Quantitative nailfold capillary microscopy findings in patients with acrocyanosis compared with patients having systemic sclerosis and control subjects

Giovanna Monticone, MD, Laura Colonna, MD, Giuliana Palermi, MD, Riccardo Bono, MD, and Pietro Puddu, MD *Rome, Italy*

Background: The morphologic capillary microscopy (capillaroscopy) pattern of acrocyanosis is characterized by hemorrhages, pericapillary edema, and widened capillaries. These findings can result in a difficult differential diagnosis with systemic sclerosis (SSc).

Objective: We sought to quantify the characteristics of the capillaroscopy pattern that distinguishes patients with acrocyanosis from patients with SSc and control subjects.

Methods: A videomicroscope with fiberoptic illumination and personal computer–based image processing was used to measure capillary density, giant capillaries, loop width, and arterial and venous limbs in 10 patients with acrocyanosis, 10 patients with SSc, and 10 healthy control subjects.

Results: Acrocyanotic patients differed in every quantitative parameter both from control subjects and patients with SSc. In particular, capillary density, which was reduced compared with that of control subjects, was much higher than that of patients with SSc: one giant capillary per finger was observed in 2 patients with acrocyanosis, whereas more than 2 giant capillaries per finger were observed in each patient with SSc.

Conclusion: These differences may aid in making the distinction between the capillaroscopy patterns in acrocyanosis and SSc. (J Am Acad Dermatol 2000;42:787-90.)

Acrocyanosis, a common disease among adolescent or young women, is characterized by 4 main symptoms: permanent and painless cyanosis of the extremities, local hypothermia, permanent sweatiness, and elastic infiltration of the integument. The symptoms usually begin in puberty, with women being mainly affected, and disappear spontaneously in the thirties. Acrocyanosis is distinguished from Raynaud's phenomenon by the absence of the characteristic paroxysmal pallor; a typical Raynaud's attack consists of sudden pallor of one or more digits followed after a few minutes by cyanosis and erythema.[1]

From Dipartimento di Immunodermatologia, Istituto Dermopatico dell'Immacolata I.D.I., IRCCS.

Accepted for publication Sept 16, 1999.

Reprint requests: Giovanna Monticone, MD, Dipartimento di Immunodermatologia, Istituto Dermopatico dell'Immacolata, IRCCS, via Monti di Creta, 104, 00167 Rome, Italy.

0190-9622/2000/$12.00 + 0 **16/1/103046**
doi:10.1067/mjd.2000.103046

Nailfold capillary microscopy (capillaroscopy) provides information on capillary morphology in vivo and has been widely used as a tool to investigate the microcirculation in various connective tissue diseases and in acrosyndromes.[2-5]

The capillaroscopy morphologic features of acrocyanosis previously described are marked congestion of the terminal capillary loop together with dilatation of the arterial and venous limbs of the capillary.[6] No study has defined the capillary pattern by means of a quantitative method.

The aim of this study was to measure and statistically discriminate the morphologic characteristics of nailfold capillaries in patients with acrocyanosis compared with those of normal healthy control subjects and patients with Raynaud's phenomenon caused by systemic sclerosis (SSc).

METHODS

Nailfold video capillaroscopy was undertaken in 10 consecutive patients with acrocyanosis, 10 patients with either diffuse cutaneous or limited cutaneous variants of SSc, and 10 age-matched

Table I. Clinical characteristics of patients with SSc

Patient No.	Age (y)	ANA	Scl-70	ACA	Lung fibrosis	Esophageal impairment	Raynaud's phenomenon (y)
1	54	–	–	+	–	–	10
2	43	+	+	–	–	–	2
3	30	–	–	+	–	–	5
4	66	–	–	+	+	+	20
5	30	+	+	–	+	+	5
6	42	+	+	–	+	–	5
7	41	+	+	–	+	–	12
8	49	+	+	–	+	+	2
9	38	+	–	–	–	–	20
10	60	+	–	–	±	+	7

ACA, Anticardiolipin antibody; *ANA,* antinuclear antibody.

Table II. Nailfold capillary dimensions

Group	Loop width (μm)	Arteriolar width (μm)	Venular width (μm)
Control subjects	42.0 ± 5.1	13.4 ± 2.7	17.6 ± 2.9
Acrocyanosis	61.7 ± 15.1	22.4 ± 7.3	28.0 ± 7.5*
SSc	122.1 ± 43.0	41.6 ± 1.65	56.0 ± 17.6*†

*$P < .0001$ versus control subjects; †$P < .0001$ versus patients with acrocyanosis.

healthy control subjects. The diagnosis of SSc was made according to the classification criteria developed by the American Rheumatism Association.[7] The clinical characteristics of patients with SSc are given in Table I.

All patients with acrocyanosis had negative test results for antinuclear antibody and did not present sclerodermatous skin, sclerodactyly, or digital pitting scars.

Nailfold capillaroscopy was performed with a videomicroscope consisting of a camera probe with contact lenses (magnification ×50 and ×200), a light source (a 150-W halogen lamp), a processing unit, and a color monitor (Alpha Strumenti, Italy). Digital images can be stored on 42-Mb removable hard-disk cartridges and processed at any time. For the evaluations, we used the DB-Dermo-MIPS software, created by Studio Dell'Eva-Burroni (Italy), which runs on the Microsoft Windows system.[8]

All the observations were made with the patient sitting with the hands at heart level and after the epithelium was made more transparent by applying immersion oil.

Density of the capillaries in the row closest to the fingernail was examined and counted at low magnification (×50) on at least 3 fingers. Capillary loops were expressed as the number per 1-mm segment of the nailfold.

On average, 3 fingers per person and at least 5 capillaries per finger were examined at maximum magnification (×200). The measurements were diameter of the arterial and venous limbs 100 μm distant from the middle of the transitional segment and largest loop width within this 100-μm section. Vascular loops were estimated to be of normal width (<35 μm), slightly widened (>50-<70 μm), definitely widened (>70-<100 μm), or giant (>100 μm). The frequency of subjects with more than 2 slightly or definitely widened capillary loops or at least one giant capillary was calculated for each patient group and for the control group.

Statistical analysis was performed with the 1-way analysis of variance and analysis of variance on ranks tests for unpaired data.

RESULTS

Capillary density

The mean capillary density in the control group was 9.5 ± 1 per millimeter. The nailfold capillary density was significantly reduced in the acrocyanosis and SSc groups compared with the control group ($P = .001$), but there was also a statistical difference between patients with acrocyanosis and SSc ($P < .0001$; Fig 1).

Capillary dimensions

The mean capillary width was 42.0 ± 5.1 μm in the control group, 61.7 ± 15.1 μm in the acrocyanosis group, and 122.1 ± 43.0 μm in the SSc group ($P < .0001$, Table II). Also, arterial and venular capillary diameters were statistically widened in the acrocyanosis group compared with those in the control group ($P < .0001$) but less than those in the SSc group ($P < .0001$, Table II).

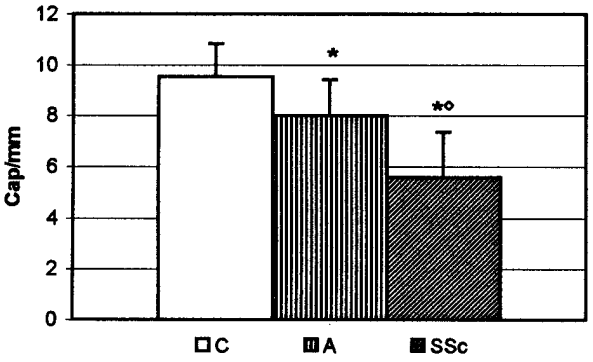

Fig 1. Mean nailfold capillary density per millimeter. Levels of significance (*P* values) are given compared with those of control subjects* and patients with SSc° ($P < .0001$). *A,* Acrocyanosis; *C,* control subjects.

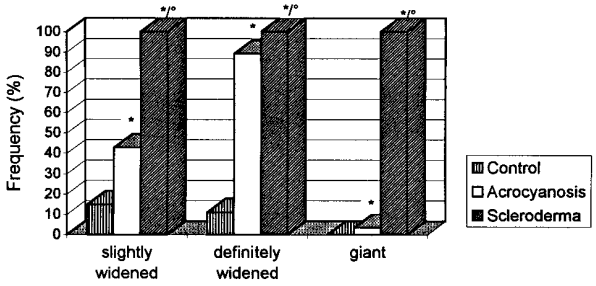

Fig 2. Frequency (%) of abnormal nailfold capillaroscopy findings. Levels of significance (*P* values) are given compared with those of control subjects* and patients with SSc° ($P < .001$).

Slightly widened capillary loops were common in the acrocyanosis group and in the control group; however, the frequency of slightly widened loops per millimeter was statistically higher in the acrocyanosis group (14.8% vs 42.8%, Fig 2).

Only 11.1% of control subjects had more than 2 capillary loops per millimeter that were definitely widened, whereas the number of patients with acrocyanosis with more than 2 definitely widened loops per millimeter per finger was much higher (89.2%, Fig 2). Less than 2 giant capillaries per finger were observed in 2 of 10 patients with acrocyanosis, whereas 2 or more giant capillaries per finger were observed in 10 of 10 patients with SSc ($P < .0001$).

DISCUSSION

Video capillaroscopy allows direct observation of the nutritional capillaries of the skin. In connective tissue disorders pathologic findings indicate systemic involvement.[9] Maricq et al[10] coined the term *scleroderma pattern* for the capillary anomalies found in SSc, dermatomyositis, and mixed connective tissue disease. It is essentially characterized by 2 striking abnormalities: enlargement of capillary loops and loss of capillaries. However, the presence of megacapillaries without avascular zones have been also observed in patients with acrocyanosis.[11,12] Our results are in agreement with those of previous studies in that the capillaroscopy pattern of patients with acrocyanosis is characterized by hemorrhages, pericapillary edema, and widened capillaries. These capillaroscopy findings can result in a difficult differential diagnosis with respect to SSc. There have been many quantitative reports about the scleroderma capillary pattern but not about acrocyanosis.[13-15] In our patients with acrocyanosis all quantitative parameters differed from those of the SSc group: (1) both arteriolar and venular diameters were widened but less than those found in patients with SSc; (2) the capillary density, even if slightly reduced compared with control subjects, was much higher than that found in patients with SSc; and (3) the frequency of slightly and definitely widened loops was high both in the acrocyanosis and SSc groups, but less than 2 giant capillaries per finger were observed only in 2 patients with acrocyanosis, whereas each patient with SSc showed 2 or more megacapillaries per finger. Some authors described a different aspect of the megacapillaries in patients with acrocyanosis compared with those in patients with SSc. In the former the dilatation affects predominantly the efferent loop, whereas in the latter it is in the top of the loop.[16] We did not observe this distinction so clearly.

Probably the most appropriate application of nailfold capillaroscopy lies in its ability to help in the diagnosis of connective tissue disorders and hence to differentiate primary from secondary Raynaud's phenomenon.[17] Specificity for a scleroderma pattern capillaroscopy for the diagnosis of SSc was reported to be as high as 93.3%.[5] It is well established that patients with Raynaud's phenomenon and a positive capillaroscopy result tend to undergo development of a connective tissue disorder.[18,19] The highest risk in detecting false-positive megacapillaries lies in patients with acrocyanosis and particularly in those with both acrocyanosis and Raynaud's phenomenon, an association that is not unusual. Some clinical characteristics help to distinguish patients with SSc from those with acrocyanosis. In winter in these patients the clinical aspect of fingers is characterized by a deep purple color, even between Raynaud's attacks. However, there are no pitting scars or other signs that would suggest a connective tissue disease.

Previous studies on the prognostic significance of nailfold capillaroscopy showed that no patients with acrocyanosis developed scleroderma. In most of

these patients capillaroscopy grading even improved during follow-up.[12] Apart from acrocyanosis, disappearance of microangiopathy seems exceptional.[20]

In conclusion, our study confirms that a slightly reduced capillary density, a regular distribution of capillary bed, the absence of avascular zones, the different widened capillary diameters, and the presence of less than 2 megacapillaries per finger allow the diagnosis of acrocyanosis. These differences, which cannot be recognized only by a qualitative evaluation, make the quantitative assessment a helpful criterion to differentiate the capillaroscopy pattern of acrocyanosis from that of Raynaud's phenomenon caused by SSc.

REFERENCES

1. Belch J. Raynaud's phenomenon. Cardiovasc Res 1997;33:25-30.
2. Houtman PM, Kallenberg CGM, Fidler V, Wouda AA. Diagnostic significance of nailfold capillary patterns in patients with Raynaud's phenomenon. An analysis of patterns discriminating patients with and without connective tissue disease. J Rheum 1986;13:556-63.
3. Lefford F, Edwards JCW. Nailfold capillary microscopy in connective tissue disease: a quantitative morphological analysis. Ann Rheum Dis 1986;45:741-9.
4. Maricq HR, Weinberger AB, Leroy EC. Early detection of scleroderma-spectrum disorders by in vivo capillary microscopy: a prospective study of patients with Raynaud's phenomenon. J Rheumatol 1982;9:289-91.
5. Blockmans D, Beyens G, Verhaeghe R. Predictive value of nailfold capillaroscopy in the diagnosis of connective tissue diseases. Clin Rheumatol 1996;15:148-53.
6. Sagher F, Davis E, Sheskin J. The small blood vessels of the skin in acrocyanosis. Br J Derm 1966;78:586-9.
7. Subcommittee for Scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581-90.
8. Seidenari S, Burroni M, Dell'Eva G, Pepe P, Belletti B. Computerised evaluation of pigmented skin lesion images recorded by a videomicroscope: comparison between polarizing mode observation and oil/slide mode observation. Skin Res Technol 1995;1:187-91.
9. Maricq HR, Spencer-Green G, Leroy EC. Skin capillary abnormalities as indicators of organ involvement in scleroderma, Raynaud's syndrome and dermatomyiositis. Am J Med 1976;61: 862-70.
10. Maricq HR, Leroy EC, D'angelo WA. Diagnostic potential of in vivo capillary microscopy in scleroderma and related disorders. Arthritis Rheum 1980;23:183-9.
11. Carpentier PH, Maricq HR. Microvasculature in systemic sclerosis. Rheum Clin Dis North Am 1991;75-89.
12. Zufferey P, Depairon M, Chamot AM, Monti M. Prognostic significance of nailfold capillary microscopy in patients with Raynaud's phenomenon and scleroderma-pattern abnormalities: a six-year follow-up study. Clin Rheumatol 1992;11:536-41.
13. Lee P, Leung FY-K, Alderdice C, Armstrong SK. Nailfold capillary microscopy in the connective tissue diseases: a semiquantitative assessment. J Rheumatol 1983;10:930-8.
14. Lefford F, Edwards JCW. Nailfold capillary microscopy in connective tissue disease: a quantitative morphological analysis. Ann Rheum Dis 1986;45:741-9.
15. Maricq HR. Comparison of quantitative and semiquantitative estimates of nailfold capillary abnormalities in scleroderma spectrum disorders. Microvasc Res 1986;32:271-6.
16. Carpentier P, Franco A. La capillaroscopie periungueale. Paris: Deltacom; 1981.
17. Houtman PM, Kkallenberg CGM, Vasek F, Wouda AA. Diagnostic significance of nailfold capillary patterns in patients with Raynaud's phenomenon. J Rheumatol 1986;13:556-63.
18. Fitzgerald O, Hess EV, O'Connor GT, Spencer-Green G. Prospective study of the evolution of Raynaud's phenomenon. Am J Med 1988;72:883-8.
19. Maricq HR, Weinberger AB, Leroy EC. Early detection of scleroderma-spectrum disorders by in vivo capillary microscopy: a prospective study of patients with Raynaud's phenomenon. J Rheumatol 1982;9:289-91.
20. Maricq HR, Harper FE, Khan MM, Tan EM, LeRoy EC. Microvascular abnormalities as possible predictors of disease subset in Raynaud phenomenon and early connective tissue disease. Clin Exp Rheumatol 1982;9:196-205.