Raynaud’s phenomenon: a mirror of autoimmune disease
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Abnormal nailfold capillaroscopy is common in patients with connective tissue disease and associated with abnormal pulmonary function tests

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ABSTRACT

Objective: To assess the presence of a systemic sclerosis (SSc) pattern on nailfold capillary microscopy (NCM) in patients with Raynaud’s phenomenon (RP) and explore its association with abnormal pulmonary function tests (PFT).

Methods: NCM patterns were assessed in 759 consecutive patients with RP. Patterns were classified as normal (n=354), non-specific (n=159), or SSc pattern (n=246). Abnormal PFT was defined as forced vital or diffusion capacity <70%.

Patients were classified as primary RP (n=245), or secondary: no definite diagnosis (n=391), SSc (n=40), primary Sjögren’s syndrome (pSS, n=30), systemic lupus erythematoses (SLE, n=30), mixed connective tissue disease (MCTD, n=7), rheumatoid arthritis (RA, n=15).

Results: An SSc pattern on NCM was frequently observed in most patients with a definite diagnosis: SSc 88%, pSS 33%, SLE 17%, MCTD 71%, RA 13%. In patients without definite diagnosis, 17% had a normal NCM pattern, 35% non-specific, and 48% SSc-pattern. Abnormal PFT was more frequent in patients with an SSc pattern (36% vs. 20%, p=0.002), even when corrected for SSc diagnosis (p=0.003). Absence of an SSc pattern had high negative predictive value (88%); positive predictive values were low.

Conclusion: SSc pattern on NCM is common in RP patients, also with connective tissue diseases other than SSc. It is associated with a higher prevalence of abnormal PFT, independent of the presence of an SSc diagnosis. Although these data need validation in a prospective setting, they underline the importance of NCM in RP and putative value to stratify the risk of pulmonary involvement in early stage of disease.
INTRODUCTION

Raynaud’s phenomenon (RP) can be primary (idiopathic), or secondary to an underlying connective tissue disease (CTD), most commonly systemic sclerosis (SSc). RP is the first presenting symptom in most SSc patients, other symptoms can occur up to years later. In secondary RP (SRP) nailfold capillary changes can be seen with nailfold capillary microscopy (NCM). This can help to differentiate between primary RP (PRP) and SRP in an early stage of the disease. These typical NCM findings are included in the classification criteria for SSc. Abnormal NCM has been shown to be associated with the presence and severity of internal organ involvement in SSc cohorts, and has even been suggested to predict mortality. A recent study shows an association between the presence of changes on NCM and the occurrence of cardiac/pulmonary involvement in SSc patients, independent of specific-antibodies.

NCM might be a supportive tool in CTDs other than SSc as well. However, in systemic lupus erythematoses (SLE), primary Sjögren’s syndrome (pSS), mixed connective tissue disease (MCTD), and rheumatoid arthritis (RA), NCM patterns and their value for these patients have been less well established. In small studies, NCM seems to be an indicator for organ involvement in MCTD. A recent review shows an association between abnormal NCM findings in SLE and disease activity. About 10% of pSS patients have SSc-like abnormalities on NCM. Twenty-one percent of the RA patients had SSc-like NCM abnormalities, although it is unknown how many of these patients experienced RP symptoms. Both in pSS and RA the association of NCM with any organ involvement is unknown. In all these CTDs pulmonary involvement can occur. Interstitial lung disease (ILD) is the most common type of pulmonary involvement in SSc, pSS, MCTD, and RA. This makes it important to find accurate biomarkers to detect this in an early stage. Assessment of NCM may facilitate awareness and early recognition of (SSc like) pulmonary involvement.

Our aim was to describe the presence of SSc patterns on NCM in a large cohort of consecutive patients with Raynaud’s phenomenon, visiting the vascular laboratory for NCM in our tertiary referral center, and to explore whether a possible association exists between NCM patterns and abnormal PFT.
PATIENTS AND METHODS

Consecutive patients with bi- or triphasic discoloration and/or discomfort of the hands provoked by cold, referred to the vascular lab for NCM, were included (n=961). All were examined for suspected RP by (vascular) internists and/or rheumatologists and underwent routine daily practice work-up, as described below. Patients visited the vascular lab between November 2008 and August 2013. NCM was performed by a standardized procedure, as described below. Clinical characteristics were collected between 2014 and 2016, two years or more following presentation. A different diagnosis, causing the discoloration or discomfort symptoms of the hands, was reported by the treating physician in 177 patients after the diagnostic work up, these patients were excluded. Twenty-five patients were excluded because capillaries were not assessable in any finger due to physical limitations (4 of these patients were diagnosed with SSc). In 759 patients RP was diagnosed, based on discoloration with at least 2 phases (white, blue and/or red) provoked by cold, or in case of diagnostic uncertainty RP was confirmed by a cooling procedure as described previously. The study was approved by the local ethics committee (Medisch Ethische Toetsingscommissie Groningen, The Netherlands, approval number METc 2016.305) and they provided exemption from written informed consent, given that the study does not fall under the Dutch law of medical research in humans.

Nailfold capillary microscopy (NCM)

NCM was carried out by widefield videocapillaroscopy with a 180x enlargement, as described previously. In short, NCM was performed at our vascular laboratory as a standardized procedure assessing the distal row of capillaries of the middle and ring finger (dig 3 and 4) of both hands. Figure 1 gives a visualization of how NCM images were taken and assessed.

Capillary loss was defined as <18 capillaries per 3mm nailfold per finger, severe capillary loss was defined as <9 capillaries per 3mm, in line with definitions of Cutolo et al. Giant capillaries and dilated capillaries were judged visually by the observer as typical SSc-like enlarged loops, for an example please refer to figure 1. The patterns, based on the patterns by Cutolo et al., were defined as follows: a normal pattern as no capillary loss, the mean number of dilated capillaries per finger was ≤3 and no giant capillaries.
Nailfold capillaroscopy and pulmonary function tests

Antinuclear antibodies (ANA), tested by indirect immunofluorescence, were measured. When they were present they were classified as speckled, homogenous, anti-centromere or nucleolar. Also extractable nuclear antigen antibodies (ENA) were tested by

Figure 1. Visualization of A. how nailfold capillary microscopy was performed with an Olympus BHMJ FW-32362 (Tokyo, Japan) set-up, with a Grundig FA-85 Z/W video camera (Fürth/Bay, Germany) and an Osram XBO 75W xenon lamp (Berlin, Germany) with 180 times enlargement and a 3mm width, B. a normal pattern, C. a non-specific pattern and D. an active pattern. The arrow indicates an example of dilated capillaries, # a hemorrhage and G giant capillaries.

were observed; a non-specific pattern as a mean number of >3 dilated capillaries or capillary loss in the absence of giant capillaries; an early pattern as ≥1 giant capillaries, without loss of capillaries or hemorrhages; an active pattern as ≥1 giant capillaries combined with capillary loss and/or hemorrhages; and a late pattern as severe loss of capillaries with none or few giant capillaries and none or few hemorrhages and signs of neovascularization.22

Clinical and laboratory characteristics

Antinuclear antibodies (ANA), tested by indirect immunofluorescence, were measured. When they were present they were classified as speckled, homogenous, anti-centromere or nucleolar. Also extractable nuclear antigen antibodies (ENA) were tested by
fluorescent enzyme immunoassay and specifically for U1-RNP, RNP70, Sm, SSA, SSB, Jo1, topoisomerase (Scl70) and CenpB. Serology was defined positive for ANA titer ≥1:80 and ENA ≥10 U/ml. Anti-centromere and Scl70 are defined as SSc specific autoantibodies.

Patients were classified as PRP if NCM was normal and serology was negative and no CTD was diagnosed during follow-up. If serology was not tested, it was presumed normal for the purpose of patient classification in this study (n=37). When not primary, patients were labeled SRP. Those patients were divided into groups with a definite diagnosis: SSc, pSS, SLE, MCTD or RA according to the classification criteria. Patients who did not meet any of the criteria were classified as having ‘no definite diagnosis’. Patients without a definite diagnosis were subdivided into early SSc, based on the LeRoy criteria, incomplete pSS (ipSS), when patients had 3 out of 4 American-European Consensus Group criteria for pSS, incomplete SLE (iSLE), when patients had 2 or 3 out of 4 Systemic Lupus International Collaborating Clinics criteria for SLE, undifferentiated CTD (UCTD), according to the proposed classification criteria of Mosca et al., and ‘other’ when not meeting any of these criteria. Patients in the group “others” are patients who have a non-specific pattern on NCM, but do not have any signs for a specific underlying disease. Because of the presence of a non-specific pattern on NCM these patients cannot be definitely classified as PRP, as was previously reported by Bernero et al., who demonstrated that 18% of the patients with non-specific changes on NCM progressed to an SSc pattern within the next five years. None were diagnosed with polymyositis or dermatomyositis. Figure 2 gives a schematic representation of this classification.

**Pulmonary involvement**

Potential pulmonary involvement was adjudicated using supplemental studies of PFT. These studies were performed in daily routine work-up of patients when deemed necessary by the treating physician based on clinical judgment or routine work-up.

An abnormal PFT was defined as the diffusion capacity of the lung for carbon monoxide (uncorrected for alveolar volume, DLCO) and/or forced vital capacity (FVC) <70%. If deemed necessary by the treating physician, HRCT and/or cardiac ultrasound were performed as additional tests. Definite pulmonary involvement was defined as an ILD, diagnosed by HRCT and judged by an experienced HRCT radiologist, or documented
Figure 2. Flowchart of patient diagnosis classification.


Suspected RP
n=961

Primary RP
n=245

No definite diagnosis
n=392

Early SSc
n=195
LeRoy criteria

ipSS
n=5
3/4 AECG criteria

iSLE
n=42
2 or 3/4 SLICC criteria

No RP
n=759

Secondary RP
n=514

NCM not assessable
n=25

Definite diagnosis
n=122
SSc
n=40
ACR/EULAR criteria

pSS
n=30
AECG criteria

SLE
n=30
SLICC criteria

MCTD
n=7
Criteria by Kasuwaka et al.

Other
n=109

Criteria by Mosca et. al.

Not meeting any of the criteria
pulmonary hypertension (PH) by mean pulmonary arterial pressure ≥25 mmHg at rest measured by right heart catheterization.\textsuperscript{30,31}

Statistics
Statistical analysis was carried out using IBM SPSS Statistics version 23. Data are described as mean ±SD, median (IQR) or number (percentage). Differences between group were tested by T-test, for normally distributed continuous data, Mann-Whitney U test, for other continuous data, or Chi-Square or Fisher’s exact test, for binomial values. Binary logistic regression was conducted with DLCO and/or FVC<70% as dependent variable and corrected for cofounders (such as age, gender, length and weight) and presence of SSc diagnosis. Values of p<0.05 were considered statistically significant Positive and negative predictive value (PPV and NPV) were calculated.

RESULTS
The total population of patients included in the analysis was 759. In figure 2, a flowchart of patient classification is given, demonstrating 245 (32%) patients with PRP, and 514 (68%) SRP of which 122 (24%) with a definite diagnosis, and 392 (76%) without definite diagnosis. All 40 SSc patients had limited cutaneous SSc. Patient characteristics are given in table 1. A normal NCM pattern was found in 354 (47%) patients, non-specific in 159 (21%), SSc pattern in 246 (32%) including early 139 (18%), active 107 (14%), and a late pattern was not present in any of the patients. PRP and SRP patients did not differ in age (p=0.862); in the SRP group female gender was more prevalent than in PRP (p=0.006). None of the patients had a history of SSc renal crisis or myositis.

NCM pattern per patient diagnosis
In table 2 the NCM patterns and PFT are outlined per patient diagnosis. In SRP patients without a definite diagnosis, a specific SSc pattern was observed in 189 (48%; early 115 [29%], active 74 [19%], late not observed). The percentage of a specific SSc pattern was similar in patients with a definite diagnosis, with a higher percentage of an active pattern.
As expected, in most SSc patients (35; 88%), an SSc pattern was observed and in 189 (97%) patients with early SSc. Additionally, an SSc pattern was also observed in a considerable proportion of the other patients with a definite diagnosis: 10 (33%) of the patients with pSS, 5 (17%) SLE, 5 (71%) MCTD, 2 (13%) RA. None of the ipSS and iSLE patients had an SSc pattern (table 2). pSS and SLE patients with an SSc pattern on NCM did not differ on their clinical characteristics from patients without an SSc pattern. For example, in pSS patients the NCM pattern did not differ between those with positive and negative anti-SSA/SSB antibodies or positive and negative salivary gland biopsy. They did not have other SSc-like symptoms, except one SLE patient who had puffy fingers. Furthermore, the 5 SLE patients with glomerulonephritis did not have an SSc pattern. Hematological abnormalities (leukocytopenia, anemia, thrombocytopenia) and serositis were not associated with an SSc pattern. U1-RNP autoantibodies were also not related to any NCM pattern.

### Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>PRP patients</th>
<th>SRP patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>759</td>
<td>245</td>
<td>514</td>
</tr>
<tr>
<td>Age (years), mean ±SD</td>
<td>42.5 ±17.4</td>
<td>41.6 ±17.9</td>
<td>42.9 ±17.1</td>
</tr>
<tr>
<td>Female gender, n(%)</td>
<td>555 (73)</td>
<td>167 (68)</td>
<td>388 (76)</td>
</tr>
<tr>
<td>Positive serology* (ANA titre≥1:80), n(%)</td>
<td>254 (33)</td>
<td>0 (0)</td>
<td>256 (50)</td>
</tr>
<tr>
<td>SSc specific autoantibodies*, n(%)</td>
<td>44 (6)</td>
<td>0 (0)</td>
<td>44 (9)</td>
</tr>
<tr>
<td>Puffy fingers or sclerodactyly, n(%)</td>
<td>43 (6)</td>
<td>0 (0)</td>
<td>43 (8)</td>
</tr>
</tbody>
</table>

**Nailfold capillary microscopy**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>PRP patients</th>
<th>SRP patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, n(%)</td>
<td>354 (47)</td>
<td>245 (100)</td>
<td>109 (21)</td>
</tr>
<tr>
<td>Non-specific, n(%)</td>
<td>159 (21)</td>
<td>0 (0)</td>
<td>159 (31)</td>
</tr>
<tr>
<td>Early, n(%)</td>
<td>139 (18)</td>
<td>0 (0)</td>
<td>139 (27)</td>
</tr>
<tr>
<td>Active, n(%)</td>
<td>107 (14)</td>
<td>0 (0)</td>
<td>107 (21)</td>
</tr>
<tr>
<td>Late, n(%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Pulmonary involvement**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>PRP patients</th>
<th>SRP patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal pulmonary function test, n(%)</td>
<td>81 (11)</td>
<td>4 (2)</td>
<td>75 (15)</td>
</tr>
<tr>
<td>ILD, n(%)</td>
<td>17 (2)</td>
<td>0 (0)</td>
<td>17 (3)</td>
</tr>
<tr>
<td>PAH, n(%)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

*Used as criteria to classify as PRP or SRP

*S Anti-centromere and topoisomerase (Scl70)

Table 2. Nailfold capillary microscopy and pulmonary function per patient diagnosis group

<table>
<thead>
<tr>
<th>NCM patterns</th>
<th>Primary RP</th>
<th>No definite diagnosis</th>
<th>Secondary RP</th>
<th>Definite diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Early SSc</td>
<td>ipSS</td>
<td>iSLE</td>
</tr>
<tr>
<td></td>
<td>n=245</td>
<td>n=195</td>
<td>n=5</td>
<td>n=42</td>
</tr>
<tr>
<td>Normal</td>
<td>245 (100)</td>
<td>4 (2)</td>
<td>4 (80)</td>
<td>31 (74)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>1 (20)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Early</td>
<td>0 (0)</td>
<td>115 (59)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Active</td>
<td>0 (0)</td>
<td>74 (38)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NCM specifics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillaries per 3mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per finger</td>
<td>23.3 (21.7-24.5)</td>
<td>21.0 (18.5-23.0)</td>
<td>23.5 (22.8-24.5)</td>
<td>22.8 (21.0-24.0)</td>
</tr>
</tbody>
</table>

Number of patients with:
- Giant capillaries: 0 (0) 188 (97) 0 (0) 0 (0) 0 (0) 35 (88) 10 (33) 5 (17) 5 (71) 2 (13)
- Loss of capillaries: 0 (0) 37 (19) 0 (0) 1 (2) 0 (0) 9 (8) 15 (40) 2 (7) 4 (14) 2 (29) 1 (7)
- Hemorrhages: 13 (5) 44 (23) 0 (0) 4 (10) 2 (5) 11 (10) 13 (32) 3 (10) 3 (10) 2 (29) 2 (13)

PFT
- Abnormal PFT: 4 (2) 27 (14) 0 (0) 6 (14) 3 (8) 3 (2) 18 (45) 4 (13) 7 (23) 3 (43) 2 (13)
- DLCO<70%: 4 (2) 27 (14) 0 (0) 6 (14) 2 (5) 3 (2) 14 (35) 4 (13) 6 (20) 1 (14) 0 (0)
- FVC<70%: 0 (0) 2 (1) 0 (0) 1 (2) 1 (3) 0 (0) 3 (8) 0 (0) 3 (10) 1 (14) 1 (7)

Data in n(%) or median (IQR)

**DLCO:** diffusion capacity of the lung for carbon monoxide, **FVC:** forced vital capacity, **iSLE:** incomplete SLE, **ipSS:** incomplete SS, **MCTD:** mixed connective tissue disease, **NCM:** nailfold capillary microscopy, **PFT:** pulmonary function tests, **pSS:** primary Sjögren’s syndrome, **RA:** rheumatoid arthritis, **RP:** Raynaud’s Phenomenon, **SLE:** systemic lupus erythematoses, **SSc:** systemic sclerosis, **UCTD:** undifferentiated connective tissue disease.
Pulmonary involvement and NCM pattern

The relation between NCM pattern and PFT is outlined in figure 3. In 293 of all the RP patients PFT were performed, of which 265 were classified as SRP. Patients with abnormal PFT were older (p<0.001) but did not differ in sex, length or weight. When analyzing the SRP patients, an abnormal PFT was more frequently observed in patients with an SSc pattern on NCM (figure 3). When corrected for age and the presence of the diagnosis of SSc, this relation remained significant (p=0.003). An abnormal PFT was still more frequently observed in SRP patients with an SSc pattern on NCM, when analyzing only those patients in whom serology was performed (p=0.007). Pulmonary involvement is outlined per patient diagnosis in table 2.

Figure 3. Abnormal pulmonary function test and nailfold capillaroscopy in secondary Raynaud’s phenomenon patients.
In addition to the NCM pattern, the presence of giant capillaries was more frequently observed in patients with abnormal PFT (figure 3), also when corrected for SSc (p=0.003). No relation was found with capillary loss or dilated capillaries; thus a non-specific pattern is, therefore, not related to an abnormal PFT.

A definite diagnosis of ILD was made in 17 patients, and one patient was diagnosed with PH. Of these patients with ILD, 8 were diagnosed with SSc, 1 SLE, 2 MCTD, 1 RA, 3 early SSc and 2 iSLE. The patient with PH was diagnosed with pulmonary arterial hypertension (PAH) associated with SSc. In these 18 patients, an SSc pattern was prevalent [normal 4 (22%), non-specific 2 (11%), early 5 (28%), active 7 (39%)].

In all patients with SRP, the negative predictive value (NPV) and positive predictive value (PPV) of positive serology was 82% and 35% for predicting an abnormal PFT. The NPV and PPV of abnormal NCM for predicting abnormal PFT was 70% and 47% respectively. When combining positive serology with abnormal NCM, the NPV and PPV increased to 88% and 46%. The NPV and PPV for abnormal PFT in the patients with SRP without a definite diagnosis (early SSc, iSLE, ipSS, UCTD and “other”) for NCM only is 84%, and 30%, respectively; for NCM and serology combined is 92% and 41% respectively.

**DISCUSSION**

To our knowledge, this is the largest study, in an academic referral center daily practice cohort, showing that SSc-like abnormalities on NCM are common in patients with SRP, even in those without a definite CTD diagnosis. Moreover, we observed that a relation existed between an SSc pattern on NCM and the presence of abnormal PFT, indicating potential pulmonary involvement, in unselected and consecutive patients with and without a CTD. This suggests that an SSc pattern is an important proxy for a first assessment of SSc-like pulmonary involvement in early stages of disease. Also, the high NPV of NCM combined with serology for PFT abnormalities in our cohort underlines the potential usefulness of NCM as a simple screening tool in all patients who present with RP in a referral care setting.
The percentages of patients with pSS, SLE and MCTD in whom an SSc pattern was found on NCM were in line with previous findings. Only for the RA patients, the percentage of patients with an SSc pattern on NCM was lower than expected. In previous studies the presence of SSc-like abnormalities on NCM in SLE patients seems to be related to the presence of U1-RNP auto-antibodies, suggesting an overlap syndrome with SSc. Also moderate/severe changes on NCM were more frequently observed in patients with pulmonary, cardiac or renal involvement, even when no relation was found with any cutaneous manifestations. In our cohort there was only 1 SLE patient with an SSc pattern who presented with puffy fingers, there were no other with SSc symptoms. Additionally we did not find a relation with U1-RNP autoantibodies and an SSc pattern on NCM in SLE patients as described.

PFTs are widely used to assess potential pulmonary involvement, as decreased DLCO and FVC have been shown to predict pulmonary involvement and are associated with the extension of ILD. Markusse et al. found NCM to have a NPV and PPV of 60% and 64% for decreased DLCO (<70%), in a group of SSc patients. In our SRP patients, including SSc but other CTDs as well, we found a somewhat higher NPV of 70% and a lower PPV of 47% for decreased DLCO and/or FVC (<70%). The addition of FVC does not explain this difference, since only 5 patients in our study presented with decreased FVC without decreased DLCO, out of 81 with abnormal PFT. A possible explanation of the discrepancy with the results of Markusse et al. in NPV and PPV might be the difference in classification of an early pattern, we defined it as SSc pattern, while Markusse et al. chose to define it as normal because of low numbers. Our study shows that when an early pattern on NCM is classified as normal, patients with pulmonary involvement might be missed. We only found an association between SSc pattern and giants on NCM with abnormal PFT, and could therefore not confirm the association between PFT and loss of capillaries as described by Castellví et al., although their cohort consisted of only SSc patients. Furthermore, our cohort consisted of patients mainly at an early stage of disease. None of these patients had a late pattern on NCM, therefore there was only little variation in capillary count. This limited diversity in capillary loss might be why no association existed between capillary loss and PFT.

NCM is a method to assess microvasculopathy in patients, which is thought to play an important role in the pathophysiology of SSc. Microvasculopathy and fibrosis are
both central features of SSc. Although an abnormal NCM is clearly a representation of microvasculopathy, an abnormal PFT could be the expression of similar underlying pathology which cannot be readily visualized in vivo. Although preliminary, this could be an explanation of the association we found between an SSc pattern on NCM and abnormal PFT. This theory is strengthened by the study of Bredemeier et al., where ground-glass opacities on HRCT in SSc patients were associated with avascular areas on NCM. Also the study of Smith et al. shows that NCM may predict novel future organ involvement in SSc patients, further studies are needed, especially for other CTDs.

**Limitations**

Because this is a study with data collected from daily practice, the main limitation of this study is a relatively high percentage of missing data, especially in patients with mild disease or those deemed to have PRP. For example, the modified Rodnan skin score was not routinely performed at the time of patient recruitment and could, therefore, not be included in the analysis. Cardiac ultrasounds were not routinely performed, hence, subclinical cardiac involvement could not be assessed. As the data were derived from daily practice, only 54 patients had an HRCT of which 18 patients had definite pulmonary involvement (ILD or PAH). This group was too small and biased to study the association between definite pulmonary involvement and NCM.

Furthermore, abnormal PFT is not always a result of pulmonary involvement, as smoking behavior and other lung diseases can decrease FVC and/or DLCO as well. However, in our current study we were unable to take these variables into account due to the missing data. Nevertheless, because patients with a normal PFT are very unlikely to have pulmonary disease, the high negative predictive value still is an accurate representation.

With the used NCM set-up it was not possible to measure the exact width of the capillaries. Therefore, the definition of giant capillaries, because of the typical appearance, was more accurate than judging dilatation only. An early or active pattern was defined by the presence of only 1 giant capillary, which could possibly lead to an overestimation of abnormal NCM findings. Follow-up would be needed to verify this. Also, initial NCM is usually performed at an early stage of the disease when a late pattern is unlikely to be present. During the period of patient recruitment it was customary at our hospital to only assess 4 fingers, instead of the more extensively used assessment of
8 fingers. Boulon et al. found that there was no difference in inter-observer agreement between examining all fingers or only the left ring finger for establishing the NCM pattern. Although the results do suggest that the left ring finger gives the same results as all fingers in terms of pattern, it was not the main objective of the study. As their method is not completely appropriate to draw this conclusion, it remains unsure if assessment of less than 8 fingers influences the outcome of the overall pattern classification.

**Conclusion**

In conclusion, an SSc pattern on NCM is common in patients with RP secondary to CTD, even in patients with other CTDs than SSc. This shows that not only SSc patients can develop this microvasculopathy, but other CTD patients with RP as well. An SSc pattern on NCM appears to be associated with a higher prevalence of abnormal PFT, even corrected for the presence of an SSc diagnosis. We found that, with a high NPV, NCM when combined with serology can help to identify patients at low risk of having an abnormal PFT. These data underline the potential importance of assessing NCM, a cheap and non-invasive tool, in all patients with RP referred to secondary or tertiary care to evaluate the risk for potential pulmonary involvement in the early stages of the disease.
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Nailfold capillaroscopy and pulmonary function tests


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