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Decreased Nailfold Capillary Density in Limited Scleroderma with Pulmonary Hypertension

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SUMMARY Approximately 20% of patients with the limited form of scleroderma will develop pulmonary hypertension which is generally a late stage fatal complication. Why pulmonary hypertension occurs in this subset of patients is unknown and it has not been possible to predict which patients are at risk. Nailfold capillary dilatation, distortion and drop occurs universally in patients with scleroderma and is generally an early finding. The present study was conducted to investigate whether quantitative nailfold capillaroscopy could distinguish those limited scleroderma patients who have established pulmonary hypertension. Quantitative nailfold capillaroscopy was performed by Visual Image Analysis in 10 healthy subjects and 20 patients with limited scleroderma (18 centromere +ve), of whom 8 had established pulmonary hypertension. It was found that scleroderma patients with pulmonary hypertension had a significant reduction in capillary density compared with patients lacking this complication ($p < 0.01$). Patients with scleroderma have significantly more dilated capillaries than controls although no significant differences were observe between the two patient subgroups. The finding of reduced nailfold capillary density in scleroderma patients with established pulmonary hypertension has possible pathogenic significance and may allow detection of this subgroup at an early stage in their disease progression.

Progressive Systemic Sclerosis (scleroderma) is an uncommon systemic autoimmune disorder characterised by skin sclerosis, microvascular abnormalities and the presence of certain autoantibodies.[1] There are three clinical variants of scleroderma. The limited form is characterised by Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangectasia, and is frequently associated with the presence of anti-centromere antibodies.[2] In contrast the diffuse form of scleroderma involves widespread skin involvement of both proximal and distal extremities and frequent visceral fibrosis often associated with Scl-70 antibodies.[2] Finally, the third group is the overlap variant where patients present with Raynaud's phenomenon, swollen fingers with small joint synovitis and additional features of other connective tissue disease (eg. polymyositis, SLE etc).[3]

Of all three types of scleroderma, the majority of patients have the limited form with a later age of onset than those with diffuse disease and a longer disease duration.[3,4]

Limited scleroderma is associated with a number of complications. These include primary pulmonary hypertension generally in the absence of interstitial lung disease. Primary pulmonary hypertension occurs in approximately 20% of patients with limited scleroderma and carries a very poor prognosis with a two-year survival rate of 40%.[5] Since there is now effective treatments for primary pulmonary hypertension, there is a need to try and identify this complication in the early stages of the disease for therapeutic interventions.

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It is known that abnormalities in nailfold capillaries occur universally in all subsets of scleroderma. These abnormalities include capillary dilatation, angiogenesis, bushy formation as well as capillary destruction and dropout.[6,7] Previous studies have examined the relationship between disease duration and capillary loss or enlargement. They found that there was no significant correlation between disease duration and capillary loss or enlargement but these studies have been qualitative in nature.[8] This present study aims to quantitatively measure the relationship between disease duration and capillary loss or enlargement in patients with limited scleroderma with and without pulmonary hypertension using our recently described technique of video image analysis.[7]

MATERIALS & METHODS

Patients and controls

Ten healthy subjects were recruited from the laboratory staff of Flinders Medical Centre as controls. Mean age of the subjects was 35 years old.

Twenty patients with scleroderma were recruited from the South Australian Scleroderma Register. Patients were chosen if they had limited scleroderma, positive anti-centromere antibody status and lived within the vicinity of Flinders Medical Centre. Of these, eight patients had pulmonary hypertension as confirmed clinically and with echocardiography and/or catheter studies. Patients were contacted by telephone and were asked to come to Flinders Medical Centre for nailfold capillaroscopy.

Nailfold microscopy and video image analysis

Nailfold capillaroscopy was performed on the ring finger of each hand. This is because the 4th and 5th digits have previously been shown to have the longest capillaries and the most prominent capillary venous plexus.[9] The capillary abnormalities are also most prominent in the distal capillary row.

The capillaries were visualised by a Micro-Orient microscope with 60 x magnification. Cold light was provided by Euromex Fibre Optic light source. A Sony CCD Colour Camera was attached to the microscope and was linked to a NEC MultiSync 3 FG computer.

To visualise the capillaries a drop of microscope oil was placed on the nailbed to reduce the refractive error. The capillaries were then digitalised on the Video Pro software. A minimum of 4 images were captured of each finger. Measurements were calibrated according to a biopsy ruler and were measured in micrometres. Video Image Analysis technique was then used to analyse the data.

Capillary diameter was taken to be the maximum width of the loop. Only well visualised capillaries were measured. A minimum of 6 images were analysed in each subject. Mean capillary diameter was then calculated for each subject.

Capillary density was measured by counting well visualised capillaries on a minimum of 6 images per patient. The capillaries were marked and counted. An average number of capillaries was calculated for each subject.

Data analysis

All data are presented as mean +/- standard deviation. Statistical analysis was performed using the Wilcoxon Rank Sum test. Differences were considered significant when the null hypothesis had a probability less than 0.01.

Determining disease duration

To determine if there is a correlation between duration of disease and capillaroscopic findings, duration of disease was plotted against capillary size and density. Duration of disease was taken from the first onset of Raynaud's phenomenon. Correlation between the variables was determined by linear regression.

RESULTS

Patient demographic details are shown in Table 1. There were 20 patients with limited scleroderma, 18 females and 2 males, of which 8 females had established pulmonary hypertension. Of the 20 patients, 18 were centromere antibody positive.

Capillary diameter

There is a significant difference in the capillary diameter between healthy controls and patients with scleroderma ($p < 0.01$). There is about a threefold increase in the capillary diameter in patients with scleroderma. Although capillary enlargement does occur in the majority of patients, there are patients with normal capillary diameter. There is however no significant difference in the size of the capillaries between the two patient subgroups (Fig. 1).

Capillary density

There is a significant reduction in the number of capillaries in patients with scleroderma as compared with the control group ($p < 0.01$). There is also a significant de-

Table 1 Clinical and demographic details of study population

	Healthy Controls	Scleroderma without pulmonary hypertension	Scleroderma with pulmonary hypertension
Number of patients	10	12	8
Age (years)			
mean	35	58	64.6
range	17 - 55	42 - 77	42 - 76
Female:Male	7:3	10:2	8:0
ACA positive	0	12	6
Disease duration (years)			
range	-	1.5 - 35	2.5 - 50
mean	-	18	19.5
Capillary diameter (μm)			
range	8.43 - 30.17	11.10 - 78.25	20.83 - 50.12
mean	13.74 ± 6.73	33.45 ± 23.88	30.48 ± 10.84
Capillary count (no/0.5 mm)			
range	4.8 - 7.4	2.0 - 7.0	1.3 - 4.1
mean	6.16 ± 0.97	4.11 ± 1.69	2.6 ± 1.00

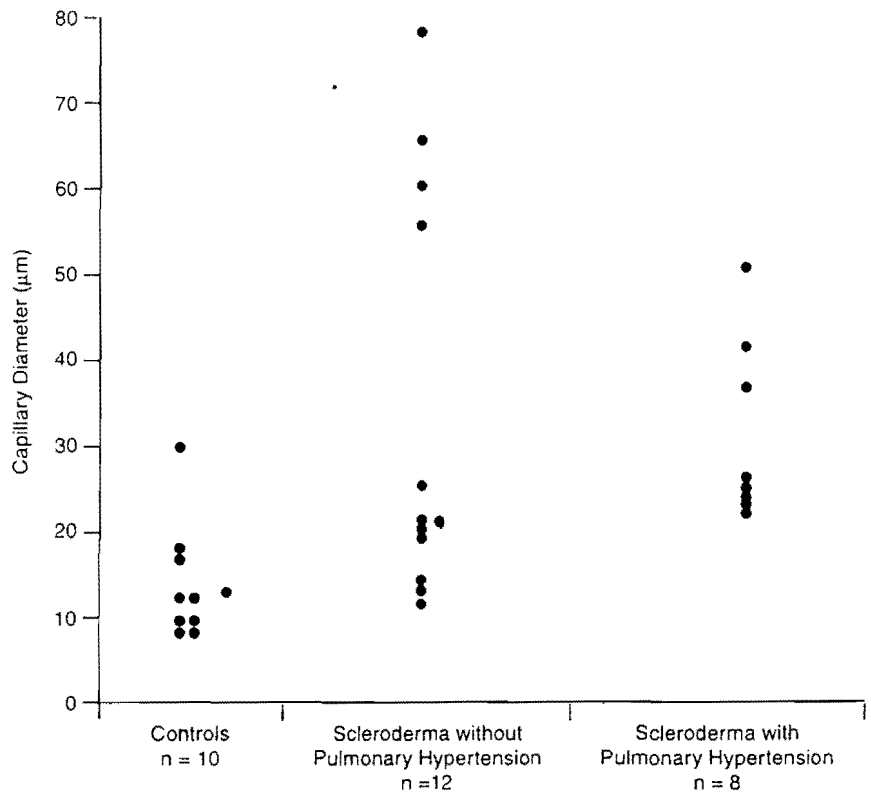

Fig. 1 Normal nailfold capillary diameter in healthy controls and patients with scleroderma.

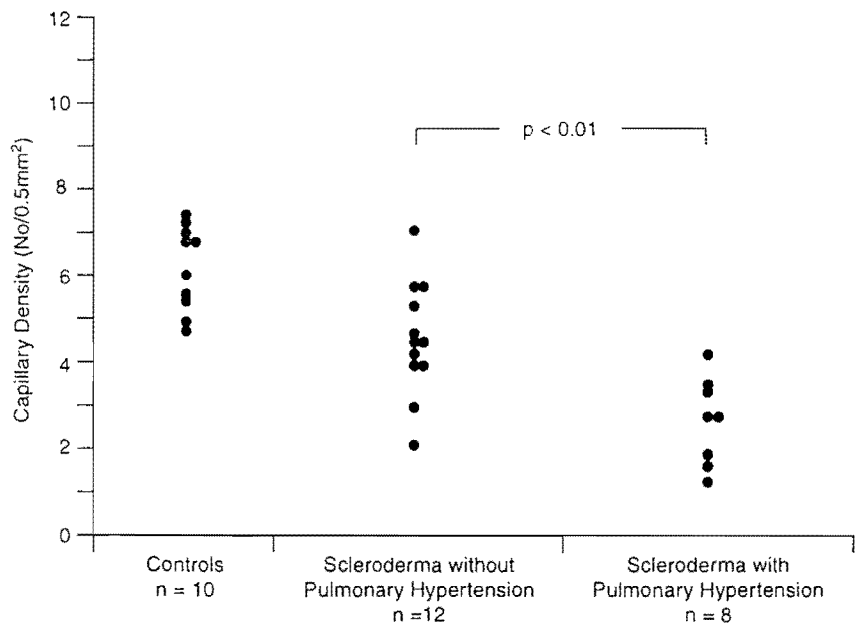

Fig. 2 Normal nailfold capillary density in healthy controls and patients with scleroderma.

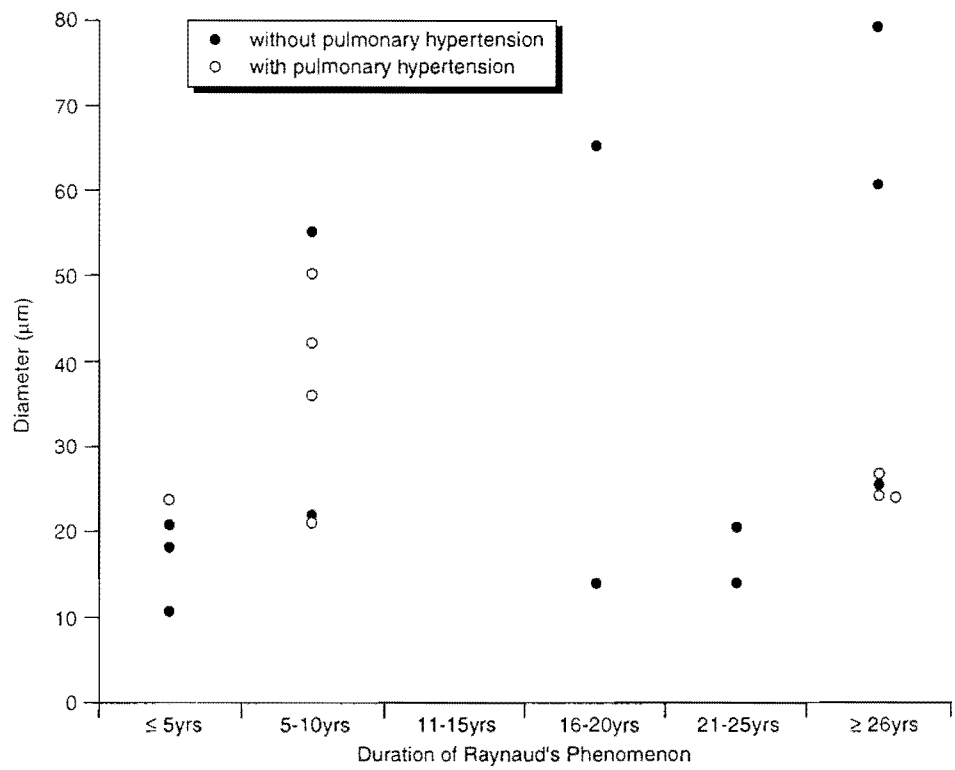

Fig. 3 Correlation between capillary diameter and disease duration in patients with scleroderma.

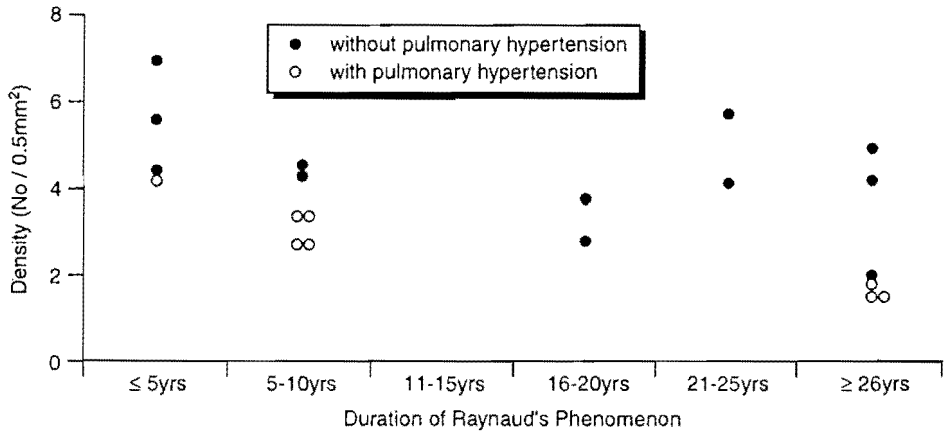

Fig. 4 Correlation between capillary density and disease duration in patients with scleroderma.

crease in capillary density in those patients with pulmonary hypertension compared with those patients without pulmonary hypertension ($p < 0.01$) (Fig. 2).

Correlation between duration of disease and capillary diameter

There is no significant correlation between capillary diameter and duration of the disease. Normal capillary diameter occurs both in early and long standing disease. Capillary dilatation may occur in early disease, however, marked dilatation tends to occur in long standing disease (Fig. 3).

Correlation between duration of disease and capillary density

There is no significant correlation between disease duration and capillary density. Normal numbers of capillaries can be preserved late in the disease, however it appears that the most severe capillary dropout tends to occur in long standing disease (Fig. 4).

DISCUSSION

Past studies have shown that in patients with scleroderma, there is significant capillary dilatation and dropout.[3,7] This study confirms the findings from previous studies. There is approximately a threefold increase in the size of capillaries in those with scleroderma compared with the normal population.

From our study, we have shown that capillary enlargement occurs in patients with limited scleroderma, with and without pulmonary hypertension. There was however no correlation between capillary enlargement and the presence of pulmonary hypertension. Capillary enlargement also had no significant relationship to disease duration, as shown in previous studies although we noted that marked enlargement seldom occurred in early disease.

Of particular interest was the finding of the significant reduction in capillary density which occurred in those patients with pulmonary hypertension compared with those without pulmonary hypertension. This suggests that the same immunological process is responsible for the capillary loss in both the lungs and the nailfold. However, capillary dropout was not limited to those patients with pulmonary hypertension. It was also seen in patients with long standing disease (> 10 years) and occurred less severely in early stage disease. It would be of interest to follow those patients with capillary dropout without pulmonary hypertension prospectively to see if capillary dropout was a predictor of lung pathology.

In conclusion, we have shown that in the subgroup of patients with limited scleroderma with pulmonary hypertension, there appears to be significant reduction in capillary density, in excess of that seen in patients without lung disease. It is possible that the same immunological mechanisms respon-

sible for the nailfold changes are responsible for the damage in the pulmonary vascular bed. Nailfold capillaroscopy may therefore be a useful technique to assess future patients for possible development of pulmonary hypertension.

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