EXTENDED REPORT

Do worsening scleroderma capillaroscopic patterns predict future severe organ involvement? a pilot study

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ABSTRACT

Objective Assessment of associations of nailfold videocapillaroscopy (NVC) scleroderma patterns ('early', 'active' and 'late') with future severe clinical involvement in a systemic sclerosis (SSc) population.

Methods Sixty-six consecutive patients with SSc according to the LeRoy and Medsger criteria underwent NVC assessment at baseline. Videocapillaroscopic images were classified into 'normal', 'early', 'active' or 'late' NVC pattern. Clinical evaluation was performed for nine organ systems (general, peripheral vascular, skin, joint, muscle, gastrointestinal tract, lung, heart and kidney) according to the disease severity scale of Medsger (DSS) at 18–24 months of follow-up. Severe clinical involvement was defined as category 2–4 per organ of the DSS.

Results NVC patterns were significantly associated with future severe, peripheral vascular/lung involvement at 18–24 months. The OR rose steadily throughout the patterns. The OR for future severe peripheral disease based on simple/multiple (correcting for disease duration, subset and medication) logistic regression was 2.49/2.52 (95% CI 1.33 to 5.43, p=0.003/1.11 to 7.07, p=0.026) for early, 6.18/6.37 for active and 15.35/16.07 for late NVC scleroderma patterns versus the normal NVC pattern. The OR for future severe lung involvement based on simple/multiple regression was 2.54/2.33 (95% CI 1.40 to 5.22, p=0.001/1.13 to 5.52, p=0.021) for early, 6.43/5.44 for active and 16.30/12.68 for late NVC patterns.

Conclusions This pilot study is the first demonstrating an association between baseline NVC patterns and future severe, peripheral vascular and lung involvement with stronger odds according to worsening scleroderma patterns. This may indicate a putative role of capillaroscopy as a biomarker.

INTRODUCTION

Systemic sclerosis (SSc) is a rare multisystemic connective tissue disease characterised by microvascular damage, fibrosis of the skin and internal organs and specific immunologic abnormalities. The clinical recognisable disease is classified on the basis of extent of skin involvement into subsets with diffuse cutaneous involvement (DcSSc) and limited cutaneous involvement (LcSSc).[1] The clinical expression and course of the disease may be coupled with serious morbidity and mortality. Moreover, as yet, there is no treatment that has proved through randomised controlled trials to halt the natural progression of the clinical recognisable disease. Consequently, eyes are geared to diagnose the disease 'early' before the clinical recognisable disease has set in. Part of the rationale behind this is to possibly be able to treat in a stage before certain complications of the disease appear. Consequently, effort is being put into the investigation of possible biomarkers (=biochemical markers or technological tools that may inform the clinical researcher of possible future disease or clinical complications). Capillaroscopy is a candidate possible biomarker. Next to its established role in the diagnosis of 'early' SSc, it would be optimal if this tool could also identify patients who would in future develop certain organ complications.[2–4] In 2000, Cutolo *et al* classified the progressive microangiopathic changes as assessed by nailfold videocapillaroscopy (NVC) of patients with SSc into the scleroderma patterns (early, 'active' and 'late') by pattern recognition (=qualitative assessment).[5]

In this regard, it was our aim to investigate in a pilot study whether the scleroderma patterns as assessed by NVC were indicative of future severe organ involvement.

Severity of organ involvement in Ssc may be evaluated robustly by the disease severity scale of Medsger which provides a scale with progressive categories 0–4 for nine organ systems (general, peripheral vascular, skin, joint, muscle, gastrointestinal tract, lung, heart and kidney).[6] For each of the nine organ systems the following research question was investigated in this pilot study: 'is there an association between baseline capillaroscopy patterns and future severe organ involvement?'

PATIENTS AND METHODS

Patients

Sixty-six consecutive patients with SSc (mean±SD age: 53±13.8 years, median disease duration 5 years with minimum–maximum range 0–37 years) according to the LeRoy and Medsger criteria visiting the Ghent University scleroderma Unit between December 2007 and October 2008 were enrolled. The patients were subsequently divided into LSSc (no skin involvement), LcSSc or DcSSc (skin involvement) according to LeRoy *et al*.[1] All patients signed informed consent which was approved by the local Ethical Committee.

Nailfold videocapillaroscopy

Collection and blinding of the NVC images

In short, the nailfold of the second, third, fourth and fifth fingers was examined bilaterally in each patient by using an optical probe videocapillaroscope

Table 1 Association between baseline NVC patterns and future (month 18–24) severe organ involvement (nine organ systems according to the DSS of Medsger)

	Not severe	Severe	p Value¶
General	52	6	0.700*
Peripheral vascular	34	24	0.003
Skin	52	6	0.352*
Joint/tendon	51	7	0.053*
Muscle	53	5	0.428*
GI-tract*	55	2	0.260*
Lung†	27	30	0.001
Heart‡	56	0	NA§
Kidney	57	1	0.253*

Future: visit at 18–24 months after the baseline capillaroscopic assessment.
Not severe: category 0–1 of the DSS of Medsger.
Severe: category 2–4 of the DSS of Medsger.
*Of one patient DSS GI-tract was missing.
†Of one patient DSS lung was missing.
‡Of two patients DSS heart was missing.
§Invalid model as there were no cases with severe heart involvement in the future.
¶Likelihood ratio p value based on logistic regression analysis with a dichotomous outcome measure of severity of future organ involvement associated with continuous baseline NVC patterns, unless too little events were present to support a linear effect on the ln(OR). In the latter cases, the LRT p values of a categorical NVC pattern covariate were reported (*).
DSS, disease severity scale; GI-tract, gastrointestinal tract; LRT, likelihood ratio; NA, not applicable; NVC, nailfold videocapillaroscopy.

equipped with a ×200 magnification contact lens and connected to image analysis software (Videocap, DS MediGroup, Milan, Italy). The images were made anonymous before being assessed. Four consecutive fields extending over 1 mm, in the middle of the nailfold, were studied per finger.[7]

Qualitative assessment of the NVC images

The following NVC definitions were used for the qualitative assessment of the NVC patterns. The 'early' NVC scleroderma pattern: the combination of few enlarged/giant capillaries, few capillary microhaemorrhages, a relatively well-preserved capillary distribution and no evident loss of capillaries. The 'active' NVC scleroderma pattern: frequent giant capillaries, frequent capillary microhaemorrhages, moderate loss of capillaries, mild disorganisation of the capillary architecture and absent or mild ramified capillaries. The 'late' NVC scleroderma pattern: irregular enlargement of the capillaries, few or absent giant capillaries and microhaemorrhages, severe loss of capillaries with large avascular areas, disorganisation of the normal capillary array and ramified/bushy capillaries. The 'normal' NVC pattern: a regular distribution of the capillaries without capillary loss and morphology without specific changes or aspecific changes.[8–10]

As SSc is recognised to be a progressive, obliterative microvasculopathic disease, the borders between the consecutive NVC patterns are delineated, in between others, by gradually more severe capillary loss.[11] To reflect this, the terminology 'worsening' NVC patterns was used throughout the manuscript.

SSC-specific antibody detection

Anticentromere and antitopoisomerase were detected by the INNO-LIA ANA Update (Innogenetics, Ghent, Belgium). Anti-RNA polymerase III and anti-PM/Scl were identified by the Systemic Sclerosis (Nucleoli) Profile Euroline (IgG) lineblot assay (Euroimmun, Lübeck, Germany).

Clinical measurements

Clinical evaluation was performed for nine organ systems (general, peripheral vascular, skin, joint, muscle, gastrointestinal tract, lung, heart and kidney) according to the disease severity scale of Medsger (DSS (scale with five categories: 0, 1, 2, 3 and 4)) at 18–24 months of follow-up.[6]

'Severe disease' for any organ system was defined starting from category 2 and up for each organ system as described previously.[12]

Statistical methods

Per organ system, the association between the NVC patterns and organ involvement was investigated by logistic regression analysis. In line with the small sample size of a pilot study, likelihood ratio p values were reported as these are appropriate to be reported when dealing with small sample sizes.[13] In line with the characteristic gradual capillary loss of the disease, reflected in the definition of the scleroderma patterns, a linear effect in the natural logarithmic OR was assumed when statistically meaningful. More specifically, we performed logistic regression analysis with a continuous nailfold NVC predictor variable. In those organ systems in which too little events (ie, future severe organ involvement) were available, we used the categorical NVC predictor variable as imposing a linear effect would not be statistically accurate in such cases. Statistical analyses were performed using IBM SPSS statistics V.19 (SPSS, an IBM company, Chicago, Illinois, USA) and R version 2.13.0 (R Foundation for Statistical Computing, 2011, Vienna, Austria).

RESULTS

Characteristics of the patients

The study group consisted of 66 patients (48 women, 18 men) who complied with the LeRoy and Medsger criteria.[1 2] The capillaroscopy criterion of the LeRoy and Medsger criteria was met by 57/66 patients. The nine patients who did not meet the capillaroscopic criterion all had SSc-specific antibodies.

The SSc-specific antibody criterion was met by 45/66 patients. Twenty-three were anticentromere positive, 14 were antitopoisomerase positive, seven were anti-RNA polymerase III positive, one was both anticentromere and antitopoisomerase positive and none were anti-PM-Scl positive.

In all, 19/66 patients were classified as LSSc, 34/66 as LcSSC and 13/66 as DcSSc.

The following medication was taken as peripheral vascular vasodilatory therapy at the time of NVC visit/follow-up visit: cyclic intravenous prostanoids in 13/15 patients and calcium channel blockers in 24/22 patients. No patients were on pulmovascular therapy: (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, intravenous or inhaled prostanoid therapy for pulmonary arterial hypertension) throughout the study. The following therapy changes took place throughout the study: start of peripheral vascular vasodilatory therapy in six and cessation in four patients.

Eight patients were lost to follow-up (see supplementary file 1).

Consequently, 58 patients were available for the future clinical visit 18–24 months after the baseline capillaroscopy.

Qualitative capillaroscopic assessment at baseline

Five patients (5/66=8%) had an early, 25 patients (25/66=38%) an active and 27 patients (27/66=41%) a late NVC scleroderma pattern. Nine patients (9/66=14%) had a normal NVC pattern.

Association between baseline NVC patterns and future severe organ involvement

Future severe organ involvement (visit at 18–24 months after baseline capillaroscopic assessment) of the nine organ systems according to Medsger is depicted in table 1.

Table 2 Association between baseline NVC pattern and future severe peripheral vascular involvement (at 18–24 months)

	Normal	Early	Active	Late	Total
Not severe*	7	4	14	9	34
Severe†	1	1	7	15	24
Total	8	5	21	24	58

p=0.003.
Future: visit at 18–24 months after the baseline capillaroscopic assessment.
***Not severe**: category 0–1 of the DSS of Medsger: category 0: patients with no Raynaud's and patients with Raynaud's not requiring vasodilators; category 1: patients with Raynaud's requiring vasodilators.
†**Severe**: category 2–4 of the DSS of Medsger: category 2: patients with digital pitting scars; category 3: patients with digital tip ulcerations; category 4: patients with digital gangrene.
DSS, disease severity scale; NVC, nailfold videocapillaroscopy.

Table 3 Association between baseline capillaroscopic pattern and future severe lung involvement (at 18–24 months)

	Normal	Early	Active	Late	Total
Not severe*	7	3	11	6	27
Severe†	1	2	10	17	30
Total	8	5	21	23	57‡

p=0.001.
Future: visit at 18–24 months after the baseline capillaroscopic assessment.
***Not severe**: category 0–1 of the DSS of Medsger: category 0: patients with DLCO 80%+; FVC 80%+; no fibrosis on radiograph; sPAP< 35 mm Hg; category 1: patients with DLCO 70–79%; FVC 70–79%; bibasilar rales; fibrosis on radiograph; sPAP 35–49 mm Hg.
†**Severe**: category 2–4 of the DSS of Medsger: category 2: patients with DLCO 50–69%; FVC 50–69%; sPAP 50–64 mm Hg; category 3: patients with DLCO<50%; FVC<50%; sPAP 65+ mm Hg; category 4: oxygen required.
‡Of one patient DSS lung was missing.
DLCO, diffusing capacity for carbon monoxide; DSS, disease severity scale; FVC, forced vital capacity; sPAP, systolic pulmonary arterial pressure.

A statistically significant and clinically meaningful association between baseline NVC patterns and future severe peripheral vascular involvement (p=0.003) and for future severe lung involvement (p=0.001) at 18–24 months was found. For the other organ systems the number of patients with 'severe' future organ involvement was low and a possible association was not detected in this study population.

For those organ systems for which a significant association was found the number of patients with severe future organ involvement is depicted along the NVC patterns in tables 2 and 3. For the other organ systems, the number of patients with severe future organ involvement along the NVC patterns is presented in the supplementary file 2.

Stronger OR for future severe peripheral vascular involvement according to worsening NVC scleroderma patterns

The number of patients with future severe peripheral vascular involvement rise according to worsening NVC pattern (table 2). In this way, 1/8 (=13%) of the patients with a normal pattern at baseline has a future severe peripheral vascular involvement, 1/5 (=20%) of the patients with an early pattern at baseline, 7/21 (=33%) of the patients with an active pattern at baseline and 15/24 (=63%) of the patients with a late NVC scleroderma pattern. In simple logistic regression analysis, the estimated OR, namely 2.49 (95% CI 1.33 to 5.43, p=0.003), to develop future severe peripheral organ involvement was stronger according to worsening NVC patterns. In this way, the OR for future severe peripheral vascular disease was 2.49 for the early, 6.18 for the active and 15.35 for the late NVC scleroderma pattern versus the normal pattern.

In a multiple logistic regression analysis, adjusting for disease duration, LeRoy subset and vaso-active medication, the OR, namely 2.52 (95% CI 1.11 to 7.07, p=0.026), for future peripheral involvement was also stronger according to worsening NVC patterns. In this way, the OR for future severe peripheral vascular disease was 2.52 for the early, 6.37 for the active and 16.07 for the late NVC scleroderma pattern versus the normal pattern.

Stronger OR for future severe lung involvement according to worsening NVC scleroderma patterns

The number of patients with future severe lung involvement rises according to worsening NVC pattern (table 3). In this way, 1/8 (=13%) of the patients with a normal pattern at baseline has a future severe lung involvement, 2/5 (=40%) of the patients with an early pattern at baseline, 10/21 (=48%) of the patients with an active pattern at baseline and 17/23 (=74%) of the patients with a late NVC scleroderma pattern.

In simple regression analysis, the estimated OR, namely 2.54 (95% CI 1.40 to 5.22, p=0.001), to develop future severe lung involvement was stronger according to worsening NVC patterns.

In this way, the OR for future severe lung disease was 2.54 for the early, 6.43 for the active and 16.30 for the late NVC scleroderma pattern versus the normal pattern.

In a multiple logistic regression analysis, adjusting for disease duration, LeRoy subset, and vaso-active medication, the OR, namely 2.33 (95% CI 1.13 to 5.52, p=0.021), for future severe lung involvement was also stronger according to worsening NVC patterns. In this way, the OR for future severe lung disease was 2.33 for the early, 5.44 for the active and 12.68 for the late NVC scleroderma pattern versus the normal pattern.

DISCUSSION

This pilot study is the first study to demonstrate an association between baseline NVC patterns and future severe organ involvement. More specifically, the number of patients having future severe peripheral vascular disease significantly differed according to baseline NVC pattern. In this way, 13% of patients with normal baseline NVC pattern, while 20%/33%/63% of patients with early/active/late scleroderma pattern developed future severe peripheral disease. Also, the number of patients having future severe lung involvement significantly differed according to baseline NVC patterns: 13% of patients with normal baseline NVC pattern, while 40%/48%/74% with early/active/late scleroderma pattern had future severe lung disease.

In addition, this study suggests that the odds rise according to worsening scleroderma patterns versus the normal pattern to develop future severe peripheral and future severe lung disease.

In this way, the odds to develop future severe peripheral vascular disease were 2.49/2.52 for the early versus the normal pattern, 6.18/6.37 for the active versus the normal pattern and 15.35/16.07 for the late versus the normal pattern on simple/multiple regression. In this way, the odds to develop future severe lung disease were 2.54/2.33 for the early versus the normal pattern, 6.43/5.44 for the active versus the normal pattern and 16.30/12.68 for the late versus the normal pattern on simple/multivariate regression. In particular, the most severe microangiopathy pattern on capillaroscopy, namely the late scleroderma pattern, had the highest ORs: 16.07 for future severe peripheral vascular disease and 12.68 for future severe lung disease.

These findings are logical as SSc is recognised to be a progressive, obliterative microvasculopathic disease as the borders between the consecutive NVC patterns are delineated, in between others, by gradually more severe capillary loss.

The fact that baseline NVC patterns are associated with future severe disease may be one of the first steps in positioning capillaroscopy as a welcome biomarker. If future studies validate this pilot study then capillaroscopy may be used to detect those patients who will develop severe disease and ultimately treat those patients preventively, before their complications set in.

Larger studies are warranted though. First of all, they should corroborate the findings of this pilot study. Second, these studies should investigate possible associations with other (than peripheral vascular and lung) severe organ involvement. As a matter of fact, our study did not detect associations with other severe organ involvement. This may be due to the fact that, as table 1 depicts, for the other (than peripheral vascular and lung) organ systems there were small numbers of patients with severe disease in this study population. Larger studies may elucidate on the one hand whether these possible associations do exist anyway and were not just revealed in our study (as it was underpowered), or on the other hand, whether these associations were in verum not there.

Third studies should further investigate the findings of this pilot study in more depth. In this way, the association between baseline NVC patterns and lung disease should be ideally subcategorised into interstitial lung disease and pulmonary (arterial) hypertension, in a well-defined, large prospective cohort. Of note, a post hoc analysis of our database shows that future interstitial lung involvement was present in 21/57 patients and was significantly (p=0.003) associated with baseline NVC patterns. In our database, no pulmonary arterial hypertension occurred in the patients studied.

Of note, next to predictive associations between clinical involvement and the qualitative (=pattern recognition: early, active and late scleroderma patterns) assessment of capillaroscopy, as attested in this pilot study, efforts have been recently also made to find predictive associations with quantitative (=counting of hallmark parameters of the scleroderma pattern). At this very moment, quantitative capillaroscopic assessment has found a definite place in research settings.[14 15] Its breakthrough to daily practice is eagerly awaited for.[12]

In conclusion: the quest for biomarkers is an ongoing topic of research in SSc. This pilot study is the first demonstrating an association between baseline NVC patterns and future severe, peripheral vascular and lung involvement. Moreover, it suggests stronger odds according to worsening scleroderma patterns. Consequently, this study may be regarded as a paramount step in positioning capillaroscopy as a possible biomarker.

Contributors FDeK, MC, ED, SD, AS and VS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study ideation: VS, MC, FDeK; study design: VS; acquisition of capillaroscopic data: VS; acquisition of serological data, more specific the SSc-specific antibodies for inclusion of SSc patients according to LeRoy: FDeK, CB; acquisition of clinical data: VS, YP; rater of capillaroscopic data: VS; database hygiene: SD; analysis and interpretation of data: VS, SD, ED, AS, FDeK, MC; manuscript preparation and finalisation: VS, SD, ED, AS, FDeK, MC. FDK and MC contributed equally to this work.

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Competing interests None.

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