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Evolving symptoms of RP in SSc

Evolving symptoms of Raynaud's phenomenon in systemic sclerosis are associated with physician and patient-reported assessments of disease severity

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Abstract (250 words)

Objectives: Assessment of Raynaud's phenomenon (RP) in systemic sclerosis (SSc) is reliant on self-report. The Raynaud's Condition Score (RCS) diary assumes discrete episodic RP attacks, although not all SSc patients identify with this paradigm. We investigated the clinical associations of SSc-RP symptom characteristics and evolution of SSc-RP symptoms with disease progression.

Methods: A cross-sectional study at UK and US sites captured digital colour changes of SSc-RP and patient's ability to identify with diagrammatic representations (and descriptive stems) of four distinct theoretical SSc-RP patterns (progressing severity through A-D) reflecting progressively severe SSc-RP experiences. SSc-RP self-management and symptom evolution were explored. Patient demographics, clinical phenotype, scleroderma Health Assessment Questionnaire (SHAQ), the 2-week RCS diary and patient and physician global assessments were collected.

Results: We enrolled 107 SSc patients (questionnaires returned by 94). A higher number of self-reported digital colour changes of SSc-RP were associated with increased SSc-RP symptom severity but not SSc clinical phenotype. Patients could identify with distinct patterns of SSc-RP. These patterns were associated with disease duration, global disease severity and conceptually-linked physician and patient assessments of peripheral vascular severity (e.g. SHAQ RP subscale and RCS diary parameters), but not conceptually unrelated outcomes (e.g. SHAQ Breathing subscale). SSc-RP characteristics and symptom severity evolve during the disease course.

Conclusions: Patients identify with distinct patterns of SSc-RP that may relate to progression of the obliterative microangiopathy of SSc. Difficulty distinguishing discrete SSc-RP attacks from persistent digital ischaemia in advanced SSc could influence diary-based approaches to assessing SSc-RP with implications for clinical trials.

Significance and Innovation

- Patients with SSc can identify with distinct patterns of RP symptoms that may reflect progression of the obliterative microangiopathy of SSc.
- The evolution of RP symptom burden in SSc reflects a complex inter-relationship between progression of the peripheral vasculopathy and successful patient adaptation
- RP symptom characteristics in SSc are not adequately reflected in existing outcome measures for assessing RP severity in clinical trials

Key Words

Raynaud's phenomenon, systemic sclerosis, patient reported outcomes, outcome measures, clinical trials

Raynaud's phenomenon (RP) is the term used to describe episodic excessive vasoconstriction of the digital microvasculature in response to cold exposure and/or emotional stress (1). RP is a major cause of disease-related morbidity in systemic sclerosis (SSc) (2-4). SSc-RP is associated with digital color changes reflecting the perfusion and oxygenation of affected tissues (1). The episodic nature of RP precludes useful assessment in the clinical setting and has led to a reliance on patient self-report. Classification (and diagnosis) of RP generally requires the presence of bi-phasic digital color changes (5-7). The assessment of RP symptoms can be undertaken using self-reported patient questionnaires with or without the aid of colour charts demonstrating the appearances of the digits during RP attacks (7, 8). A previous study reported uni-phasic digital color changes of RP in over half of patients with SSc could have implications for disease classification (9). The relationship between specific digital color changes and clinical phenotype has not previously been explored but could provide a readily available tool in the clinical setting (3, 4). Assessment of SSc-RP severity is also reliant on patient-reported outcome (PRO) instruments such as the Raynaud's Condition Score (RCS) diary. The 2-week RCS diary collects information on the frequency, duration and severity/impact of SSc-RP attacks (10). SSc-RP attack frequency is frequently the primary endpoint in SSc-RP clinical trials (11, 12). The RCS diary assumes a paradigm of discrete attacks of SSc-RP in which patients are cognizant of the emergence and abatement of symptoms. Consistent with other clinician-derived PRO instruments developed at the time, there was no direct patient involvement in the development of the RCS diary (13). Recent work examining the patient experience of SSc-RP and patient perceptions of the RCS diary suggests patients conceptualize SSc-RP in a more nebulous fashion that incorporates both discrete exacerbations on a background of more persistent digital ischemia (4, 14). Indeed some patients report difficulty knowing what an "attack" of SSc-RP represents (4, 14). These experiences are consistent with the recognized progressive obliterative microangiopathy of SSc and might explain the poor agreement between RCS diary parameters and non-invasive

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microvascular imaging assessments of digital microvascular function (15, 16). No previous studies have examined whether different patterns of RP exist in SSc, and whether RP symptoms evolve with disease progression. The Raynaud's Symptom Study (RSS) is a multi-center longitudinal study designed to assess the nature and determinants of RP symptoms in SSc. The present report focuses on the potential clinical associations of digital color changes of RP in SSc, self-management of SSc-RP symptoms, the presence of distinct patterns of SSc-RP and possible evolution of RP symptoms throughout the disease course.

Patients and Methods:

Patients

SSc patients fulfilling the 2013 ACR/EULAR classification criteria for SSc (6) were enrolled from SSc clinics held in Bath, UK and Salt Lake City, US at routine clinical care visits between April 2015 and January 2017. The study had ethical approval at both sites and all participants provided informed written consent.

Patient questionnaires

Participants were issued with a pack containing the RSS questionnaire and a RCS diary. The first section of the RSS questionnaire focused on RP symptoms including digital colour changes, body parts affected, presence of numbness, non-thermal triggers and self-management approaches (supplementary material available online). A history of white, blue, red and purple digital discolouration was captured in accordance with earlier work examining the specific self-reported digital colour changes used to diagnose/classify RP (7, 8)). Patients were subsequently classified as having uni-, bi-, tri- or quadri-phasic digital colour changes on the basis of the number of digital colour changes reported. Diagrammatic representations and descriptive stems of four theoretical SSc-RP patterns (A-D) were presented to the participants (Figure 1). These theoretical patterns of SSc-RP were developed using

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experiences described by people with SSc and primary RP during instruction on completion of the RCS diary in an earlier study (16). It was during this work that many patients expressed difficulty completing the RCS diary because of difficulty differentiating RP attacks from background persistent digital ischaemia. The resulting images (and accompanying stems) were reviewed and refined with support from patient research partners affected by SSc-RP to ensure good comprehension. The 4 SSc-RP patterns describe symptoms of increasing severity (A through to D); with progressively greater amounts of time spent experiencing RP features (pain, numbness and discolouration) when symptomatic. Patterns C and D describe a symptom state in which the fingers feel cold with poor blood supply the majority of the time and rarely return to feeling normal (with difficulty identifying attacks of Raynaud's from background digital ischaemia). Participants were presented with the images/stems and asked to indicate which pattern best described their SSc-RP symptoms currently and at the time their SSc-RP symptoms first emerged. SSc-RP symptom evolution over the disease course was further explored using direct questioning. Participants completed existing 100mm visual analogue scales (VAS) for patient global assessment, DU severity, SSc-RP severity alongside the Scleroderma Health Assessment Questionnaire (SHAQ) and its disease-specific 150mmVAS subscales (17). Patients were issued with the 2-week RCS diary alongside instructions for completion. Participants returned the completed questionnaire and RCS diary. The RCS diary was used to calculate the mean daily RCS (a 0-10 numeric rating scale assessing the overall impact/severity of RP symptoms on each day of diary collection), mean daily frequency of RP attacks and mean daily duration of RP attacks over the course of the 2-week RCS diary collection (10). Each of the RCS diary parameters were only calculated provided a minimum of 10 days (of 14) of the diary had been completed satisfactorily.

Clinician case report form (CRF)

A clinician CRF collected information on patient demographics (age, gender, ethnicity, disease duration based on time since 1st non-RP symptom), smoking history, clinical

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phenotype and autoimmune serology. The clinical phenotype sought documented evidence from the case notes of gastro-esophageal reflux disease (GERD) symptoms, puffy fingers, sclerodactyly, digital ulcers (DU), digital pitting (DP), telangiectases, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) and autoantibody specificity; using definitions described in the 2013 ACR/EULAR classification criteria for SSc (6). Patients were sub-classified according to limited versus diffuse cutaneous SSc according to standard practice (18, 19). Relevant co-morbidities and vasoactive medication use were documented. Physicians completed 100mm VAS scores physician global assessment, RP severity and DU severity.

Statistical analysis

Descriptive statistics were applied and shall be defined were applicable. The Chi square test was used to compare observed frequencies across two or more categories. The unpaired t-test was used to compare distributions of continuous data when examining demographic data from the Bath and Utah cohorts. One way ANOVA or Kruskal-Wallis tests were applied to examine distribution of data across three or more independent samples as appropriate.

Logistic regression models were used to compare observed frequencies across categories of digital colour changes, which are not mutually exclusive. This was an explorative study with multiple comparisons. In an effort to avoid overlooking relevant signals, we chose not to apply a formal Bonferroni correction but we have been cautious in our interpretation of the significance of sporadic associations and only drawn conclusions where multiple comparisons lead to consistent positive associations.

Results:

One hundred and seven SSc patients were enrolled to the RSS (57 in Bath and 50 from Utah). Ninety-four patients (82 female, 14 patients with diffuse cutaneous SSc) returned completed questionnaires. The patient demographics and clinical phenotype of the participants are

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presented in Table 1. The clinical phenotype of the two cohorts were similar, although patients from Bath were older (65.1 vs. 56.4 years, $p<0.001$), had a higher age at diagnosis (54.6 vs. 47.3 years, $p=0.02$) and higher use of ACE inhibitors/Angiotensin II antagonists ($p=0.02$, Table 1). The reported prevalence of GERD (82% vs. 98%, $p=0.01$) and history of digital ulcer (DU, 43% vs. 68%, $p=0.02$) was higher in the Utah cohort.

Digital color changes

Virtually all patients reported digital color changes related to their SSc-RP (92/94, 98%). Digital color changes were typically related to cold exposure, although 47 patients (50%) reported color change or numbness at normal temperature in response to emotional stress. The individual fingers were affected equally (90%-98%) but there was relative sparing of the thumbs (58/94, 62%). Similarly, the toes (63/94, 67%), nose (26/94, 28%) and ears (18/94, 19%) were less often affected by SSc-RP. No patients reported involvement of the nipples. The commonest reported digital color change was white (81/94, 86%), followed by purple (72/94, 77%), blue (69/94, 73%) and red (68/94, 72%). Over half of patients (48/94, 51%) reported quadri-phasic color changes, with smaller numbers reporting tri-phasic (20/94, 21%), bi-phasic (14/94, 16%) and monophasic RP (only 10/94, 11%; the majority of whom reported isolated blanching [6/10]). A significant association was identified between the number of phases and the RCS with higher median “mean RCS score” for quadri-phasic RP (median 3.0 [inter-quartile range (IQR) 1.0-4.9]), compared to tri-phasic (1.7 [0.6-7.1]) and bi-phasic (0.5 [0.2-2.9]) SSc-RP symptoms ($p=0.006$). A similar relationship was identified for the number of digital color changes and both the median “mean frequency of attacks” (medians 2.1 [quadri-phasic], 1.5 [tri-phasic] and 0.3 [bi-phasic] respectively, $p<0.001$) and median “mean daily duration” of attacks (33.2, 12.3 and 5.4 respectively, $p=0.008$). There was no relationship between digital color changes and individual components of the SHAQ. The only associations between patient demographics/clinical phenotype and either individual

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digital color changes reported or the number of reported digital color changes were an association between telangiectases and number of phases of RP ($p=0.033$) and the presence of sclerodactyly in patients reporting digital cyanosis ($p=0.044$). These sporadic associations are likely to be the consequence of statistical issues concerning multiple testing and quasi-complete separation respectively rather than clinically meaningful associations (data not reported).

Self-management of SSc-RP

Virtually all patients reported wearing layers of clothes to keep warm (89/94, 95%) and carrying gloves (81/94, 86%) to avoid attacks of SSc-RP. The majority of participants reported using hand warmers (67/94, 71%), seeking help from others (e.g. getting food from the fridge/freezer) (49, 52%) and avoiding going out when cold (65, 69%) as additional methods of avoiding SSc-RP symptoms. Many respondents reported using hand warmers (51/94, 54%) to ameliorate SSc-RP symptoms but a greater percentage reported submerging their hands in warm water (72/94, 77%). The majority of patients reported feeling better able to avoid SSc-RP attacks (48 [51%] participants agree/strongly agree vs. 22 [23%] disagree/strongly disagree) and shorten SSc-RP attacks (with 44 [47%] agree/strongly agree vs. 19 [20%] disagree/strongly disagree) over time.

Patterns of SSc-RP

Ninety-three (99%) of respondents could identify with a pattern of SSc-RP that corresponded to their current experience of SSc-RP. The majority of patients (44%) identified pattern B as being most representative of their current SSc-RP symptoms with 17% of subjects identifying with patterns C or D (Table 2). Ninety-two patients were able to identify with a pattern of SSc-RP that corresponded to their experience of SSc-RP at the time their symptoms first emerged (Table 2, Row 2). More patients identified with pattern A when their SSc-RP

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symptoms first emerged than currently (50/92 vs. 36/93, $p=0.04$) and the observed frequencies within each pattern appears to have evolved over time ($p=0.08$, Table 2). Indeed, there was a strong signal to suggest greater disease duration in patients identifying with progressive SSc-RP patterns ($p=0.05$, Table 2). Overall, 28 patients (30%) reported advancement of the SSc-RP pattern over time; with 44 (48%) reporting a static pattern (this group also had a shorter mean disease duration) and 20 (22%) reporting an improvement in SSc-RP pattern. Participants reporting progression of the SSc-RP pattern were found to have higher RCS diary parameters ($p<0.005$) and a higher SHAQ RP VAS ($p=0.001$) than those whose SSc-RP remained static or improved (data not shown).

Statistically significant associations were identified between reported SSc-RP patterns and conceptually-linked physician and patient assessments of peripheral vascular severity (e.g. physician RP VAS [$p=0.007$], SHAQ RP VAS [$p<0.001$] and the RCS diary parameters [$p<0.005$ for all], Table 2). Significant associations were also identified between SSc-RP patterns and both patient ($p=0.002$) and physician ($p=0.02$) global VAS assessments. There was no association between SSc-RP patterns and conceptually unrelated outcomes such as the SHAQ breathing VAS ($p=0.27$, Table 2), although associations were found with the SSc-RP patterns and the SHAQ GI VAS scores.

Evolution of SSc-RP symptoms over time

The cohort was evenly split with respect to whether SSc-RP symptoms had evolved over the course of the disease. Thirty-six participants (38%) reported worsening of their SSc-RP over time, whereas 22 (23%) felt there had been an overall improvement, with the remaining 36 (38%) patients reporting their symptoms as stable (or undecided). Most participants (43/94, 46%) reported an increase in the frequency of SSc-RP episodes, whereas 20 (21%) respondents felt they had become less frequent and the remaining 31 (33%) felt the frequency was unchanged (or undecided). Similarly, the duration/length of SSc-RP episodes was

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reported as increased in 39 (41%), decreased in 20 (21%) and unchanged in the remaining 35 (37%) participants. A similar distribution was found for evolving severity of SSc-RP episodes (36 [38%] worse, 20 [21%] better and 38 [40%] the same). Consistent with the aforementioned patterns of RP, a significant number of participants (21, 22%) reported finding it harder to distinguish SSc-RP attacks from background digital ischemia. The majority of patients (35, 37%) were undecided whether or not their SSc-RP medications were working better as their disease advanced. Thirty (32%) of respondents agreed/strongly agreed that their SSc-RP medications had become more effective over time whereas 14 (15%) disagreed/strongly disagreed with this statement [data missing on 15 subjects]. The choice and availability of new treatments (e.g. phosphodiesterase inhibitors) makes it difficult to fully understand the relationship between SSc-RP symptom burden and medication use.

Discussion

We report the findings of a large study investigating the nature and evolution of RP symptoms in SSc. The apparent evolution of RP symptoms, characterised by more persistent symptoms of digital ischemia, could reflect progression of the obliterative microangiopathy of SSc. These findings shed light on possible determinants of SSc-RP and have implications for future RP management and clinical trial design.

In contrast with earlier work (9), monophasic RP was only reported in 11% of our SSc patients although this could still have implications for disease classification in early SSc when disproportionate weighting is attached to achieving definitions for RP (“two-phase colour change in fingers”) given other organ manifestations may have yet to emerge (6). Our prevalent cohort study design does not allow examination of digital colour changes at diagnosis, which may differ from that of established disease considering our findings supporting SSc-RP symptom evolution. A higher number of reported digital colour changes was associated with higher overall SSc-RP severity assessed using the RCS diary parameters

but we did not identify any differences in clinical phenotype associated with specific patient-reported digital colour changes of SSc-RP (or combinations thereof) suggesting repeated enquiry is of limited value in the clinical setting. We were surprised by the lack of association between digital colour changes and clinical outcomes (having hypothesized that cyanosis [blue and/or purple] might be a marker of more severe digital vasculopathy). We undertook an extensive review of each of the digital colour changes (and combinations thereof) but did not identify any meaningful associations. One explanation for this might be the high prevalence of all the digital colour changes (72-86%) across the group making it difficult to identify clinical associations. It is possible that the use of colour charts or clinician-observed digital colour changes might be more effective than self-report at identifying clinical associations with specific digital colour changes of SSc-RP.”

We explored self-management approaches taken by patients to avoid or ameliorate symptoms of SSc-RP and our analysis suggests the majority of patients feel better able to manage their symptoms over time, supporting the findings of previous qualitative research that identified successful adaptation as an important determinant of the overall burden of SSc-RP (4). For the first time, we have shown that SSc patients identify with different patterns of SSc-RP. The apparent evolution in SSc-RP pattern since symptom onset and association between worsening RP pattern and disease duration is suggestive of a possible relationship with the progressive obliterative microangiopathy of SSc, although additional work exploring the relationship between patterns of SSc-RP and capillary morphology at the nail fold would strengthen this supposition. Worsening SSc-RP patterns were associated with physician and patient assessments of global disease burden and peripheral vascular severity. This included assessment of RP severity using RCS diary parameters. We had hypothesised that more persistent symptoms of digital ischaemia may translate into the reporting of fewer SSc-RP attacks (with major implications for current SSc-RP trial design and interpretation) but our data did not support this. This does not negate the potential importance of different patterns

of SSc-RP with respect to treatment outcomes and clinical trial design, which should form the focus of further research. Indeed, over 20% of patients reported difficulty distinguishing discrete attacks of SSc-RP from background digital ischemia, which might have an important influence on diary-based approaches to RP assessment. There was no relationship between SSc-RP patterns and the conceptually-unrelated SHAQ breathing VAS but a surprising relationship was identified with the SHAQ GI VAS. This might reflect a true association between GI disease and peripheral vascular dysfunction in SSc. Alternatively, the relationship may reflect shared experiences around pain with both RP and GI disturbance (but not breathlessness) in SSc. These observations could form the focus of further research.

The cohort was relatively evenly split when asked whether their SSc-RP symptoms have worsened (~35%), remained the same (~35%) or improved (~20%) over time. A number of factors might contribute to these findings including progression (or regression) of peripheral microangiopathy, treatment efficacy, self-efficacy, habituation and adaptation (20).

This study benefits from being a comparatively large multi-centre study of SSc but the questionnaire design limits the extent to which we can explore the potential mechanisms underpinning SSc-RP symptom characteristics and symptom burden. Future longitudinal studies incorporating microvascular imaging shall help further elucidate determinants of RP symptom evolution in SSc and the implications for management.

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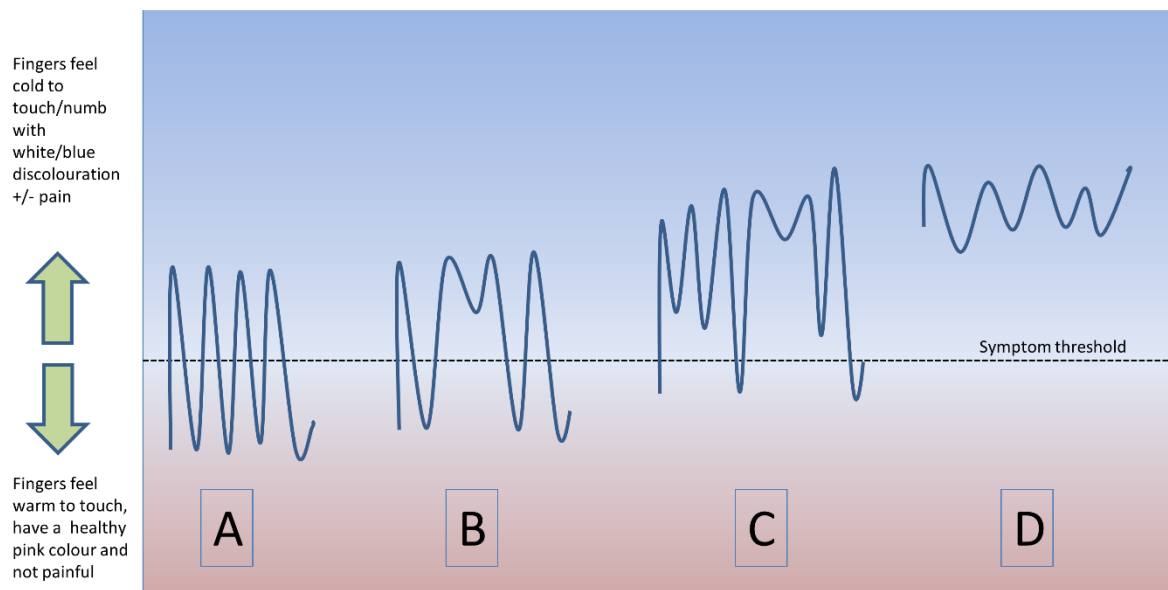
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Figure 1. Diagrammatic representations and descriptive stems for four theoretical patterns of Raynaud's phenomenon



The four labelled images represent theoretical patterns of Raynaud's symptoms. Participants were asked to consider which image and stem best described their experience of Raynaud's phenomenon. The dotted line indicates the threshold at which they might experience symptoms of Raynaud's phenomenon. Each image was accompanied by the following statements to aid participants when making their choice:

- A) Intermittent short-lasting attacks of Raynaud's with the circulation in the fingers always returning to normal in between attacks (the fingers feel warm to touch with good blood supply the majority of the time).
- B) Intermittent longer-lasting attacks of Raynaud's with the circulation in the fingers not always returning completely back to normal (warm and pink) in between attacks. My fingers feel cold and appear discoloured as often as they feel normal.
- C) Intermittent attacks of acute Raynaud's but the fingers feel cold with poor blood supply the majority of the time and rarely return to feeling normal. It can be difficult to identify actual attacks of Raynaud's from how they feel constantly.
- D) The fingers are cold and discoloured all of the time and I find almost impossible to appreciate distinct attacks of Raynaud's as the blood supply to the fingers appears to be permanently reduced.

Table 1. Patient demographics and clinical phenotype of participants.

* comparing Bath with SLC using unpaired t test or Chi square as appropriate

‡ We are unable to attribute the chief indicator for individual vasodilator medication which may include SSc-RP, digital ulcer disease, pulmonary arterial hypertension and conventional cardiovascular disease.

	All	Bath	SLC	P value*
Number of patients	94	44	50	N/A
Age in years, mean (SD)	60.5 (11.9)	65.1 (9.1)	56.4 (12.7)	<0.001
Age at diagnosis, mean (SD)	50.6 (14.9)	54.6 (12.8)	47.3 (16.2)	0.02
Disease duration, mean (SD)	9.9 (9.1)	10.6 (9.8)	9.2 (8.7)	0.45
Time from RP to 1 st non RP symptom, mean (SD)	4.9 (9.4)	6.5 (9.2)	3.6 (9.5)	0.14
Female, n (%)	82 (87)	40 (91)	42 (84)	0.37
Male, n (%)	12 (13)	4 (9)	8 (16)	
Limited cutaneous SSc, n (%)	78 (83)	38 (86)	40 (80)	0.67
Diffuse cutaneous SSc, n (%)	14 (15)	5 (12)	9 (18)	
SSc sine scleroderma, n (%)	2 (2)	1 (2)	1 (2)	
Raynaud's, n (%)	94 (100)	44 (100)	50 (100)	1.00
GERD, n (%)	85 (90)	36 (82)	49 (98)	0.01
Sclerodactyly, n (%)	79 (84)	36 (82)	43 (86)	0.78
History of digital ulcers, n (%)	53 (56)	19 (43)	34 (68)	0.02
Telangiectasia, n (%)	80 (85)	37 (84)	43 (86)	1.00
Pulmonary hypertension, n (%)	17 (18)	7 (16)	10 (20)	0.79
Interstitial lung disease, n (%)	34 (36)	13 (30)	21 (42)	0.28
Caucasian, n (%)	88 (94)	42 (95)	46 (92)	0.68
Current smoker, n (%)	8 (9)	3 (7)	5 (10)	0.72
Ex-smoker, n (%)	23 (25)	12 (27)	11 (22)	
Never smoker, n (%)	61 (65)	27 (61)	34 (68)	
Antibody profile (not all mutually exclusive)				

Evolving symptoms of RP in SSc

Anticentromere, n (%)	47 (50)	25 (57)	22 (44)	0.18
Anti-Scl 70, n (%)	13 (1)	7 (16)	6 (12)	
Anti-U1-RNP, n (%)	11 (11)	3 (7)	8 (16)	
Anti- RNA Pol III, n (%)	9 (9)	2 (5)	7 (14)	
Anti-Th/To	4 (4)	3 (7)	1 (2)	
Anti-Ro 60	7 (7)	6 (14)	1 (2)	
Anti-R0 52	1 (1)	1 (2)	0	
Anti-PM-Scl	3 (3)	0 (0)	3 (6)	
Anti-U3-RNP	1 (1)	0 (0)	1 (2)	
Vasodilator medication [‡]				
Calcium channel antagonists	51 (54)	18 (41)	33 (66)	0.03 [‡]
ACE inhibitors / Angiotensin II antagonists † p=0.02 for this medication class	18 (19.1)	13 (30)	5 (10)	
PDE5 inhibitors	15 (16)	9 (20)	6 (12)	
ERA	7 (7)	4 (9)	3 (6)	

Table 2. The relationship between physician and patient assessments of disease severity and SSc-RP patterns identified by participants

All values mean (SD) unless stated. *one way ANOVA or Chi squared as appropriate.

SSc, Systemic sclerosis; RP, Raynaud's phenomenon; VAS, visual analogue scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; GI, Gastrointestinal; DU, digital ulcer; RCS, Raynaud's Condition Score;

	Pattern A	Pattern B	Pattern C	Pattern D	p value *
Current SSc-RP pattern, n (%)	36 (39)	41 (44)	13 (14)	3 (3)	0.08
Initial SSc-RP pattern, n (%)	50 (54)	25 (27)	12 (13)	5 (3)	
Disease duration, years	8.5 (9.9)	9.0 (8.3)	15 (8.23)	18 (1.73)	0.05
Physician and patient 100mm VAS scores					
Physician RP VAS (0-100)	20.5 (19.1)	30.9 (21.9)	33.9 (25.9)	61 (35.9)	0.007
Physician global VAS (0-100)	24.5 (22.0)	32.8 (25.6)	37.7 (25.2)	68.3 (28.4)	0.02
Patient global VAS (0-100)	28.3 (25.1)	43.8 (23.2)	49.2 (32.6)	76.7 (12.4)	0.002
Scleroderma Health Assessment Questionnaire (SHAQ) indices					
HAQ-DI (0-3.0)	0.5 (0.5)	1.0 (0.7)	1.3 (0.8)	1.9 (0.5)	<0.001
Pain VAS (0-3.0)	0.7 (0.8)	1.2 (0.9)	1.6 (0.9)	2.3 (0.3)	<0.001
GI VAS (0-3.0)	0.5 (0.6)	0.8 (0.8)	1.5 (1.2)	2.6 (0.5)	<0.001
Breathing VAS (0-3.0)	0.5 (0.6)	0.8 (0.8)	0.8 (0.9)	1.2 (1.1)	0.27
RP VAS (0-3.0)	0.3 (0.6)	0.9 (0.8)	1.1 (0.9)	2.8 (0.2)	<0.001
DU VAS (0-3.0)	0.2 (0.5)	0.5 (0.8)	0.9 (1.2)	1.5 (1.5)	0.007
Global VAS (0-3.0)	0.6 (0.7)	1.3 (0.8)	1.5 (1.1)	2.7 (0.2)	<0.001
RCS diary parameters					
Mean daily RCS score (0-10)	1.6 (1.8)	3.5 (2.5)	4.0 (2.4)	5.4 (2.1)	<0.001
Mean daily RP frequency (per day)	1.1 (1.1)	2.3 (1.7)	3.6 (1.9)	4.4 (4.4)	<0.001
Mean daily RP duration (mins)	17.4 (22.8)	66.6 (80.7)	94.9 (103.1)	125.1 (114.3)	0.002