SUMMARY

The aim of the study was to measure nailfold capillary dimensions and capillary density in patients with primary Raynaud's phenomenon (PRP) and systemic sclerosis (SSc) compared to control subjects. Ten controls, nine patients with PRP and 10 patients with SSc were studied. All dimensions other than distance between limbs were significantly increased in both the PRP and SSc groups compared to controls ($P < 0.01$), with the SSc group showing the most marked increases (SSc *vs* PRP, $P < 0.05$ for all dimensions). Capillary density was significantly reduced in the SSc group compared to controls ($P = 0.004$). These results suggest that structural vascular changes occur in PRP as well as in SSc, and that PRP may, therefore, not be entirely benign.

KEY WORDS: Scleroderma, Systemic sclerosis, Primary Raynaud's phenomenon, Nailfold capillary microscopy, Capillary dimensions.

THE technique of wide-field capillary microscopy has for many years been used in the assessment of patients with connective tissue disease [1], and abnormalities in patients with systemic sclerosis (SSc), including capillary dilatation and loop dropout, are well recognized. Photographing the nailfold allows subsequent examination of the capillaries with measurement of capillary density. More recently, video capillaroscopy, which has the advantage of allowing immediate measurement of individual capillaries using a video camera and digitizing system, is emerging as a useful tool in the assessment of the microvasculature of patients with Raynaud's phenomenon. In this study, we used this technique of video capillaroscopy to compare nailfold capillary dimensions and capillary density in patients with primary Raynaud's phenomenon (PRP), SSc and healthy control subjects.

PATIENTS AND METHODS

Patients

Nine patients with PRP, 10 with SSc and 10 healthy control subjects were studied (Table I). Included in the PRP group were patients with Raynaud's phenomenon of at least 3 yr duration, in whom no clinical or serological evidence of underlying connective tissue disease had been found. Patients with SSc fulfilled the American Rheumatism Association criteria for the disease [2]. Of the patients with SSc, eight had limited cutaneous systemic sclerosis (LCSSc), one diffuse disease (DSSc) and one had an overlap syndrome. Those classified as LCSSc had skin involvement confined to the extremities and face, whereas patients with DSSc had proximal scleroderma. With respect to vasodilator therapy, seven of the patients with SSc were on vasodilator therapy (six nifedipine, one thymoxamine) and two of the PRP group were on vasodilators (one nifedipine, one thymoxamine). In the control group, none were on vasodilator medication. Regarding immunology, seven of the SSc patients were antinuclear factor (ANF) positive. Five were anticentromere antibody positive and one anti Scl-70 positive. Testing for antinuclear factor, anticentromere antibody and anti Scl-70 was negative in all PRP patients.

Video capillaroscopy

Each patient/control was acclimatized for 30 min at 30°C prior to capillaroscopy. The index finger of the dominant hand was studied. In two SSc patients, this finger had been amputated and so the middle finger was examined.

The capillaries were observed at $\times 200$ and $\times 600$ magnification using a light microscope incorporating a flexilux 300 long-life fibreoptic light source and filter (Scholly Fibre optic GMBH, Germany). The video camera used was the Moritex Europa Ltd, UK camera, Model MS-500. The capillaries were projected on a 14″ Grundig tp 623 television and the image was analysed using capiflow software as developed by the Karolinska Institute for Microelectronics and Diagnostika HB (Stockholm, Sweden). The software was installed on a standard IBM-compatible 386 computer with an Intel 33 MHz central processing unit and 4 MB of RAM with 280 MB of hard disk. Hard copy was obtained by videotaping the images on a standard Hitachi M930E video cassette recorder.

The largest capillary on the distal row was selected and the following dimensions obtained ($\times 600$ magnification) (Figure 1): (A) arterial diameter (μm): the diameter of the arterial limb at its widest point; (B) venous diameter (μm): the diameter of the venous limb at its widest point; (C) loop diameter (μm): the diameter at the apex of the capillary loop; (D) capillary width (μm): the width of the capillary at its widest point; (E) distance between limbs (μm): the distance

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TABLE I
Clinical features of control subjects, patients with primary Raynaud's (PRP) and patients with systemic sclerosis (SSc). Results are medians (range in parentheses). Duration refers to the duration of Raynaud's phenomenon

	Sex M/F	Age (yr)	Smoking Y/N	Duration
Controls (n = 10)	2/8	36	3/7	
PRP (n = 9)	2/7	48	3/6	9 (4–26)
SSc (n = 10)	2/8	44	4/6	18 (3–34)

between the afferent and efferent limbs (measured at the same level of the capillary as 'D'); (F) capillary density (loops/mm^2): this was the number of capillary tufts within a predetermined mm^2 area projected onto the television screen ($\times$200 magnification).

Statistical analysis

Results were compared between groups using a Mann–Whitney U-test.

RESULTS

The results are shown in Table II and Fig. 2. Compared to control subjects, all dimensions (with the exception of distance between limbs in PRP patients) were significantly increased in both patient groups, with dimensions in the SSc patients being significantly greater than those in the PRP group. Capillary density was significantly reduced in patients with SSc compared to PRP patients and controls. Capillary density was similar in PRP patients and control subjects.

Although patients with PRP and SSc were older than controls, age differences between the groups were not statistically significant.

DISCUSSION

Our finding of increased capillary dimensions in patients with PRP, as well as in patients with SSc, suggests that PRP is not necessarily a benign vasospastic disorder, but is associated with structural abnormalities of the microvasculature. While there was overlap between groups, dimensions were increased in patients with PRP compared to control subjects, but not to the degree seen in patients with SSc. However, capillary density, reduced in patients with SSc, did not differ between PRP patients and controls, consistent with the suggestion that capillary enlargement occurs prior to, rather than as a result of, capillary loss [3]. These increased dimensions are an important finding

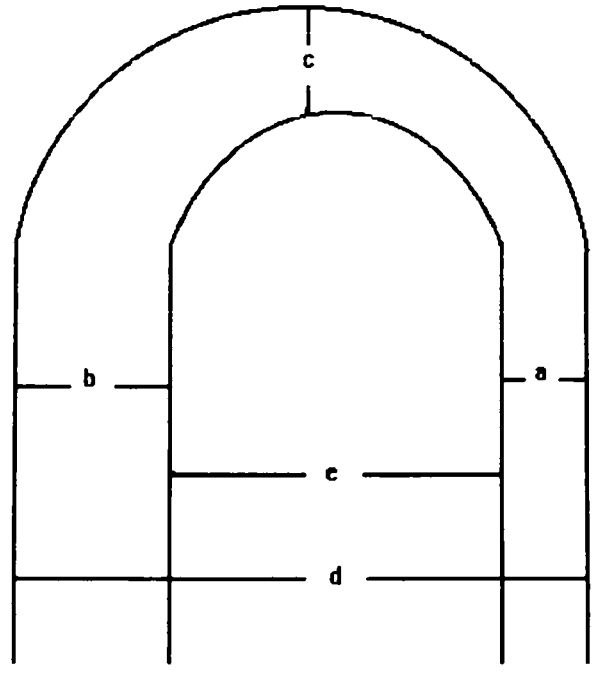

FIG. 1.—Measurements performed on nailfold capillaries.

and relevant to the observation that a proportion of patients presenting with Raynaud's phenomenon without any evidence of underlying connective tissue go on to develop SSc [4]. Our observations in this study, therefore, lend further weight to the hypothesis that the distinction between PRP and SSc may be one of degree.

We set out to quantitate carefully any nailfold capillary abnormalities in patients with PRP and SSc. While many studies of capillary microscopy in patients with Raynaud's phenomenon have been qualitative, some studies do include quantitative or semi-quantitative assessment [5–12]. Quantitative assessment is difficult: within any one nailbed, capillary dimensions vary, especially in patients with connective tissue disease [6]. Further difficulties in quantitation include irregularity and criss-crossing of capillaries [6]. In our study, we selected the most 'abnormal-looking' capillary for analysis. If all capillaries looked similar (which was usually the case in control subjects), then a representative capillary was chosen. Maricq [7], in her quantitative assessment of nailfold capillary abnormalities in 'scleroderma-spectrum' disorders, used the largest capillary dimension. We feel that this

TABLE II
Median dimensions and P values in controls (C), patients with primary Raynaud's phenomenon (PRP) and patients with systemic sclerosis (SSc)

	C	PRP	SSc	C *vs* PRP	C *vs* SSc	PRP *vs* SSc
Arterial diameter (μm)	7 (4–21)	17 (10–93)	35 (11–121)	0.004	0.0005	0.03
Venous diameter (μm)	11 (6–17)	19 (13–29)	33 (17–126)	0.0009	0.0002	0.01
Loop diameter (μm)	14 (6–19)	23 (17–36)	50 (15–126)	0.0003	0.0003	0.03
Capillary width (μm)	36 (29–53)	46 (33–81)	109 (38–287)	0.009	0.0009	0.009
Distance between limbs (μm)	18 (10–21)	18 (7–22)	30 (11–55)	0.842	0.0007	0.0006
Capillary density (loops/mm^2)	35 (27–40)	33 (18–43)	17 (7–40)	0.16	0.004	0.03

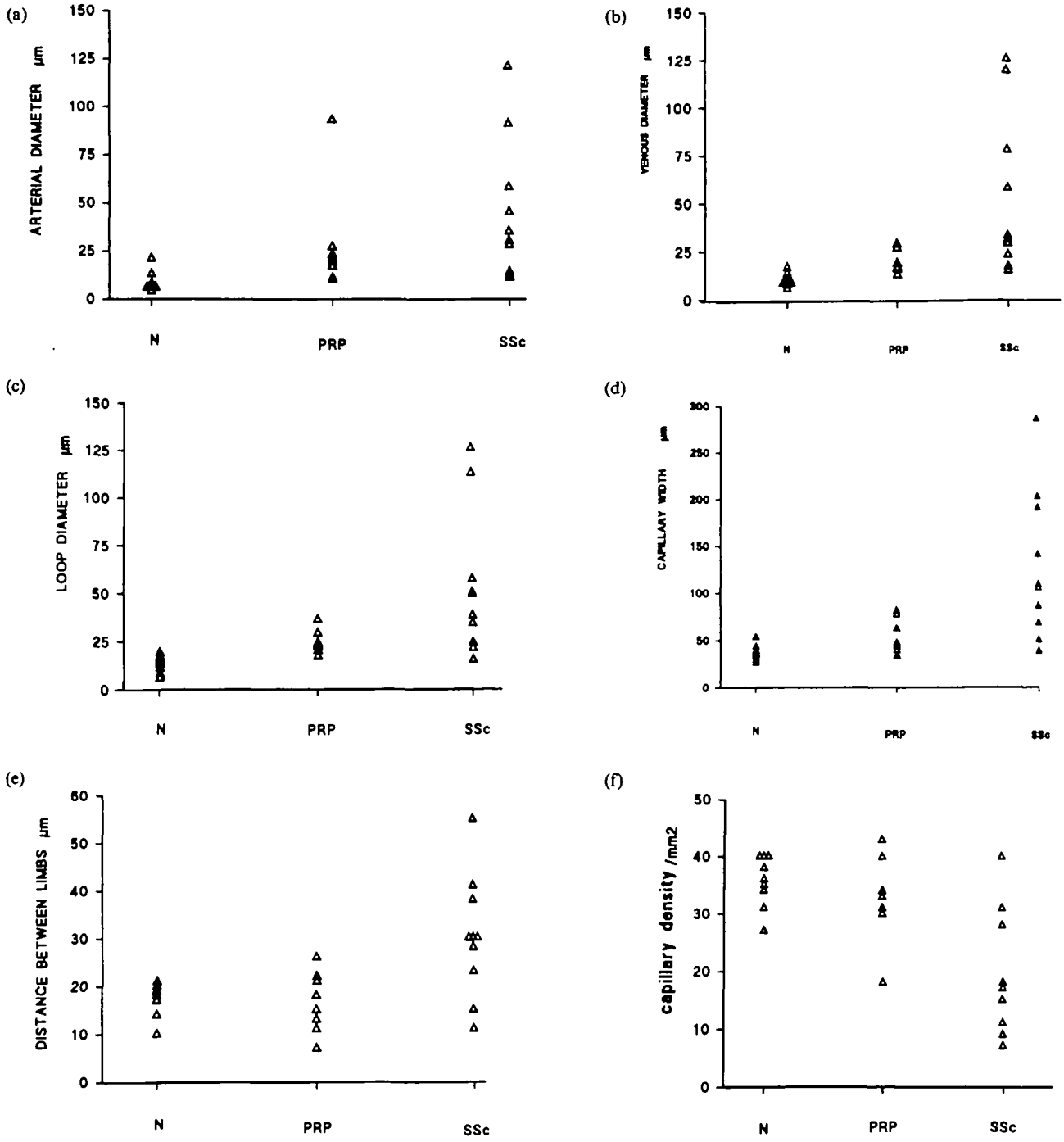

FIG. 2.—Arterial diameter (A), venous diameter (B), loop diameter (C), capillary width (D), distance between limbs (E) and capillary density (F) in 10 control subjects (N), nine patients with PRP and 10 patients with SSc.

approach is justified. The alternative approach—to average dimensions from a given number of consecutive capillaries—is time consuming and causes problems in patients with gross abnormalities, as in SSc, when it can be difficult to define consecutive capillaries.

Amongst the small number of studies including quantitative assessments, different parameters for differentiating between capillaries from patients with and without connective tissue disease have been suggested. Lefford and Edwards [6] suggested that an index derived from apex width and maximum limb width discriminated abnormal from normal capillary loops. This study did not include patients with PRP. Houtman *et al.* [8] found that the number of capillaries in the distal row (measured over 5 mm) was the best discriminant between patients with primary and secondary Raynaud's, and was significantly reduced in patients with CREST and mixed connective tissue disease compared to patients with PRP and controls.

However, their study did not include capillary dimensions. Carpentier and Maricq [10] found that the mean diameter of the capillary loops (averaged across the whole nailfold) and capillary density were the best discriminators between controls and patients with 'SSc related disorders'. In a recent study in which a digitizing system was applied to a video image derived from a photomicrograph of the nailfold. Michoud *et al.* [12] found that mean capillary surface area, and to a lesser degree capillary density, discriminated between control subjects and patients with SSc or dermatomyositis.

In our study, increased capillary dimensions were observed in patients with PRP as well as in patients with SSc. Previous capillaroscopy studies which include patients with PRP have reported variable findings. In the studies by Houtman *et al.* and Carpentier and Maricq referred to above, capillary morphology and the number of capillary loops/5 mm [8], and mean capillary diameter and capillary density [10], were similar in patients with PRP and controls. Lee *et al.* [13] reported abnormal capillary microscopy in only 3/16 patients with PRP, and in two patients these abnormalities were very minor. Maricq *et al.* have made extensive studies of microvascular abnormalities as determined by nailfold microscopy. Tortuous capillaries were found in 4/11 patients with PRP [14]. Interestingly, the one PRP patient in this study with a 'scleroderma-pattern' of capillary abnormality went on to develop SSc 5 months later. A later paper by Maricq *et al.* [15] reported a 'scleroderma-pattern' of capillary in 7/40 patients with PRP and three of these seven patients went on to develop features of a scleroderma-spectrum disorder. Taken together, these findings suggest that capillary abnormalities are unusual in PRP and that when they do occur they may be a forerunner of connective tissue disease. In contrast, Statham and Rowell [9] found that afferent and efferent luminal diameters were increased in patients with PRP compared to controls, but to a lesser degree than in patients with SSc, consistent with our own observations. However, in contrast to our studies and those of others [8, 10], capillary density was reduced in patients with PRP compared to healthy controls.

Differences in methodology may be important in explaining why some studies but not others describe nailfold capillary abnormalities in patients with PRP. When Carpentier and Maricq [10] reported increased capillary diameter in patients with SSc, but not in patients with PRP, compared to controls, the mean capillary width of the whole nailbed, rather than the capillary width of the most abnormal capillary, was examined. It is possible that our method of concentrating on the most abnormal-looking capillary is more sensitive in differentiating between groups, although it may also be less specific: the various dimensions overlapped between groups. However, Statham and Rowell [9], whose findings with respect to luminal diameters paralleled our own, did not concentrate on the most abnormal capillary. Our study included a more comprehensive range of capillary dimensions than that of Statham and Rowell, and we demonstrated statistically significant differences in dimensions between the PRP and SSc groups, as well as between PRP and SSc groups and controls.

Another possible explanation for our finding of capillary abnormalities in patients with PRP is that our patient group with PRP included a cohort of patients likely to develop connective tissue disease. We feel that this is unlikely; none of the patients had recently developed Raynaud's and all had been carefully screened, clinically and immunologically, for evidence of underlying disease.

Ours is the first study to use the non-invasive technique of video capillaroscopy to assess capillary dimensions in patients with PRP and SSc compared to control subjects. An advantage over the more traditional technique of wide-field microscopy is that dimensions can be obtained instantaneously from the projected image during the microscopic examination. Storage of the video allows later analysis or re-analysis if required. We believe that an important finding from our study is confirmation of the observation by Statham and Rowell that capillary dimensions are increased not only in patients with SSc, but also in those with PRP, compared to control subjects. This has major implications for understanding the pathophysiology of both PRP and SSc. While structural vascular abnormalities are a well-recognized and characteristic feature of SSc [16], these have not been considered a feature of PRP. However, our findings challenge this view, suggesting that PRP may not be entirely benign and unassociated with structural vascular change, but rather at one pole of a spectrum of connective tissue disease characterized by capillary changes. What are now required are larger studies to establish the reproducibility of the technique, and to examine patients with primary and secondary Raynaud's phenomenon prospectively.

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