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Combination of capillaroscopic and ultrasonographic evaluations in systemic sclerosis: Results of a cross-sectional study

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Running heading: Capillaroscopic and PDUS evaluations in SSc

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Abstract

Objectives: To compare microvascular damages on nailfold capillaroscopy (NC) with macrovascular manifestations evaluated by hand power doppler ultrasonography (PDUS) in Systemic Sclerosis (SSc) patients, and to assess the associations of these damages with the main digital manifestations of the disease: digital ulcers (DU), acro-osteolysis and Calcinosis.

Methods: NC, hand X-Rays and PDUS were systematically performed in 64 unselected SSc patients. PDUS evaluation with assessment of ulnar artery occlusion (UAO) and finger pulp blood flow (FPBF) was performed blinded for the results of X-Rays and NC.

Results: UAO and pathologic FPBF were associated with severe capillary loss (<4 capillaries/mm) on NC (respectively OR=4.04 (1.23-13.29); p<0.05 and OR=3.38 (1.03-11.05); p<0.05). DU history was associated with UAO (OR=10.71 (3.36-34.13); p<0.0001), pathologic FPBF (OR=7.67 (2.52-23.28); p<0.0001), late pattern (OR=6.33 (2.03-19.68; p=0.001) and severe capillary loss (OR=8.52 (2.15-33.78); p=0.001). Acro-osteolysis was also associated with UAO (OR=15.83 (3.95-63.54); p<0.0001), pathologic FPBF (5.52 (1.71-17.90) p=0.003), late NC pattern (OR=6.86 (2.18-21.53); p=0.001) and severe capillary loss (OR=7.20 (2.16-24.02), p=0.001). Calcinosis on X-rays were associated with late NC pattern (OR=5.41 (1.82-16.12); p=0.002), severe capillary loss (OR=12.69 (3.14-51.26); p<0.0001) and UAO (OR=3.19 (1.14-8.92); p=0.025). Combination of UAO and severe capillary loss in a same patient was especially associated with DU history (OR=18.60 (2.24-154.34); p=0.001) and acro-osteolysis (OR=10.83 (2.56-45.88); p=0.001).

Conclusions: Microvascular damages evaluated by NC and macrovascular features like UAO assessed by PDUS show concordant associations with the main digital manifestations of the disease.

Key words: Systemic sclerosis, Scleroderma, Digital Ulcers, Acro-osteolysis, Calcinosis, Vasculopathy, Power Doppler Ultrasonography, Capillaroscopy, Ulnar artery, Digital ischemia.

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Significance and innovations :

-Ulnar artery occlusion (UAO) is associated with DUs, pitting scars, calcinosis and acro-osteolysis in systemic sclerosis.

-UAO and pathologic finger pulp blood flow are associated with a severe capillary loss on capillaroscopic evaluation.

-Combination of Power Doppler Ultrasonography and nailfold capillaroscopy findings may help to detect patients with a more severe vasculopathy.

Introduction:

Vascular involvement in Systemic sclerosis (SSc) is characterized by two main mechanisms. The first one is an early destructive vasculopathy with progressive loss of capillaries. The second one is an obliterative vasculopathy due to intimal hyperplasia with proliferation of vascular cells and intimal fibrosis. Microvascular damages result in digital ulcers (DUs) secondary to chronic hypoxemia, and pulmonary arterial hypertension (PAH) caused by fibroproliferative and obliterative vasculopathy. If PAH is one of the main causes of mortality in SSc, hand involvement and DUs are major aspects of the disease and are responsible for a high morbidity.

Microvascular damages of the hand can easily be evaluated using nailfold capillaroscopy (NC). Among the capillaroscopic features, the number of capillaries per millimetre in the middle finger of the dominant hand seems to be a reproducible and reliable predictive parameter to assess the risk of DU recurrence in SSc [1]. Digital manifestations of SSc also include sub-cutaneous calcinosis and acro-osteolysis. There is a lack of therapeutic measures to tackle these digital manifestations of the disease and a better characterization of the mechanisms underlying acro-osteolysis and calcinosis is therefore needed. Recent cross-sectional studies have reported an association of these digital manifestations with the Cutolo's late capillaroscopic pattern defined by severe capillary loss and proliferative neo-vascularization, supporting a vascular etiology of both acro-osteolysis and calcinosis [2,3].

Ultrasonographic (US) evaluation has dramatically improved joint and tendon evaluation in rheumatoid arthritis and other rheumatic diseases. US assessment of the hand is now therefore used in daily practice in many rheumatic disorders. B-mode analysis and power Doppler evaluation are thus widely available. Recent articles have highlighted the relevance of Doppler US evaluation to assess the severity of hand involvement and digital vasculopathy in SSc [4-8]. More specifically, these

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articles have supported that US evaluation may help to better characterize macrovascular involvement. Although micro-vessel alterations have been largely described, macrovascular involvement is also frequent in SSc. Macrovascular damages specifically involve narrowing or occlusions of proper palmar digital arteries (PPDA) and ulnar artery [4-7]. On the contrary, radial artery is rarely concerned. Ulnar artery occlusion (UAO) assessed by Power Doppler Ultrasonography (PDUS) has proven to be predictive of the onset of new ischemic DUs in two longitudinal studies [4,6]. PDUS could also be a reliable tool to evaluate finger pulp blood flow (FPBF) [6,7]. Only few studies have explored the association between macrovascular damages evaluated by PDUS and microvascular involvement assessed by NC [9,10]. The association between macrovascular disease and calcinosis or acro-osteolysis is still to be determined in SSc. Cutolo and colleagues have recently insisted on the necessity of conducting further surveys evaluating the relevance of macrovascular involvement as a reliable marker of severe vasculopathy in SSc [11].

The aim of this study was to further evaluate the relationship between microvascular damages assessed by NC and macrovascular features evaluated by PDUS of the hand, and to assess the associations of these damages with the main digital manifestations of the disease represented by DUs, acro-osteolysis and Calcinosis.

Methods:

Patients

Between November 2014 and November 2015, 64 unselected consecutive SSc patients referred to the rheumatology unit were included in this observational cross-sectional study. Previous history of DUs was noted using medical records of patients and clinical examination (pitting scars) at inclusion. The diagnosis of SSc was initially based on LeRoy's classification criteria but 93.8% of the patients (n=60) also fulfilled the ACR/EULAR 2013 classification criteria for SSc [12].

The ethics committee of Rennes Hospital approved this observational study (approvals 14.53 and 15.09). The study complied with the recommendations of the Declaration of Helsinki. Informed consent of all patients was obtained prior to investigations.

PDUS evaluation:

The same trained rheumatologist (GC) (8 years of experience in musculoskeletal and vascular imaging) performed all PDUS evaluations as previously described [6]. A standardized US evaluation of FPBF on the third and fourth fingers of both hands was performed after 15 minutes of acclimatization in our US laboratory with an ambient temperature ranging from 19 to 22°C. Pathologic FPBF was defined objectively as a decrease of doppler signal on the sub-hypodermal part of finger pulp or on the entire finger pulp recorded at least on one of the two evaluated fingers. Ulnar artery blood flow was measured on the wrist using a transversal view of Guyon's canal including the Pisiform bone. UAO was defined as an abolition of blood flow assessed by PDUS. An Allen test was also performed and UAO was confirmed when deep palmar arch showed no PDUS signal when radial artery was temporarily compressed by the examiner. US measurements were performed using the MyLab™ Class C system (Esaote, Florence Italy) equipped with a 6-18 MHz dedicated linear-array probe. Power Doppler settings were standardized (Doppler frequency 10 MHz, Gain 55%, PRF 750 Hz). Kappa coefficients of inter and intra-rater agreements of this method have already been published [6]. The investigator performing PDUS evaluation was blinded for the results of NC and X-ray evaluations.

Capillaroscopic evaluation:

NC were performed by the same examiner (AL) at inclusion, with a DermLite dermatoscope (Heine Delta™ 20). Microvascular damages were classified using Cutolo's classification. The number of capillaries per millimetre in the middle finger of the dominant hand was specifically noted. A severe capillary loss was defined by a count of less than 4 capillaries per millimetre. The results of PDUS features with NC analysis were combined to select the patients with a more severe vasculopathy, characterized by an association of both macro and microvascular damages.

X-Ray assessments:

Standard postero-anterior X-rays of both hands were obtained for all patients at inclusion. Calcinosis was defined by the presence of at least one calcification in soft tissues. Acro-osteolysis was defined as any bone resorption of at least one distal phalanx. The investigator assessing X-ray and NC was also blinded for the results of PDUS evaluations.

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Statistics

Qualitative data associations were analysed conducting Chi-square test or Fisher exact test and expressed with odds ratio (OR) and 95% confidence intervals. Quantitative data were analyzed conducting the unpaired two-tailed student-t-test or Mann and Whitney U test depending on Gaussian distribution. We performed all tests with a significance level of $P<0.05$. Statistical analysis was performed using SPSS 20.0 software.

Results :

Patient characteristics:

Patient characteristics are summarized in Table 1; 50% of the patients had a history of DU. Acro-osteolysis and calcinosis were present in respectively 34.4% and 43.8% of patients. Thirty-one patients (48.4%) had UAO and 33 had a pathologic FPBF (51.6%). Association of UAO and pathologic FPBF was present in 24 patients (37.5%). In NC, 17 (26.6%) patients had a normal or early pattern, 22 (34.4%) an active pattern and 25 (39.0%) a late pattern. A severe capillary loss was found in 18 (28.1%) patients.

Calcinosis and acro-osteolysis were both associated with DU history (respectively, OR=3.74 (1.31-10.62); $p<0.05$ and OR=9.00 (2.55-31.70); $p<0.0001$) and pitting scars on clinical examination at inclusion (respectively OR=7.3 (2.42-22.67); $p<0.0001$ and OR=10.88 (3.20-37.00); $p<0.0001$). Acro-osteolysis was associated with dSSc (OR=3.38 (1.14-10.01); $p<0.05$). Acro-osteolysis and UAO were both associated with the presence of skin telangiectasia (respectively; OR=12.92 (1.58-105.59); $p<0.01$ and OR=12.08 (2.47-59.15); $p<0.0001$). UAO was not associated with smoking (OR=1.12 (0.05-1.44) p=0.814).

Association between capillaroscopic findings and PDUS features (Table 2):

UAO was significantly associated with the late NC pattern (OR=3.80 (1.31-11.01); $p<0.05$) and a severe capillary loss (OR=4.04 (1.23-13.29); $p<0.05$). A normal or early NC pattern tended to be protective from UAO (OR=0.34 (0.10-1.11); p=0.06). A pathologic FPBF was associated with severe capillary loss in NC (OR=3.38 (1.03-11.05) $p<0.05$) but was not associated with any of the NC patterns.

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Associations of NC or PDUS features with the main digital complications of SSc (Table 3):

History of DU and pitting scars were significantly associated with UAO, pathologic FPBF on PDUS evaluation, late pattern and severe capillary loss on NC (Table 3A and 3B). On the contrary, normal or early NC patterns tended to be associated with less DU history (OR=0.31 (0.09-1.02); p=0.05). Acro-osteolysis was significantly associated with UAO, pathologic FPBF, late NC pattern and severe capillary loss (Table 3C). Calcinosis were associated with late NC pattern, severe capillary loss and UAO but were not associated with pathologic FPBF (Table 3D).

Combinations of PDUS features with NC findings and their associations with digital complications of SSc (supplementary Table 1):

The combination of UAO and severe capillary loss in a same patient was associated with pitting scars (OR=28.8 (3.43-241.64); p<0.0001), DU history (OR=18.60 (2.24-154.34); p=0.001), acro-osteolysis (OR=10.83 (2.56-45.88); p=0.001) and to a lesser extent with calcinosis (OR=6.11 (1.49-25.08); p=0.007). This combination of UAO on PDUS and severe capillary loss on NC showed higher associations with pitting scars, DU and acro-osteolysis than severe capillary loss on NC evaluation taken alone (Table 3). The combination of UAO, pathologic FPBF and severe capillary loss altogether in a same patient was also associated with pitting scars (OR=24.75 (2.94-208.30); p<0.0001), DU history (OR=16.24 (1.95-135.38); p=0.001) and to a lesser extent with acro-osteolysis (OR=9.00 (2.11-38.35); p=0.002) and calcinosis (5.21 (1.25-21.63); p=0.015); (other combinations shown in supplementary data available at *Arthritis Care & Research* online).

Discussion :

The results of this cross-sectional study suggest that microvascular damages evaluated by NC and some of the macrovascular features of SSc assessed by PDUS show concordant associations with the main digital manifestations of the disease. The proliferative obliterative vasculopathy characterizing Cutolo's late NC pattern is especially associated with UAO in our study, supporting the hypothesis that micro and macrovascular damages could be linked in SSc. Rosato *et al.* had previously reported a correlation between macrovascular features in the hands of SSc patients evaluated by PDUS and micro-vessel involvement assessed by laser Doppler perfusion imaging or digital photoplethysmography [9,10]. Our cross-sectional study reveals associations of macrovascular damages with DUs but also with other digital manifestations of SSc such as acro-osteolysis and calcinosis, both supposed to be the consequences of microvascular damages [2]. We can hypothesize that the same pathogenic pathways may partly support micro and macrovascular involvement,

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however the cross-sectional design of this study limits any conclusions about causality. Only prospective longitudinal studies with long-term follow-up will allow us to draw conclusions regarding any common causal factors of micro and macro-vascular involvement.

Two recent studies have highlighted the associations of calcinosis with digital ischemia and late NC pattern in SSc [2,3]. Morardet *et al.* have also reported an association between acro-osteolysis and late NC pattern [2]. Our results are consistent with these data and further support an implication of SSc vasculopathy in the pathogenesis of these digital manifestations of the disease. The association of acro-osteolysis on X-Rays and UAO assessed by PDUS in our study may suggest an involvement of macro-vascular disease in the pathogenesis of acro-osteolysis. However, any direct pathogenic links emerged from our study should be taken cautiously given its cross-sectional design that limits causal conclusions. Acro-osteolysis is associated with a neovascularization and an angiogenesis that remain insufficient to balance chronic ischemia. The reasons why this neo-angiogenesis remains ineffective are still to be determined. We could hypothesize that this endothelial proliferation may contribute to the macrovascular obliterative damages reflected by UAO and could therefore maintain chronic ischemia. In our study, the association of UAO with the presence of skin telangiectasia also supports the hypothesis of a link between macrovascular obliterative damages and neo-angiogenesis. These results are consistent with other studies considering skin telangiectasia as a marker of severe vascular disease in SSc [13]. As suggested by Lüders *et al*, a further characterization of other macro-vessels of the hand such as PPDA would also be relevant to support this hypothesis [5].

Detecting patients with a severe vascular involvement and at higher risk of DU is a major issue in SSc. The combination of macrovascular and microvascular evaluations by PDUS and NC respectively may help to detect patients with a more severe vasculopathy. In our study, combining PDUS and NC results reveals highly significant associations with the main digital manifestations of the disease. The association of both macro and microvascular damages in a same patient might therefore be a relevant marker reflecting the severity of the vasculopathy in SSc. The odds ratios assessing these associations are quite high but with wide confidence interval, highlighting the need for future studies with larger sample size to characterize these associations more precisely. Moreover we have not performed multivariable analyses in this exploratory cross-sectional study, given the small sample size that would have strongly limited the strength and relevance of a multivariable logistic regression model. Therefore even if clinical parameters such as smoking and disease duration were not associated with macrovascular features in univariable analyses, such factors may nonetheless constitute confounding factors that will need to be further studied in multivariable models based on wider SSc populations.

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One of the limitations of our study is the heterogeneity of vasodilator treatments taken by the patients. It was recently reported that Calcium channel blockers (CCB) were inversely associated with calcinosis in a retrospective study including a large number of patients (n=1305) [3]. In our study, 65.6% of the patients had CCB at inclusion. This is less than reported in the study by Morardet *et al* [2]; this difference may explain the higher prevalence of calcinosis found in our work as compared to the prevalence reported by Morardet *et al.* The prevalence of calcinosis in our study is nonetheless consistent with the results of Johnstone *et al* [14]. Treatments may have also influenced PDUS evaluation of FPBF and this could explain some inconsistent associations of pathologic FPBF with digital manifestations of SSc in our study. The small sample size of this single-center study may have also resulted in a lack of power to reveal some other relevant associations. Multi-center studies are warranted to confirm our data, to better characterize the impact of vasodilating therapies on FPBF and to evaluate more precisely the associations of calcinosis or acro-osteolysis with FPBF evaluated by PDUS or by other perfusion assessment tools such as laser Doppler perfusion imaging and laser speckled contrast analysis [10,15].

In a recent study conducted by our group and using the same methodology, Kappa coefficients of inter-rater agreement were 0.94 for the presence of pathologic FPBF and 0.97 for the presence of UAO on PDUS images. Kappa coefficients of intra-rater agreement were 0.90 for the presence of pathologic FPBF and 0.93 for the presence of UAO [6]. These results are close to the performances of other assessment tools of peripheral blood perfusion such as laser speckle contrast analysis [15]. Macro-vascular evaluation using these PDUS parameters thus seems to be reproducible. As PDUS is a widely available non-invasive tool, used in daily practice by an increasing number of rheumatologists, it may therefore prove to be relevant to detect patients with a more severe vasculopathy in daily practice [4-6]. Recent clinical trials, evaluating therapeutic measures supposed to prevent new DU occurrence have failed to reach their primary outcome [16,17]. Therefore, both macro and microvascular evaluations of the hand may help to better identify patients at high risk of DUs for future studies evaluating DU prevention strategies in SSc.

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Table 1. Demographic and clinical characteristics at inclusion

Patients characteristics at inclusion (%/ SD)	**SSc (n=64)**
Demographics	
Female	47 (73.4)
Mean age at inclusion, years (SD)	58.6 (11.5)
Clinical characteristics	
Fulfilling ACR 2013 SSc classification criteria	60 (93.8)
Disease form	
lSSc	41 (64.1)
dSSc	23 (35.9)
Mean disease duration since first non-RP symptom, years (SD)	7.4 (8.8)
Mean modified Rodnan Skin Score (SD)	8.7 (8.0)
Telengiectasia	47 (73.4)
Puffy fingers	18 (28.1)
Antibodies	
ACA	30 (46.9)
ATA	17 (26.6)
ARNAPIII	4 (6.3)
Other	13 (20.3)
DU Characteristics	
DU History	32 (50.0)
Multiple episodes of DU	21 (32.8)
Ischemic DU	27 (42.2)
Calcinosis related DU	8 (12.5)
Pitting scars	27 (42,2)
X-ray Features	
Acro-osteolysis	22 (34.4)
Calcinosis	28 (43.8)
PDUS Features	
UAO	31 (48.4)
bilateral	21 (32.8)
Pathologic FPBF	33 (51.6)
bilateral	27 (42.2)
Association of UAO and Pathologic FPBF	24 (37.5)
Capillaroscopic Features	
Normal or early pattern	17 (26.6)
Active pattern	22 (34.4)
Late pattern	25 (39.0)

Severe capillary loss (< 4 capillaries/mm)	18 (28.1)
Treatments	
Calcium channel blockers	42 (65.6)
Bosentan	8 (12.5)
Sildenafil	6 (9.4)
History of treatment with prostacyclins IV	19 (29.7)

SD= standard deviation, SSc=systemic sclerosis, lSSc= limited cutaneous systemic sclerosis, dSSc=diffuse cutaneous systemic sclerosis, RP=Raynaud Phenomenon, ACA= Anti-centromere antibody, ATA=Anti-topoisomerase I antibody, ARNAPIII=anti-RNA polymerase III antibody, DU= digital Ulcers, PDUS= Power Doppler UltraSonography, UAO=Ulnar Artery Occlusion, FPBF= Finger Pulp Blood Flow.

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Table 2*:* Association between capillaroscopic patterns and PDUS features (n=64)

A. Association of Capillaroscopic patterns with Ulnar Artery Occlusion

	Ulnar Artery Occlusion	
	OR (95%CI)	p
Capillaroscopic patterns		
Normal or early	0.34 (0.10-1.11)	0.06
Active	0.63 (0.22-1.79)	0.38
Late	3.80 (1.31-11.01)	0.012*
Severe capillary loss	4.04 (1.23-13.29)	0.02*

B. Association of Capillaroscopic patterns with Pathologic Finger Pulp Blood Flow

	Pathologic FPBF	
	OR (95%CI)	p
Capillaroscopic patterns		
Normal or early	0.57 (0.18-1.74)	0.32
Active	0.91 (0.32-2.55)	0.86
Late	1.75 (0.63-4.84)	0.28
Severe capillary loss	3.38 (1.03-11.05)	0.04*

PDUS= Power Doppler UltraSonography, FPBF= Finger Pulp Blood Flow, OR= Odds Ratio.

*Level of significance: *p<0.05*

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Table 3*:* Association between NC or PDUS features and main clinical manifestations involving hand in 64 SSc.

A. Association of capillaroscopic or PDUS features with DU history

	DU history	
	OR (95%CI)	p
PDUS features		
UAO	10.71 (3.36-34.13)	<0.0001*
Pathologic FPBF	7.67 (2.52-23.28)	<0.0001*
Association of UAO and pathologic FPBF	11.67 (3.28-41.49)	<0.0001*
NC features		
Late pattern	6.33 (2.03-19.68)	0.001*
Severe capillary loss	8.52 (2.15-33.78)	0.001*

B. Association of capillaroscopic or PDUS features with pitting scars at inclusion

	Pitting scars	
	OR (95%CI)	P
PDUS features		
UAO	9.45 (2.96-30.20)	<0.0001*
Pathologic FPBF	3.90 (1.35-11.26)	0.01*
Association of UAO and pathologic FPBF	7.29 (2.34-22.65)	<0.0001*
NC features		
Late pattern	8.57 (2.72-27.01)	<0.0001*
Severe capillary loss	14.17 (3.48-57.65)	<0.0001*

C. Association of capillaroscopic or PDUS features with Acro-osteolysis on X-Ray

	Acro-osteolysis	
	OR (95%CI)	p
PDUS features		
UAO	15.83 (3.95-63.54)	<0.0001*
Pathologic FPBF	5.52 (1.71-17.90)	0.003*
Association of UAO and pathologic FPBF	7.86 (2.46-25.09)	<0.0001*
NC features		
Late pattern	6.86 (2.18-21.53)	0.001*
Severe capillary loss	7.20 (2.16-24.02)	0.001*

D. Association of capillaroscopic or PDUS features with Calcinosis on X-Ray

	Calcinosis	
	OR (95%CI)	p
PDUS features		
UAO	3.19 (1.14-8.92)	0.025*
Pathologic FPBF	1.93 (0.71-5.27)	0.196
Association of UAO and pathologic FPBF	2.60 (1.93-24.87)	0.069
NC features		
Late pattern	5.41 (1.82-16.12)	0.002*
Severe capillary loss	12.69 (3.14-51.26)	<0.0001*

PDUS= Power Doppler UltraSonography, NC=Nailfold Capillaroscopy, FPBF= Finger Pulp Blood Flow, OR= Odds Ratio, DU= Digital Ulcers, UOA=Ulnar Artery Occlusion

*Level of significance: *p<0.05*

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