Association Between Nailfold Capillaroscopy Findings and Pulmonary Function Tests in Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To determine whether there is an association between different capillaroscopic findings and pulmonary function tests in systemic sclerosis (SSc).

Methods. We did a retrospective observational study in a cohort of patients with SSc and early SSc. Patients with at least 1 nailfold videocapillaroscopy (NVC) magnified 120× were included. Pathological findings were giant capillaries, angiogenesis, and density loss. Findings were compared with lung function values: percent expected value of forced vital capacity (FVC), DLCO, and FVC/DLCO ratio. Other variables collected were sex and SSc type, and the presence of digital ulcers (DU), interstitial lung disease (ILD), scleroderma renal crisis, and/or pulmonary hypertension (PH).

Results. Of 136 patients with SSc, 85 had undergone an NVC. The frequency of ILD, DU, and PH was 24.1%, 28.7%, and 17.2%, respectively. Data analysis showed that patients with density loss had worse FVC% (86.91 ± 19.42 vs 101.13 ± 16.06, $p < 0.01$) and DLCO% (71.43 ± 21.19 vs 85.9 ± 19.81, $p < 0.01$) compared to those without.

Conclusion. Patients with loss of density present worse FVC and DLCO values. Prospective studies are warranted to determine whether NVC is useful for studying pulmonary function in SSc. (J Rheumatol First Release Nov 15 2014; doi:10.3899/jrheum.140276)

Key Indexing Terms:
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Systemic sclerosis (SSc) is a connective tissue disease of unknown cause, characterized by dysregulation of the immune system, microcirculation dysfunction, and fibrosis of several organs[1]. Microvascular impairment is crucial for the onset of the disease, and has a critical role in the stimulation and proliferation of fibroblasts[2]. Currently, nailfold videocapillaroscopy (NVC) is the best tool for the study of microcirculation in SSc, because it allows identification of the structural vasculopathy that occurs in the disease.

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Several morphological alterations of the capillaries in patients with SSc have been described, with giant capillaries[3], capillary loss of density[4], and angiogenesis phenomena[5] being the most characteristic[3]. Some authors have grouped them to define patterns: initially active and slow sclerodermiform patterns[6], and more recently, initial or early, active, and late patterns[7]. Several studies have shown the association of patterns with greater evidence of microvascular damage and more severe impairment[7,8,9,10]. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of mortality in the disease[11], and pulmonary function tests (PFT) are important for evaluation of patients with SSc and pulmonary involvement[12,13]. Some studies have linked capillaroscopic findings with hemodynamic variables in PAH-SSc[14] and have also linked interstitial disease with loss of capillary density in patients with and without SSc[15]. However, to date no work has been carried out to link these findings with pulmonary function values. The objective of our study was to determine whether PFT values relate to the different capillaroscopic impairments typical of patients with SSc.

MATERIALS AND METHODS

Patients. We did a retrospective study in a cohort of patients with SSc according to classification criteria proposed by LeRoy, *et al*[16] and followed by the Rheumatology Unit of Hospital de la Santa Creu i Sant Pau,

Barcelona, Spain. We recruited consecutive patients with SSc who had undergone at least 1 videocapillaroscopy in the same year as the PFT. The inclusion period was January 2009 to December 2011. We considered only the most recent videocapillaroscopy and PFT dates for the analysis. The PFT variables that were collected were the expected percentage according to population group of forced vital capacity (FVC%) and expected DLCO% and FVC/DLCO ratio. For all patients, the following variables were collected for the same year as the capillaroscopy: sex; type of SSc according to the degree of skin impairment; history of digital ulcers (DU) related to digital ischemia (patients with ulcers secondary to trauma or calcinosis were not included); history of scleroderma renal crisis (SRC); history of ILD confirmed by ground glass opacities, reticular pattern, or honeycomb pattern in high-resolution computed tomography or pathological study; and history of suspected pulmonary hypertension (PH) by echocardiographic determination of estimated pulmonary artery systolic pressure (sPAP) > 40 mmHg. Data were collected from medical charts.

Capillaroscopic technique and image analysis. Images were obtained from the patients who had undergone a capillaroscopy done with a videocapillaroscope with a 120× magnification lens (VM001-Quermed SA). These images were analyzed using specific computer software for analysis of images (Motic Image Plus 2.0-Motic Group Corp.). The videocapillaroscopy was carried out at room temperature (23–25°C) with the patient sitting and the examined hand at the level of the heart. The data were analyzed for the videocapillaroscopy of the nailfold bed of the second to fifth fingers of both hands of all patients. Nailfold beds presenting trauma, microtrauma, or severe digital ischemia phenomena were disregarded. Nailfold beds that did not provide a correct display for image interpretation were also disregarded. A drop of immersion oil was applied to the nailfold bed of each finger analyzed to maximize viewing. The following capillaroscopic alterations were qualitatively determined in each patient: giant capillaries (capillaries over 50 μm diameter in more than 2 fingers in the same patient), angiogenesis (bushy capillaries or ramified capillaries), and loss of density (fewer than 7 capillaries in 1 mm; Figure 1). There was no analysis of bleeding, thrombosis, or minor capillaroscopic alterations such as tortuous capillaries. All videocapillaroscopic examinations were performed by the same experienced observer (IC).

Pulmonary evaluation. PFT were performed according to the guidelines[17,18] using Compact MasterLab equipment (Jaegger Master Screen-PFT).

Statistical analysis. First, the existence of SSc complications was analyzed with different structural capillaroscopic alterations. Subsequently, each of the NVC variables studied was analyzed using the mean expected values of FVC%, DLCO%, and the FVC/DLCO ratio, depending on the various capillaroscopic abnormalities (giant capillaries, angiogenesis, and capillary density loss). The comparison between qualitative variables was performed using the chi-square test, while the analysis between capillaroscopic alterations and the value of the PFT was carried out using the t test for analysis of independent variables. The statistical analysis was carried out using IBM SPSS statistics V.17 (SPSS and IBM). Values with $p < 0.05$ were considered significant.

RESULTS

Characteristics of the patients. Of 136 patients in the cohort, 85 (62.5%) had at least 1 NVC performed. The characteristics of these patients are summarized in Table 1. The frequency of women was 92.9% (79 out of 85). The mean age at diagnosis was 50.13 ± 15.14 years, and disease duration was 13.3 years. The most frequent type of SSc in the sample was the limited cutaneous form (lcSSc; 68.2%), followed by pre-SSc (20%). Diffuse cutaneous SSc (dcSSc) was reported in 10.6% of cases. The low proportion of dcSSc can be explained by the poor quality of image that these patients presented. Only 1 patient had the *sine* scleroderma form. Most patients (94.4%) had positive antinuclear antibodies. The most common specific antibody was anticentromere (50.6%) followed by antitopoisomerase I (8.2%). Digital ulcers, present in 25 out of 85 patients (29.4%), were the most common clinical complication. Twenty-one had a history of ILD (25%). Fifteen patients (17.6%) had sPAP > 40 mmHg, according to echocardiographic signs. SRC was identified in only 1 patient with NVC. Most patients had normal PFT results, with average FVC% 90.68 ± 20.73 and average DLCO% of 75.71 ± 22.48. The FVC/DLCO ratio suggested no vascular involvement (1.28 ± 0.36).

Capillaroscopic findings and relation to disease complications. Most patients with SSc (74%) showed structural changes in the NVC compatible with an SSc pattern. The most common was the active pattern, observed in 30 cases (40.1%), followed by the late pattern and the early pattern as defined by Cutolo, *et al*[8], present in 13 (17.8%) and 11 (15.1%) cases, respectively. The NVC of 11 patients (15.1%) did not show specific SSc pattern findings. Analyzing the typical structural alterations separately, most patients had capillary loss of density (72%) and giant capillaries (65.5%). Angiogenesis phenomena were observed in 47.9% of cases. The relationship between different complications and specific capillaroscopic findings is summarized in Figure 2. The 3 studied complications had different relationships with the structural abnormalities of the nailfold capillaroscopy. Loss of density was associated with ILD ($p < 0.01$) and angiogenesis with suspected PH based on

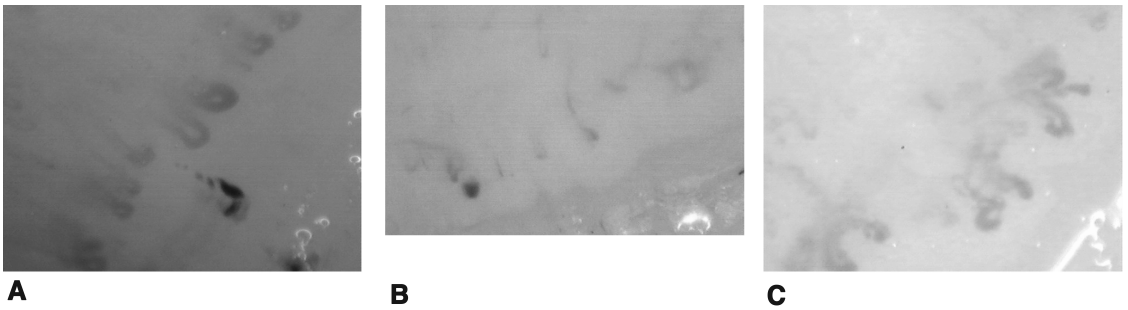

Figure 1. Images of videocapillaroscopy (120×). A. Presence of giant capillaries. B. Loss of capillary density. C. Neoangiogenesis phenomena.

Table 1. Characteristics of the 85 study patients who underwent capillaroscopy.

Characteristics	No. Patients, or Mean ± SD	Percent of Patients
Women	79	92.9
Diagnosis age, yrs	50.13 ± 15.14	
Duration of disease, yrs	13.3 ± 0.97	
Limited SSc	58	68.2
Diffuse SSc	9	10.6
Pre-SSc	17	20
Digital ulcers	25	29.4
Suspected PH	15	17.6
Interstitial lung disease	21	25
Megacapillaries	55	65.5
Capillary density loss	59	72
Angiogenesis	35	47.9
Sclerodermiform pattern	54	74
sPAP, mmHg*	31.68 ± 7.12	
LVEF% **	67.99 ± 13.66	
%FVC	90.68 ± 20.73	
%DLCO	75.71 ± 22.48	
FVC/DLCO	1.28 ± 0.36	

* Estimated pulmonary artery systolic pressure by echocardiogram. ** Left ventricular ejection fraction. SSc: systemic sclerosis; FVC: forced vital capacity; PH: pulmonary hypertension.

echocardiographic signs ($p < 0.05$). However, DU was related to 2 alterations: giant capillaries ($p < 0.01$) and capillary density loss ($p < 0.01$).

Relationship between PFT and NVC. Studying the relationship between giant capillaries or angiogenesis and the results of patient PFT (Figure 3) showed that the patients with capillaroscopic findings had slightly worse FVC and DLCO values compared to those without, but the difference was not significant. However, patients with loss of capillary density did show worse DLCO values (71.43 ± 21.2% vs 85.09 ± 19.81% in patients with and without capillary loss, respectively; $p < 0.01$) and FVC values (86.91 ± 101.13 in patients with and without density loss; $p < 0.01$). None of the 3 groups showed associations with the FVC/DLCO ratio. When we studied patients with abnormal PFT (FVC and/or DLCO < 80% predicted), those patients did not present differences in capillaroscopic findings in comparison with normal PFT patients (data not shown).

Relationship between PFT and NVC by subgroup. The presence of different capillaroscopic findings was then analyzed in each group of clinical involvement and cutaneous involvement. No differences were found among DLCO, FVC, and the FVC/DLCO ratio or the 3 different capillaroscopic findings analyzed in patients with suspected PH or ILD. However, patients with a history of DU and density loss had worse DLCO values (68.52 ± 21.7 vs 86.5 ± 0.7, $p < 0.01$), FVC values (87.72 ± 19.01 vs 103.5 ± 0.7, $p < 0.01$), and FVC/DLCO values (1.41 ± 0.37 vs 1.19 ± 0.018, $p < 0.05$) than did patients without density loss. Note that only 2 patients with DU showed no loss of capillary density.

The differences of the cutaneous groups were divided into dcSSc, lcSSc, and pre-SSc. All patients with dcSSc showed extensive loss of capillary density, so no statistical analysis was performed on that subgroup. However, we

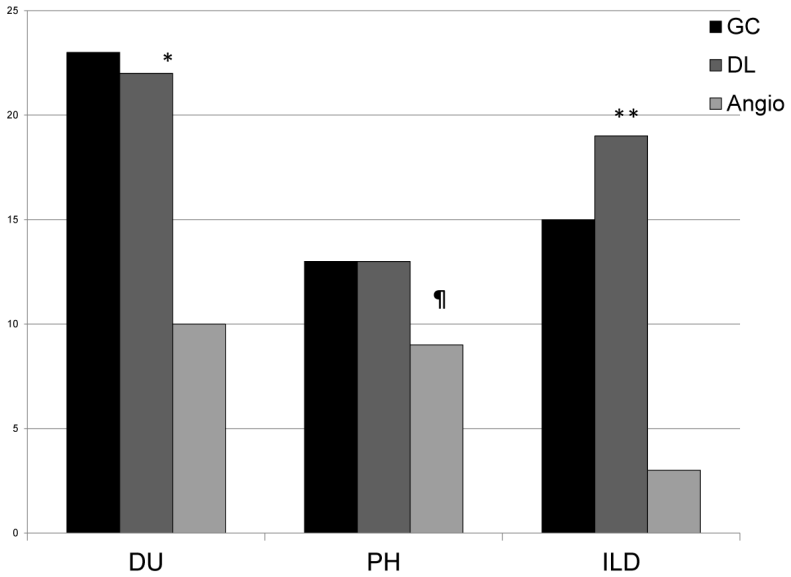

Figure 2. Relationship between patients with clinical impairment and capillaroscopic findings. DU: digital ulcers; PH: pulmonary hypertension; ILD: interstitial lung disease; GC: giant capillaries; DL: capillary density loss; angio: angiogenesis. *$p < 0.01$ compared to patients without GC or DL and DU. **$p < 0.01$ compared to patients with ILD without DL. ¶$p < 0.05$ compared to patients with PH without angiogenesis.

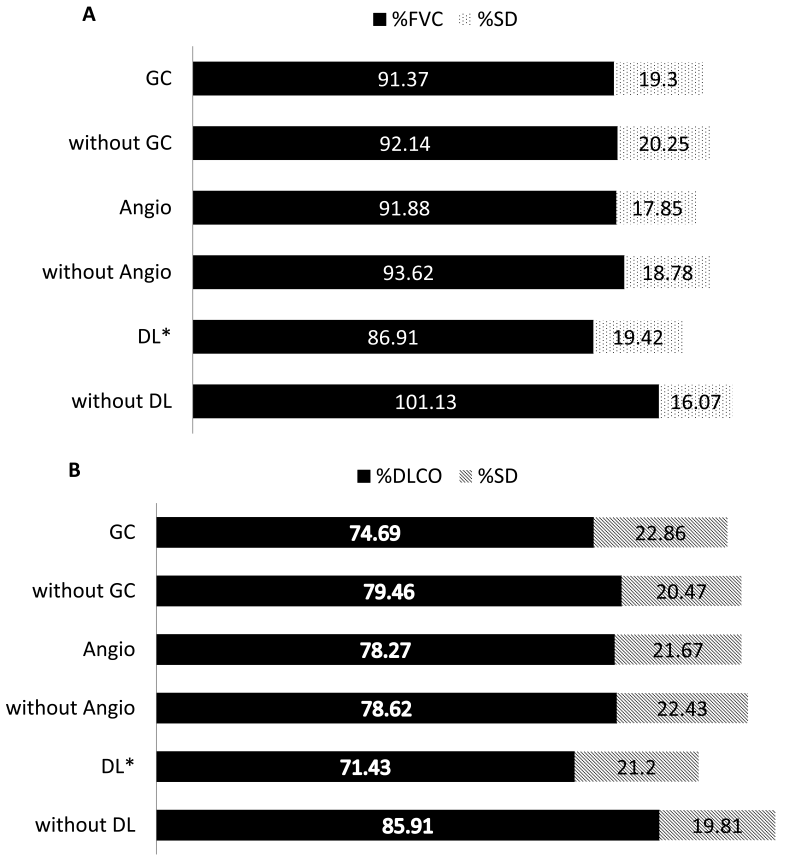

Figure 3. Relationship between findings of NVC and respiratory function variables. NVC: nailfold videocapillaroscopy; FVC: forced vital capacity; DL: capillary density loss; angio: angiogenesis; GC: giant capillaries. *p < 0.01.

found no differences between the result of PFT and the presence of giant capillaries and angiogenesis. Neither were differences found among all variables and pre-SSc patients. In patients with lcSSc, a relationship was again found between the worst FVC% (87.43 ± 18.15 vs 99.09 ± 13.55, p = 0.02) or DLCO% values (72.51 ± 17.19 vs 85.3 ± 9.01, p = 0.03) and the presence of capillary density loss.

DISCUSSION

We analyzed the relationship between values of PFT and the different specific findings of periungual capillaroscopy. Ours is the first study, to our knowledge, that finds an association between capillaroscopic alterations and impaired lung function. Patients with SSc and less capillary density had lower FVC and DLCO values, which therefore led to worse lung function. We also observed a comparable decrease in FVC and DLCO values, with no difference observed in the FVC/DLCO ratio of patients with or without density loss. A similar drop in these variables suggests that the component of lung function impairment is caused by a more interstitial than vascular impairment in contrast with an isolated drop in DLCO in patients with SSc who do not have altered FVC[13,14,15,16,19]. However, in the subgroup of patients with DU, differences were observed in the FVC/DLCO ratio. Patients with density loss and DU showed a greater decrease in DLCO than in FVC, which in these patients may translate into greater microvascular damage such as DU. There are numerous studies that correlate different SSc patterns and different clinical impairments and demographic data in patients with SSc[7,8]. However, there is little evidence of an association of different capillaroscopic features that may appear in SSc analyzed separately.

Sato and colleagues studied the relationship between organ involvement and capillaroscopic abnormalities in patients with SSc[20]. They found more loss of density in patients with the involvement of 3 or more organs. However, when they studied ILD involvement, their work did not show differences of capillary density. These results are the opposite of our findings — we found differences in capillary density between patients with or without ILD. Indeed, we observed differences in PFT values and the presence or the absence of loss of density. Sato, *et al* did not analyze this variable.

Our findings are partially consistent with the results of the work of Corrado, *et al*[15], who analyzed capillaroscopic findings in a small group of patients with ILD and SSc, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease. The authors found a loss of capillary density in patients with ILD compared to those without ILD, and this was more pronounced in patients in whom the ILD was associated with SSc. But, unlike in our work, these authors compared the capillaroscopic findings with patients without SSc and without ILD. Further, they do not relate the pulmonary function variables to capillaroscopic results. Caramaschi, *et al* did study the relationship between initial, active, or late patterns and PFT values[10] and found a strong association between FVC and DLCO values and NVC patterns. However, the 3 capillaroscopic changes may appear in the different patterns analyzed, without specifying the isolated importance of each of these specific morphological impairments outside SSc patterns. Bredemeier, *et al*[21] found a correlation between avascular areas in NVC and ILD and, as in our study, did not find an association of avascular areas with patients with worse PFT levels (patients with FVC and DLCO < 80% and 75% expected). However, this group determined avascular areas, in contrast to our study, which determined loss of density according to NVC variables defined by Cutolo, *et al*[8] and did not compare the presence or absence of avascular areas with FVC and DLCO values of all patients with SSc.

The relationship in SSc between fibrotic impairment and microvascular damage could partly justify the results of our study. Microvascular damage is one of the most important etiological and clinical characteristics of the disease[22], and the best tool for the study of structural microvasculopathy is NVC. Further, several cytokines and growth factors, such as vascular endothelial growth factor (VEGF) and endothelin 1, play important roles in both processes[23]. One study has demonstrated VEGF deficiency in patients with ILD and SSc[24], but no association has been found between VEGF levels and FVC or DLCO values. VEGF is critical for the process of neoangiogenesis at the microcirculatory level[25,26,27] and its deficiency is one of the causes of the lack of capillary regeneration and the presence of capillary density loss. The relationship between changes in the PFT and NVC may be important for monitoring patients with SSc. Several studies show low levels of DLCO as a predictor of PH and ILD[13,27,28,29]. A study by Smith, *et al*[30] demonstrated the association of baseline capillaroscopic variables and future organ impairment in patients with SSc and found that patients with late pattern were the ones most likely to have severe pulmonary involvement. These data may be consistent with our results, because the late pattern predominates over capillary density loss[8].

Our study has several limitations. As a retrospective study, it is based on data collected from capillaroscopic reports that include the qualitative presence or absence of the microvascular alterations described, but do not report the numerical values (for example, the number of capillaries per mm). Indeed, our study cohort showed a low proportion of patients with dcSSc. This subset of patients is more prone to develop ILD and it would have been interesting to have more NVC from the dcSSc subgroup of patients. Unfortunately the NVC quality for some patients with dcSSc was poor and we could not use those NVC. Another limitation was the lack of collection of biomarkers or growth factors that could be associated with the capillaroscopic findings and PFT. Finally, the subgroup analyzed as patients with suspected PH was based on sPAP > 40 mmHg by echo-cardiography and not based on right heart catheterization.

Ours is the first study, to our knowledge, to show a possible association between a specific alteration of NVC in patients with SSc, and pulmonary function variables in patients with loss of capillary density presenting worse lung function values. Given the usefulness of capillaroscopy as a marker of the disease, more work is needed to study the possible association between NVC and PFT in monitoring the disease.

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