Correlation between capillaroscopic classifications and severity in systemic sclerosis: results from the SCLEROCAP study at inclusion

C. Boulon[1], S. Aiouaz[2], S. Blaise[3], M. Mangin[1], J. Decamps-Le Chevoir[4], P. Senet[5], I. Lazareth[6], N. Baudot[5], L. Tribout[5], B. Imbert[3], F.-X. Lapebie[7], P. Lacroix[8], M.-E. Truchetet[9], J. Seneschal[10], A. Solanilla[11], S. Skopinski[1], E. Lazaro[12], I. Quéré[13], M.-A. Pistorius[14], C. Le Hello[15], P. Perez[2], P. Carpentier[6], J. Constans[1]

Affiliations: see page S-67.

Carine Boulon, MD
Soraya Aiouaz, MD
Sophie Blaise, MD, PhD
Marion Mangin
Joelle Decamps-Le Chevoir, MD
Patricia Senet, MD
Isabelle Lazareth, MD
Nathalie Baudot, MD
Laurent Tribout, MD
Bernard Imbert, MD
François-Xavier Lapebie, MD
Philippe Lacroix, MD PhD
Marie-Elise Truchetet, MD, PhD
Julien Seneschal, MD, PhD
Anne Solanilla, MD, PhD
Sophie Skopinski, MD
Estibaliz Lazaro, MD, PhD
Isabelle Quéré, MD, PhD
Marc-Antoine Pistorius, MD, PhD
Claire Le Hello, MD, PhD
Paul Perez, MD, PhD
Patrick Carpentier, MD, PhD
Joël Constans, MD, PhD

Please address correspondence to:
Dr Joel Constans,
Service de Médecine Vasculaire,
Hôpital St. André,
1 rue Jean Burguet,
33075 Bordeaux, France.
E-mail: joel.constans@chu-bordeaux.fr

Received on January 18, 2019; accepted in revised form on April 1, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 119): S63-S68.

Key words: systemic sclerosis, capillaroscopy, prognosis, microcirculation

Funding: Financial support for the research was granted by: Société Française de Médecine Vasculaire, Société Française de Microcirculation and Actelion Pharmaceuticals.

Competing interests: none declared.

ABSTRACT

Objective. *We assessed the correlation between severity of systemic sclerosis (SSc) and current staging systems based on nailfold capillaroscopy.*

Methods. *SCLEROCAP is a multicentre prospective study including consecutive scleroderma patients who have a yearly routine follow-up with capillaroscopy and digital blood pressure measurement. Capillaroscopy images were read by two observers blinded from each other, then by a third one in the case of discordance. A follow-up of 3 years is planned. The present study assessed the correlation between severity of systemic sclerosis (SSc) and current staging systems based on nail fold capillaroscopy at enrollment in the SCLEROCAP study. Univariate and multivariate logistic regression analysis was performed for both the Maricq and Cutolo classifications.*

Results. *SCLEROCAP included 387 patients in one year. Maricq's active and Cutolo's late classifications were very similar. In multivariate analysis, the number of digital ulcers (OR for 2 ulcers or more, respectively 2.023 [1.074-3.81] and 2.596 [1.434-4.699]) and Rodnan's skin score >15 (OR respectively 32.007 [6.457-158.658] and 18.390 [5.380-62.865]) correlated with Maricq's active and Cutolo's late stages. Haemoglobin rate correlated with Cutolo's late stage (haemoglobin<100 vs. >120 g/dl: OR 0.223 [0.051-0.980]), and total lung capacity with Maricq's active one: increase in 10%: OR0.833 [0.717-0.969].*

Conclusion. *The correlations found between capillaroscopy and severity of SSc are promising before the ongoing prospective study definitively assesses whether capillaroscopy staging predicts complications of SSc. Only two capillaroscopic patterns seem useful: one involving many giant capillaries and haemorrhages and the other with severe capillary loss.*

Introduction

Systemic sclerosis (SSc) primarily involves microcirculation and Raynaud's phenomenon is usually the first clinical sign of the disease. Nailfold capillaroscopy explores this microcirculatory involvement and may show specific signs of the disease in patients who have Raynaud's phenomenon but no skin involvement. These findings led LeRoy and Medsger to propose the term "limited SSc" for such patients with immunological or capillaroscopic specific findings in the absence of skin disease (1). More recently, capillaroscopy was considered as part of the EULAR/ACR criteria for SSc (2). Capillaroscopy and antinuclear antibodies are now considered as pivotal exams in patients with Raynaud's phenomenon (3). Capillaroscopy may give useful information about prognosis in patients with an established diagnosis of SSc. Indeed, the capillaroscopic pattern progresses over time in SSc patients from giant capillaries to destruction of the capillary bed (4).

Maricq and more recently Cutolo proposed capillaroscopic classification systems in order to identify patients at different stages of the disease (5, 6). These systems have also been correlated with the severity of disease in limited observational studies (7-9). Capillaroscopy may be used to detect a window of opportunity for treatment in patients who progress from giant

capillaries to capillary bed destruction (10, 11). In fact, SSc is a heterogeneous disease that may progress to fatal complications after several months or may remain limited to sclerodactyly and Raynaud's phenomenon. Detecting an increased risk of complications in scleroderma patients is an important issue for identifying patients at risk of progression to severe complications. The SCLEROCAP study was designed to validate and compare Maricq and Cutolo's capillaroscopic staging systems for predicting the severe progression of SSc, and to propose a new system if neither of the classifications is informative. The present paper presents the results of the analysis of patients at inclusion in order to correlate their capillaroscopic features with severity of SSc.

Patients and methods

Study design

The main hypothesis of the SCLEROCAP study is that one or both of Maricq and Cutolo's prediction predicts outcome of systemic sclerosis complications. SCLEROCAP is a French prospective, observational, longitudinal multicentre study that is ongoing and complies with good clinical practices and the Declaration of Helsinki. Patients were enrolled between March 2014 and August 2015. The end of the study is planned for end of 2019 after three years of follow-up. Formal ethics committee approval was obtained (7 March 2014). The patients gave informed written consent. The present article reports transversal correlations between capillaroscopic data and the descriptive parameters of SSc collected at inclusion in SCLEROCAP.

Setting and patients

The patients were consecutively included from 10 departments (vascular medicine, rheumatology, internal medicine, dermatology). The inclusion criteria were a diagnosis of SSc according to LeRoy and Medsger's definition (1) in order to include systemic sclerosis without skin involvement as well, and age above 18 years. The SCLEROCAP study aims to follow these patients for three years with a yearly routine check-up including capillaroscopy and finger systolic pressure measurement. The main objective is to validate the current Cutolo and Maricq's systems, or to develop a new one if they prove inadequate. Progression after three years will be considered as severe in the case of heart, lung, pulmonary artery or kidney involvement. Progression will be validated by an event validation committee (12). Capillaroscopy images are read in the clinical centre by an unblinded expert at the time where clinical and paraclinical exams are done, and capillary images are then read anonymously by another blinded from the patient's status. A third expert is consulted in the event of disagreement.

Study procedures

Demographics, medical history, SSc subtype, and clinical and biological SSc characteristics were collected at inclusion. For each patient, capillaroscopic images were analysed for qualitative and quantitative abnormalities using the same tool, *i.e.* a standardised record sheet, at each visit, first in the clinical centre by the investigator, then by another investigator blind to the first assessment. A third expert was consulted in the event of disagreement. The images from four fingers on each hand (total of eight fingers) were classified according to Maricq's and Cutolo's scoring systems (5, 6).

For Maricq's classification, two patterns were considered (5). The slow one consisted of giant capillaries with no or minimal avascular area; the active one consisted of few or absent giant capillaries, large avascular areas and architectural disorganisation.

For Cutolo's classification, three patterns were considered (6). The early pattern consisted of few giant capillaries and haemorrhages, preserved capillary organisation and no evident capillary loss. The active pattern involved frequent giant capillaries and haemorrhages and moderate capillary loss. The late pattern consisted of few or absent giant capillaries, absence of haemorrhages, severe capillary loss with large avascular areas, disorganisation of capillary loops and presence of bushy capillaries.

Acquisition of nailfold capillaroscopic images

Images were recorded at inclusion and during the follow-up on eight fingers (all fingers except thumbs) by using the same wide-field videocapillaroscopy device in all centres (x50 to x100 magnification, CapXview Perimed, Järfälla, Sweden). The images were recorded on a disk, then blinded by a research assistant and given to experimented observers not aware of the patient's identity or status for assessment/classification. During the first meeting the investigators agreed upon a sheet for recording: a) capillaroscopic elementary abnormalities and Maricq's and Cutolo's classifications for each finger; and b) for all fingers as a whole taking into account the aspect observed in most fingers. Abnormalities were analysed from the first row of capillaries. The classification took into account the most frequent capillary landscape but not the worst one when one finger was more severe than the others.

Outcomes and measurements

Quantitative and qualitative data contained in the capillaroscopic images were assessed by the investigators. Two other meetings were then held to analyse discordant findings and to improve agreement about the definition of abnormalities. The need to define each elementary abnormality more precisely was identified, so consensus definitions were established. An agreement between the investigators was found after the three meetings. These definitions and results of inter- and intra-observer agreement were published previously (13).

A descriptive analysis and a binary logistic regression were performed for each capillaroscopic classification, one for Maricq's and one for Cutolo's classifications, in order to correlate them with the severity of SSc at inclusion using clinical and para-clinical variables. For Maricq's classification, we compared the active pattern with the grouping of unspecific and slow patterns. For Cutolo's classification, we compared the late pattern with the grouping of unspecific, early and active patterns. Clinical explanatory variables were Rodnan's skin score (RSS), and

number of active and cicatrised digital ulcers. Para-clinical explanatory variables were C-reactive protein (CRP), haemoglobin rate, total lung capacity (TLC), diffusion lung capacity for carbon monoxide (DLCO), and anti-topoisomerase 1 (SCL70 auto-antibodies (Ab) and anti-centromere Ab.

Statistical analysis

A cross-sectional analysis of associations based on inclusion data was conducted. Binary logistic regression analysis was used to determine associations between each capillaroscopic classification and candidate explanatory variables. Linearity conditions were assessed for quantitative variables. Only TLC and DLCO verified the log linearity assumption and were kept as continuous variables. RSS, number of fingers with trophic disorders, CRP and haemoglobin level were transformed into qualitative variables. RSS was indexed in three classes: RSS 0, RSS between 1 and 14 and RSS≥15. Number of fingers with trophic changes was indexed in three classes: 0, 1 or ≥2 fingers affected. CRP was indexed in three classes: <5mg/l, between 5 and 20 mg/l, ≥20 mg/l. Haemoglobin level was indexed in three classes: ≥12, between 10 and 12, and ≤10 g/dl. Univariate logistic regression was performed first, followed by multivariate logistic regression. All candidate explanatory variables were included in the model, then selected through a backward step-by-step selection process (exclusion criteria: $p>0.20$). However, explanatory variables could be kept in the model when considered to have a high clinical significance. SAS software was used for statistical analysis (SAS France, Brie Comte Robert).

Results

Three hundred and eighty-seven patients were included in the SCLEROCAP study (327 females, 60 males). Of these 387 patients, 59 had an unspecific or normal capillaroscopic pattern. The others were separated by Maricq's classification into 211 slow and 117 active patterns. By Cutolo's classification, the patients were separated into 87 early, 144 active and 97 late patterns. Maricq and Cutolo's classifications largely overlapped, Maricq's active stage corresponding to Cutolo's late stage in 80% patients, and Cutolo's late stage corresponding to Maricq's active stage in 97% (Table I). The clinical and para-clinical characteristics of patients according to Mariq or Cutolo's classification are given in Tables II and III. To summarise, Maricq's active and Cutolo's late stages were associated with more frequent diffuse SS, anti-SCL 70 Ab, higher number of digital ulcers, higher RSS, CRP, and a decrease in TLC and DLCO. Multivariate analysis showed that Maricq's active stage and Cutolo's late stage were strongly and significantly associated with severity features: higher RSS, at least one digital ulcers ≥2 and lower haemoglobin level (Tables IVa and IVb). As far as treatments are concerned, immunosuppressive drugs were taken by 19 patients, steroids by 18, calcium channel inhibitors by 81, endothelin receptor antagonists by 25, phosphodiesterase inhibitors by 8, iloprost by 23, aspirin or clopidogrel by 31 patients.

Table I. Relationship between Maricq and Cutolo's classifications in the 329* classified patients.

Maricq Cutolo	Slow (N=211)	Active (N=117)
Early (N=87)	87	0
Active (N=144)	121	23
Late (N=97)	3	94

*Among the 387 patients, 59 (15%) had normal capillaroscopy or were unclassifiable for Maricq and Cutolo's classifications.

Table II. SCLEROCAP Study: Maricq's classification at inclusion according to scleroderma type and severity.

Maricq's classification	Normal or unclassifiable	Slow	Active
Number of patients	59	211	117
Female/male	52/7	176/35	99/18
Age	55 (14)	56 (12)	61 (14)
SSc duration years mean (SD)	12.2 ± 9.3	9.6 ± 8.1	8.9 ± 9.9
SSc type			
Limited	22 (37%)	50 (24%)	16 (14%)
Cutaneous limited	28 (46%)	145 (69%)	70 (60%)
Diffuse	9 (15%)	16 (8%)	31 (26%)
Antinuclear Ab type			
Anti-centromere	29 (50%)	128 (61%)	66 (56%)
Anti-SCL70	8 (14%)	30 (14%)	31 (26%)
Anti-RNA polymerase III	5 (9%)	6 (3%)	4 (3%)
Rodnan's skin score	3.2 (4.3)	4.6 (5.2)	8.8 (6.9)
Digital ulcer or scar (%)	9 (15%)	46 (22%)	58 (50%)
CRP mg/l	4.2 (4.3)	5.0 (12.2)	8.5 (12.9)
Haemoglobin g/l	132 (13)	136 (12)	126 (15)
Total lung capacity % predicted	109.6 (23.2)	104.5 (18.0)	94.6 (20.0)
Forced vital capacity % predicted	106.7 (17.6)	107.6 (17.8)	101.5 (21.8)
Carbon oxide diffusion % predicted	77.7 (15.9)	75.8 (17.6)	70.4 (16.8)
Renal involvement	2	2	3
Cardiac involvement	1	7	7
Digestive involvement	89	62	25

Values are given as mean (standard deviation) for quantitative variables, absolute numbers (percentages) for other variables.

Discussion

Maricq and Cutolo's classifications largely overlap. Cutolo's late and Maricq's active stages look basically similar. Classification into three stages instead of two by Cutolo does not seem to improve the correlation with the severity of disease and statistical analysis was performed only in two classes: between Cutolo's late or Maricq's active stages, on one hand, and the remaining

Table III. SCLEROCAP Study: Cutolo's classification at inclusion according to scleroderma type and severity.

Cutolo's classification	Normal or unclassifiable	Early	Active	Late
Number of patients	59	87	144	97
Female/male	52/7	73/14	118/26	84/13
Age	56 ± 15	57 ± 12	55 ± 13	63 ± 14
SSc duration years mean ± SD	12.2 ± 9.3	9.6 ± 8.1	9.9 ± 8.6	13.9 ± 10.6
SSc type				
Limited	22 (37%)	22 (25%)	30 (21%)	14 (14%)
Cutaneous limited	28 (47%)	59 (68%)	100 (69%)	56 (58%)
diffuse	9 (15%)	6 (7%)	14 (10%)	27 (28%)
Antinuclear Ab type				
Anticentromere	29 (50%)	52 (60%)	88 (61%)	54 (56%)
Anti-SCL70	8 (14%)	13 (15%)	21 (15%)	54 (56%)
Anti-RNA polymerase III	5 (9%)	1 (1%)	5 (3%)	4 (4%)
Rodnan's skin score mean±SD	3.2 ± 4.3	3.9 ± 4.3	5.3 ± 5.8	9.1 ± 7.1
Digit ulcer or scar presence (%)	9 (15%)	14 (16%)	42 (29%)	47 (49%)
CRP mg/l mean ± SD	4.2 ± 4.3	5.0 ± 7.4	5.6 ± 15.2	8.4 ± 11.5
Hb g/l mean ± SD	132 ± 13	137 ± 10	135 ± 12	125 ± 16
Total lung capacity % predicted mean ± SD	109.6 ± 23.2	108 ± 17.9	100.1 ± 19.0	95.4 ± 19.3
Forced vital capacity % predicted mean ± SD	106.7 ± 17.6	107.6 ± 20.2	105.8 ± 17.7	102.9 ± 21.2
Carbon oxide diffusion % predicted mean ± SD	77.7 ± 15.9	78.5 ± 16.1	74.3 ± 18.2	69.0 ± 16.6
Renal involvement	1	1	2	2
Cardiac involvement	1	3	4	7
Digestive involvement	25	35	63	53

Values are mean ± (standard deviation for age, absolute numbers (percentages) for other results. 59 patients had a capillaroscopic pattern considered as normal or unclassifiable according to both classifications.

patients, on the other hand. In multivariate logistic regression, Cutolo's classification was dichotomised because the results of a polytomial regression are more difficult to interpret and it also made it possible to compare the results to those of Mariq's. Moreover, the precision of odds ratios was improved.

The main result of the present study is the correlation between both capillaroscopic classifications and markers of SSc severity. The number of digital ulcers and RSS correlated with Maricq's active and Cutolo's late stages. Haemoglobin rate and lung total capacity correlated with both classifications. Both haemoglobin and lung functional markers are established markers of prognosis (12, 14).

Overall, the findings are in accordance with previous reports on the relationship between capillaroscopy and complications of SSc. In a small sample of 19 patients, Maricq reported more frequent organ involvement during the follow-up of active-stage patients than in slow-stage ones (5 out of 8 *vs*. 1 out of 11, respectively). Chen showed that active stage was correlated with skin fibrosis, pulmonary hypertension and renal crisis (5, 7). Cutolo's late stage was found to be associated with age,

Table IV. SCLEROCAP Study: multivariate associations between severity markers of scleroderma and capillaroscopic classifications at inclusion.

Table IVa: Maricq's classification.

	Odds ratio	Odds ratio 95% confidence interval	*p*-value*
Number of digital ulcers (ref. 0)			0.021
1 digital ulcer	2.88	1.04-7.93	
≥2 digital ulcers	2.02	1.07-3.81	
Rodnan's skin score (ref. 0)			0.0001
1-14	13.13	3.07-56.22	
≥15	32.01	6.46-158.66	
Haemoglobin level (g/l) (ref >120g/l)			0.022
≤100 g/l	3.21	0.36-28.39	
>100 g/l and ≤ 120 g/l	2.83	1.30-6.18	
Total lung capacity (decrease of 10%)	1.20	1.03-1.39	0.018

*Wald's test.

Table IVb: Cutolo's classification

	Odds ratio	Odds ratio 95% confidence interval	*p*-value*
Number of digital ulcers (ref. 0)			0.005
1 digital ulcer	0.90	0.32-2.52	
≥2 digital ulcers	2.60	1.43-4.70	
Rodnan's skin score (ref. 0)			<.0001
1-14	7.11	2.41-20.93	
≥15	18.39	5.38-62.86	
Haemoglobin level (g/l) (ref >120g/l)			0.0001
≤100 g/l	4.48	1.02-19.69	
>100 g/l and ≤120 g/l	4.01	1.99-8.06	

*Wald's test

duration of disease, more extensive skin involvement, cardiopulmonary or renal complications (16), (17-20, 8). While these studies are limited by their cross-sectional design or small number of patients, our findings in a prospective randomised study of 387 patients are in accordance with these results.

Capillaroscopy abnormalities have been associated with mortality in Raynaud's syndrome (21, 22). There is a lack of consensus regarding patients with SSc. Data mortality will become available in our prospective study after a three- year follow-up. Capillaroscopic findings have also been recently correlated with progression from VEDOSS to the ACR criteria of SSc (25) .

In the present study we report a transverse correlation between capillaroscopic abnormalities and severity of disease. This result is encouraging for the prospective SCLEROCAP study that aims to predict prognosis by capillaroscopy. Another point is the ability of capillaroscopy to underline the potential severity of existing disease in a patient and to closely monitor those patients who have severity criteria on capillaroscopy.

Capillary loss may occur early after the onset of SSc or during the follow-up. It is important to know whether a worsening capillaroscopy pattern predicts future severe involvement in order to start active therapies (9). Avouac addressed this question with positive results (26). He found that the reduction of the number of capillaries was associated with overall disease progression, occurrence of new digital ulcers, lung vascular progression, progression of skin fibrosis and worsening of the Medsger severity score (26) .

The main limitation of capillaroscopy in predicting the prognosis of SSc is its reproducibility. Nailfold capillaroscopy was found to have excellent inter- and intra-observer agreement for the diagnosis of scleroderma pattern in patients suffering from Raynaud's phenomenon (27) but this agreement was not satisfactory for either Maricq's or Cutolo's classification (13, 28). However, we showed that reproducibility dramatically improves with training (13). The results of the present study are not hampered by this limitation since the images were read by two observers blinded from each other and a third one in the event of discrepancy. This limitation must be taken into account if these results are to be extrapolated to clinical practice, so specific training should be proposed to practitioners who intend to use capillaroscopic classifications to assess the prognosis of SSc. This is key to improving clinical practice.

SCLEROCAP is the first prospective longitudinal study designed to assess the contribution of capillaroscopic classifications for predicting the risk of severe complications of SSc. It is also the first to use both Maricq's and Cutolo's classifications. Both staging systems correlate with the severity of SSc at inclusion but Cutolo's classification should be limited to two stages so that it is very close to Maricq's. For prognostic purposes, only two capillaroscopic patterns seem useful in our hands: one consisting of many giant capillaries and haemorrhages and the other with severe capillary loss. The results of the prospective follow-up of SCLEROCAP patients will become available in 2019.

Acknowledgements

Thanks to Romain Griffier, public health resident, who carried out additional statistical analyses.

Affiliations

[1]Service de Médecine Vasculaire, Hôpital Saint-André, Bordeaux; [2]Unité de Soutien Méthodologique à la Recherche Clinique, Pôle de Santé Publique, CHU de Bordeaux; [3]Hôpital Universitaire de Grenoble, Département de Médecine Vasculaire, Grenoble; [4]Service de Médecine Interne, Hôpital de la Pitié, Paris; [5]Service de Dérmatologie, Médecine Vasculaire et Allergologie, Hôpital Tenon, Paris; [6]Service de Médecine Vasculaire, Hôpital Saint-Joseph, Paris; [7]Service de Médecine Vasculaire, Hôpital Rangueil, Toulouse; [8]Service de Médecine Vasculaire, Limoges; [9]Service de Rhumatologie, Hôpital Pellegrin, Bordeaux; [10]Service de Dermatologie, Hôpital Saint-André, Bordeaux; [11]Service de Médecine Interne, Clinique Mutualiste de Lesparre, Lesparre; [12]Service de Médecine Interne et Maladies Infectieuses, Hôpital Haut-Lévêque, Pessac; [13]Service de Médecine Vasculaire, Hôpital Saint Eloi, Montpellier; [14]Service de Médecine Vasculaire, Hôtel Dieu, Nantes; [15]Service de Médecine Vasculaire, CHU Nord Saint-Etienne, Université Jean Monnet, Campus Santé et Innovations, Saint-Etienne, France.

References

1. LEROY EC, MEDSGER TA: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573-6.
2. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al*.: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737-47.
3. BELCH J, CARLIZZA A, CARPENTIER PH *et al*.: ESVM guidelines - the diagnosis and management of Raynaud's phenomenon. *VASA Z Gefasskrankheiten* 2017; 46: 413-23.
4. KOENIG M, JOYAL F, FRITZLER MJ *et al*.: Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. *Arthritis Rheum* 2008; 58: 3902-12.
5. MARICQ HR, HARPER FE, KHAN MM, TAN EM, LEROY EC: Microvascular abnormalities as possible predictors of disease subsets in Raynaud phenomenon and early connective tissue disease. *Clin Exp Rheumatol* 1983; 1: 195-205.
6. CUTOLO M, SULLI A, PIZZORNI C, ACCARDO S: Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. *J Rheumatol* 2000; 27: 155-60.
7. CHEN ZY, SILVER RM, AINSWORTH SK, DOBSON RL, RUST P, MARICQ HR: Association between fluorescent antinuclear antibodies, capillary patterns, and clinical features in scleroderma spectrum disorders. *Am J Med* 1984; 77: 812-22.
8. CARAMASCHI P, CANESTRINI S, MARTINELLI N *et al*.: Scleroderma patients nailfold videocapillaroscopic patterns are associated with disease subset and disease severity. *Rheumatology* (Oxford) 2007; 46: 1566-9.
9. SMITH V, DECUMAN S, SULLI A *et al*.: Do worsening scleroderma capillaroscopic patterns predict future severe organ involvement? a pilot study. *Ann Rheum Dis* 2012; 71: 1636-9.
10. PAULING JD: Could nailfold videocapillaroscopy usher in a new era of preventative disease-modifying therapeutic intervention in systemic sclerosis? *Rheumatology* (Oxford) 2017; 56: 1053-5.
11. PAXTON D, PAULING JD: Does nailfold capillaroscopy help predict future outcomes in systemic sclerosis? A systematic literature review. *Semin Arthritis Rheum* 2018; 48: 482-94.
12. CONSTANS J, GERMAIN C, GOSSE P *et al*.: Arterial stiffness predicts severe progression

in systemic sclerosis: the ERAMS study. *J Hypertens* 2007; 25: 1900-6.
13. BOULON C, DEVOS S, MANGIN M *et al*.: Reproducibility of capillaroscopic classifications of systemic sclerosis: results from the SCLEROCAP study. *Rheumatology* (Oxford) 2017; 56: 1713-20.
14. MANGO RL, MATTESON EL, CROWSON CS, RYU JH, MAKOL A: Assessing Mortality Models in Systemic Sclerosis-Related Interstitial Lung Disease. *Lung* 2018; 196: 409-16.
15. INGEGNOLI F, ARDOINO I, BORACCHI P, CUTOLO M, EUSTAR CO-AUTHORS: Nailfold capillaroscopy in systemic sclerosis: data from the EULAR scleroderma trials and research (EUSTAR) database. *Microvasc Res* 2013; 89: 122-8.
16. GHIZZONI C, SEBASTIANI M, MANFREDI A *et al*.: Prevalence and evolution of scleroderma pattern at nailfold videocapillaroscopy in systemic sclerosis patients: Clinical and prognostic implications. *Microvasc Res* 2015; 99: 92-5.
17. MARKUSSE IM, MEIJS J, DE BOER B *et al*.: Predicting cardiopulmonary involvement in patients with systemic sclerosis: complementary value of nailfold videocapillaroscopy patterns and disease-specific autoantibodies. *Rheumatology* (Oxford) 2017; 56: 1081-8.
18. CUTOLO M, PIZZORNI C, TUCCIO M *et al*.: Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. *Rheumatology* (Oxford) 2004; 43: 719-26.
19. SULLI A, PIZZORNI C, SMITH V, ZAMPOGNA G, RAVERA F, CUTOLO M: Timing of transition between capillaroscopic patterns in systemic sclerosis. *Arthritis Rheum* 2012; 64: 821-5.
20. MUELLER M, GSCHWANDTNER ME, GAMPER J *et al*.: Relation of nailfold capillaries and autoantibodies to mortality in patients with raynaud phenomenon. *Circulation* 2016; 133: 509-17.
21. BOULON C, CONSTANS J: Letter by Boulon and Constans regarding article, «Relation of nailfold capillaries and autoantibodies to mortality in patients with Raynaud phenomenon». *Circulation* 2016; 133: e668.
22. SCUSSEL-LONZETTI L, JOYAL F, RAYNAULD J-P *et al*.: Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine* (Baltimore) 2002; 81: 154-67.
23. KAYSER C, SEKIYAMA JY, PROSPERO LC, CAMARGO CZ, ANDRADE LEC: Nailfold capillaroscopy abnormalities as predictors of mortality in patients with systemic sclerosis. *Clin Exp Rheumatol* 2013; 31 (Suppl. 76): S103-8.
24. TIEU J, HAKENDORF P, WOODMAN RJ, PATTERSON K, WALKER J, ROBERTS-THOMSON P: The role of nailfold capillary dropout on mortality in systemic sclerosis. *Intern Med J* 2018; 48: 517-23.
25. VASILE M, AVOUAC J, SCIARRA I *et al*.: From VEDOSS to established systemic sclerosis diagnosis according to ACR/EULAR 2013 classification criteria: a French-Italian capillaroscopic survey. *Clin Exp Rheumatol* 2018; 36 (Suppl. 113): S82-7.
26. AVOUAC J, LEPRI G, SMITH V *et al*.: Sequential nailfold videocapillaroscopy examinations have responsiveness to detect organ progression in systemic sclerosis. *Semin Arthritis Rheum* 2017; 47: 86-94.
27. BOULON C, BLAISE S, LAZARETH I *et al*.: Reproducibility of the scleroderma pattern assessed by wide-field capillaroscopy in subjects suffering from Raynaud's phenomenon. *Rheumatology* (Oxford) 2017; 56: 1780-3.
28. SMITH V, PIZZORNI C, DE KEYSER F *et al*.: Reliability of the qualitative and semiquantitative nailfold videocapillaroscopy assessment in a systemic sclerosis cohort: a two-centre study. *Ann Rheum Dis* 2010; 69: 1092-6.