Factors Influencing Raynaud Condition Score Diary Outcomes in Systemic Sclerosis

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ABSTRACT. ***Objective.*** Raynaud phenomenon (RP) in systemic sclerosis (SSc) could be influenced by clinical phenotype, environmental factors (e.g., season), and personal factors (e.g., coping strategies and ill-health perceptions). We studied the relative influence of a range of putative factors affecting patient-reported assessment of SSc-RP severity.

Methods. SSc patients were enrolled at UK and US sites. Participants completed the 2-week Raynaud Condition Score (RCS) diary alongside collection of patient demographics, clinical phenotype, the Coping Strategies Questionnaire, Pain Catastrophizing Scale, Scleroderma Health Assessment Questionnaire (SHAQ), and both patient/physician visual analog scale (VAS) assessments for RP, digital ulcer disease, and global disease. Environmental temperature data were obtained at each site. A second RCS diary was completed 6 months after enrollment.

Results. We enrolled 107 patients (baseline questionnaires returned by 94). There were significant associations between RCS diary variables and both catastrophizing and coping strategies. There were significant associations between RCS diary outcomes and both environmental temperature and season of enrollment. Age, disease duration, sex, disease subtype, smoking, and vasodilator use were not associated with RCS diary outcomes. The best-fitting multivariate model identified the patient RP VAS, SHAQ pain VAS, and SHAQ gastrointestinal VAS subscales as the strongest independent predictors of the RCS.

Conclusion. Patient-reported assessment of SSc-RP severity is associated with a number of factors including pain, catastrophizing, and coping strategies. The effects of seasonal variation in environmental temperature on SSc-RP burden has implications for clinical trial design. Treatments targeting SSc-RP pain and the development of behavioral interventions enhancing coping strategies may reduce the burden of SSc-RP. (J Rheumatol First Release May 15 2019; doi:10.3899/jrheum.180818)

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Raynaud phenomenon (RP) describes episodic excessive vasoconstriction of the digital microvasculature in response to cold exposure and/or emotional stress[1]. It is the most common manifestation of systemic sclerosis (SSc) and a major cause of disease-related morbidity[2,3,4]. The severity of the underlying digital obliterative microangiopathy and the relative efficacy of vasodilator medications are likely to contribute to the wide interindividual variation in the severity and effect of SSc-RP[5]. A number of additional factors contribute to SSc-RP burden, including seasonal variation in environmental exposure to cold and the positive steps taken by patients to avoid or ameliorate the conditions responsible for SSc-RP symptoms[4,6,7]. Symptom habituation and adaptation further moderate the effect of SSc-RP symptoms[4]. The Raynaud Condition Score (RCS) diary is currently the preferred endpoint for SSc-RP clinical trials[8]. Collected over a 1- to 2-week period, the RCS diary provides an estimate of the mean daily frequency of SSc-RP attacks, the mean daily duration of SSc-RP attacks, and a mean daily assessment of the effect/severity of SSc-RP symptoms [applied as either an 11-point numerical rating scale (NRS) or 100-mm visual analog scale VAS)]. The mean daily frequency and duration of RP attacks during 2-week RCS diary collection have been relatively consistent across studies (between 3–4 attacks per day with a mean daily aggregate duration of 30–90 min/day, equating to an average duration of ~15–20 min per attack[3]). Similarly, the mean RCS in patients with SSc is typically ~4.4/10 on an 11-point NRS[3]. Much of these data have been obtained in clinical trial settings, typically undertaken during

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winter and often mandating a minimum threshold number of RP attacks in the period prior to study entry[3]. Establishing treatment efficacy using RCS diary variables has been challenging, with clinical trials of promising vasodilator therapies yielding negative or modestly positive findings at best[9,10,11,12,13]. The high placebo response and poor agreement between RCS diary variables and objective assessments of digital perfusion have caused consternation[5,14]. Additional concerns about the RCS diary have been raised among patients and SSc experts[7,15]. A thorough understanding of the factors contributing to RCS diary outcomes could provide insight into its performance as an endpoint in clinical trials, influence future SSc-RP clinical trial design, and support the development of novel approaches to SSc-RP management. The Raynaud Symptom Study (RSS) is a multicenter longitudinal study designed to assess the features and determinants of RP symptoms in SSc. We have recently reported the clinical significance of RP symptom characteristics in SSc[16]. This second report from the RSS focuses on the relative influence of putative factors including clinical phenotype, patient demographics, coping strategies, catastrophizing, and seasonal variation in environmental temperatures on patient-reported assessment of RP severity.

MATERIALS AND METHODS

Patients. SSc patients fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[17] were enrolled at routine clinical care visits from SSc clinics in Bath, UK, and Utah, USA, between April 2015 and January 2017. All patients spoke English. The study received ethical approval at each site (Bath REC 15/LO/1521 and Utah IRB #80665) and all participants provided informed written consent.

Clinician case report form (CRF). A clinician CRF collected information on patient demographics (age, sex, ethnicity, disease duration based on time since first non-RP symptom), smoking history, clinical phenotype, and autoimmune serology. The clinical phenotype was established using documented evidence from the case notes of gastroesophageal reflux disease symptoms, puffy fingers, sclerodactyly, digital ulcers (DU), digital pitting, telangiectases, pulmonary arterial hypertension, interstitial lung disease, and autoantibody specificity. Relevant comorbidities and vasoactive medication use were documented. Clinicians completed 100-mm VAS for the physician's global assessment, physician RP severity, and physician DU severity.

Patient questionnaires. Each participant received an RSS questionnaire containing the Scleroderma Health Assessment Questionnaire [SHAQ; comprising the HAQ–Disability Index (HAQ-DI) and SSc-specific 150-mm VAS subscales[18]], the 1-item Coping Skills Questionnaire (CSQ[19]; a validated abridged version of the original CSQ[20]), the Pain Catastrophizing Scale (PCS)[21], and separate 100-mm VAS assessments for SSc-RP severity, patient's global assessment, and DU severity (Supplementary Data, available from the authors on request). The 7 items of the 1-item CSQ are scored using a 7-point NRS (0–6, ranging from "never do" to "always do that"), with each representing distinct domains pertaining to the following: diverting attention, reinterpreting pain sensations, catastrophizing, ignoring sensations, praying and hoping, coping self-statements, and increasing behavioral activities[19,20]. Patients were dichotomized for each domain according to low coping strategies (score 0–2) and high coping strategies (score 3–6). The 13-item PCS was developed to investigate mechanisms by which catastrophizing affects pain experiences[21]. Each item is scored using a 5-point NRS (0–4, ranging from "not at all" to "all the time"). A composite score (0–52) was derived and a cutoff of 30 applied to dichotomize the group into copers and catastrophizers (based on earlier work identifying a score of 30 as corresponding to the 75th percentile in samples of chronic pain patients)[21]. Subscales for rumination (items 8–11), helplessness (items 1–5, 12) and magnification (items 6, 7, 13) were also derived from the PCS, as previously described[21]. Participants were instructed on completion of the 2-week RCS diary from which we derived the mean daily RCS, mean daily frequency of RP attacks, and mean aggregate daily duration of RP attacks (providing a minimum of 10 days out of 14 had been completed satisfactorily). Participants completed a second RCS diary 6 months following enrollment.
Weather data. The daily maximum and minimum temperature from Bath, and Salt Lake City, Utah, weather stations was obtained using UK Meteorological Office data for April 2015 through July 2017.

Statistical analysis. Descriptive statistics are defined where applicable. The chi-square test was used to compare observed frequencies across 2 or more categories. The unpaired t test was applied when comparing continuous data between groups for patient demographics. Mann-Whitney U and Kruskal-Wallis tests were applied to examine distributions of scores across multiple independent samples as appropriate. Spearman ρ correlation coefficients were used to assess the relationship between independent continuous variables. Multiple linear regression models assessed the combined effect of several variables on the mean daily RCS as the major response variable. A univariate simple linear regression model was first developed before establishing the best-fitting multivariate model according to all possible combinations of the variables found to be significant at $p < 0.01$ in the univariate analysis. The baseline RCS diary variables were used for analyses examining associations with baseline questionnaire outcomes (e.g., relationship with CSQ and PCS). The effect of season was assessed by pooling RCS diary returns and categorizing patients according to season of enrollment (winter: December 1–February 28, spring: March 1–May 31, summer: June 1–August 31, and fall: September 1–November 30). Local Meteorological Office data during the period of RCS diary collection were used to further examine the relationship between environmental temperature exposure and SSc-RP symptoms. The corresponding mean daily maximum and minimum temperatures were calculated within each period of RCS diary collection.

RESULTS

Patient demographics and missing data. The RSS enrolled 107 patients with SSc (57 in Bath and 50 from Utah). Ninety-four patients (82 female, 14 patients with diffuse cutaneous SSc) returned completed baseline questionnaires. The patient demographics and clinical phenotype of the cohort are summarized in Table 1. The 2 cohorts were similar and we did not consider the lower age of the Utah cohort (mean of 56.4 yrs vs 65.1 yrs) clinically meaningful or likely to have influenced our pooled analyses. The CSQ was adequately completed by 87 participants and the PCS by 84 participants. Baseline RCS diaries were returned by 88 participants (with at least 1 of the 3 RCS diary variables being adequately completed in 86 subjects). Sixty-eight subjects returned the 6-month diary (mean of 198 days ± SD 76 between diaries), allowing a total pooled analysis of up to 154 RCS diary returns. Adequately completed baseline and 6-month RCS diaries were available for 66 patients (70.2%). A full breakdown of missing data is available as Supplementary Data (available from the authors on request).

Associations between patient coping strategies on SSc-RP symptom burden. Higher scores for "praying and hoping" and "catastrophizing" domains of the CSQ were associated with significantly higher RCS ($p < 0.05$; Table 2), indicating a

Table 1. Patient demographics and clinical phenotypes of participants.

Variables	All	Bath (UK)	Utah (USA)	p *
No. patients	94	44	50	
Age, yrs, mean (SD)	60.5 (11.9)	65.1 (9.1)	56.4 (12.7)	**< 0.001**
Age at diagnosis, yrs, mean (SD)	50.6 (14.9)	54.6 (12.8)	47.3 (16.2)	**0.02**
Disease duration, yrs, mean (SD)	9.9 (9.1)	10.6 (9.8)	9.2 (8.7)	0.45
Time from RP to 1st non-RP symptom, mean (SD)	4.9 (9.4)	6.5 (9.2)	3.6 (9.5)	0.14
Female	82 (87)	40 (91)	42 (84)	0.37
Male	12 (13)	4 (9)	8 (16)	
Limited cutaneous SSc	78 (83)	38 (86)	40 (80)	0.67
Diffuse cutaneous SSc	14 (15)	5 (12)	9 (18)	
SSc sine scleroderma	2 (2)	1 (2)	1 (2)	
RP	94 (100)	44 (100)	50 (100)	1.00
GERD	85 (90)	36 (82)	49 (98)	**0.01**
Sclerodactyly	79 (84)	36 (82)	43 (86)	0.78
History of digital ulcers	53 (56)	19 (43)	34 (68)	**0.02**
Telangiectasia	80 (85)	37 (84)	43 (86)	1.00
Pulmonary hypertension	17 (18)	7 (16)	10 (20)	0.79
Interstitial lung disease	34 (36)	13 (30)	21 (42)	0.28
White	88 (94)	42 (95)	46 (92)	0.68
Current smoker	8 (9)	3 (7)	5 (10)	0.72
Ex-smoker	23 (25)	12 (27)	11 (22)	
Never smoker	61 (65)	27 (61)	34 (68)	
Antibody profile				
ACA	47 (50)	25 (57)	22 (44)	0.18
Scl-70	13 (14)	7 (16)	6 (12)	
U1-RNP	11 (12)	3 (27.3)	8 (72.7)	
RNA polymerase III	9 (10)	2 (5)	7 (14)	
Anti-Th/To	4 (4)	3 (7)	1 (2)	
Anti-Ro 60	7 (7)	6 (14)	1 (2)	
Anti-Ro 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‡	18 (19.1)	13 (30)	5 (10)	
PDE5 inhibitors	15 (16)	9 (20)	6 (12)	
ERA	7 (7)	4 (9)	3 (6)	

* Comparing Bath (UK) with Utah (USA) data using unpaired t test or chi-square as appropriate; reproduced with permission from[16]. ‡P = 0.02 for this medication class. Values in bold face are statistically significant. Values are n (%) unless otherwise specified. RP: Raynaud phenomenon; SSc: systemic sclerosis; GERD: gastroesophageal reflux disease; ACA: anticentromere antibodies; ACE: angiotensin-converting enzyme; PDE5: phosphodiesterase type 5; ERA: endothelin receptor antagonist.

relationship between these thoughts and higher burden of RP. Significantly higher RCS were also identified among participants reporting the adoption of coping strategies to "reinterpret symptoms," and "coping self-statements" (Table 2). Efforts to effectively "ignore sensations" was associated with lower RCS (not statistically significant). There was no significant relationship between "increased behaviors" (doing other activities despite symptoms) or "diverting attention" and the distribution of the RCS. Fewer statistically significant associations were identified between coping strategies and either the frequency/duration of SSc-RP attacks, although trends were present that mirrored the findings with the RCS (Table 2).

Association between catastrophizing and SSc-RP symptom burden. The relationship between catastrophizing and RCS diary outcomes was replicated using the PCS data. When dichotomizing the group (< or > a composite score of 30), "copers" had significantly lower median (interquartile range) mean daily RCS compared to the "catastrophizers" [1.7 (0.6–3.7) vs 4.7 (2.8–6.9), $p < 0.01$; Table 2]. Similar trends were observed for the mean daily frequency and duration of SSc-RP attacks. There was a moderate positive correlation between the total PCS and RCS across the cohort (Spearman ρ 0.42, $p < 0.01$; Table 3). This relationship was strongest for domains concerning "helplessness" (ρ 0.47) and "magnification" (ρ 0.43) when compared to "rumination" (ρ 0.35).

Table 2. The relationship between coping strategies and RCS diary returns.

Patient-reported Outcome Measure	Score	RCS N	RCS Mean Daily RCS (0–10)	RP Attacks N	RP Attacks Mean Daily Frequency	RP Duration N	RP Duration Mean Daily Duration, min
CSQ Diverting attention	Low, 0–2	51	1.7 (0.6–3.9)	50	1.3 (0.4–3.1)	50	19.0 (7.3–57.1)
	High, 3–6	23	3.4 (1.7–5.8)	24	2.0 (1.4–3.1)	24	31.3 (16.9–85.3)
CSQ Reinterpreting	Low, 0–2	36	1.6 (0.5–3.7) *	36	1.1 (0.4–2.4) *	36	11.2 (4.7–33.5) *
	High, 3–6	38	3.2 (1.5–4.9)	38	2.3 (1.1–3.6)	38	44.5 (16.4–102.3)
CSQ Catastrophizing	Low, 0–2	47	1.5 (0.5–3.4) *	48	1.3 (0.4–3.0)	48	20.5 (5.2–51.8)
	High, 3–6	27	3.9 (2.3–6.9)	25	2.4 (1.3–3.5)	25	37.9 (14.1–118.4)
CSQ Ignoring sensations	Low, 0–2	29	3.0 (1.4–5.7)	28	2.3 (1.2–3.4)	28	33.4 (12.4–71.6)
	High, 3–6	43	2.0 (0.5–3.9)	43	1.3 (0.4–3.0)	43	19.6 (5.4–54.2)
CSQ Praying and hoping	Low, 0–2	45	1.7 (0.5–4.1) *	44	1.2 (0.4–3.1)	44	20.0 (4.7–55.8)
	High, 3–6	29	3.4 (1.8–6.1)	29	2.1 (1.3–3.0)	29	33.1 (12.5–103.3)
CSQ Coping self-statements	Low, 0–2	13	0.6 (0.3–1.8) *	13	0.6 (0.3–1.9)	13	5.4 (1.7–22.3)
	High, 3–6	62	2.8 (0.9–4.9)	62	1.8 (0.8–3.1)	62	33.0 (11.3–77.7)
CSQ Increased behaviors	Low, 0–2	19	1.4 (0.6–6.9)	19	1.4 (0.5–3.5)	19	11.5 (5.1–43.2)
	High, 3–6	56	2.8 (0.9–6.9)	55	1.8 (0.9–3.1)	55	29.3 (10.6–76.1)
PCS	Low, < 30	64	1.7 (0.6–3.7)**	64	1.4 (0.5–2.6)	64	20.5 (4.8–61.4)
	High, > 30	8	4.7 (2.8–6.9)	8	3.0 (1.3–3.9)	8	29.1 (18.6–89.0)

* P < 0.05 for low vs high scores. ** P < 0.01. All values are median (interquartile range) unless otherwise specified. Distribution of values between groups was assessed using Mann-Whitney U test. N: total number of patients completing CSQ and at least 10 days for each of the 2-week RCS diary variables; RP: Raynaud phenomenon; CSQ: Coping Strategies Questionnaire; PCS: Pain Catastrophizing Scale; RCS: Raynaud Condition Score.

Table 3. Relationship between RCS diary outcomes and catastrophizing.

Variables	Total PCS	PCS Rumination	PCS Magnification	PCS Helplessness
Disease duration, yrs	0.034	0.31	–0.009	0.039
Age at diagnosis, yrs	–0.27*	–0.24*	–0.19	–0.26*
Physician's global VAS (0–100)	0.06	–0.03	0.12	0.16
RCS mean score, baseline (0–10)	0.42**	0.35**	0.43**	0.47**
Mean daily RP frequency, baseline (2-week RCS diary)	0.11	0.08	0.18	0.13
Mean daily RP duration, baseline, min	0.19	0.17	0.20	0.20
Physician DU VAS (0–100)	0.18	0.14	0.12	0.14
Physician RP VAS (0–100)	0.23*	0.14	0.29**	0.22*
Patient global VAS (0–100)	0.47**	0.39**	0.37**	0.54**
Patient DU VAS (0–100)	0.33**	0.24*	0.19	0.29**
Patient RP VAS (0–100)	0.35**	0.33**	0.28**	0.39**
HAQ-DI (0–3.0)	0.42**	0.33**	0.35**	0.48**
SHAQ GI (0–3.0)	0.37**	0.32**	0.38**	0.38**
SHAQ pain (0–3.0)	0.38**	0.31**	0.22*	0.48**
SHAQ breathing (0–3.0)	0.12	0.10	0.14	0.15
SHAQ RP (0–3.0)	0.46**	0.36**	0.34**	0.53**
SHAQ DU (0–3.0)	0.33**	0.21	0.14	0.29**
SHAQ global (0–3.0)	0.41**	0.33**	0.30**	0.48**

Spearman ρ correlation coefficients: * p < 0.05; ** p < 0.01. RCS: Raynaud Condition Score; PCS: Pain Catastrophizing Scale; VAS: visual analog scale; RP: Raynaud phenomenon; DU: digital ulcers; HAQ-DI: Health Assessment Questionnaire–Disability Index; SHAQ: Scleroderma HAQ; GI: gastrointestinal.

No significant correlation was identified between the total PCS and frequency/duration of RP attacks (Table 3). Significant correlation coefficients were also identified between PCS total scores (and subdomains) and patient RP VAS (ρ 0.35), patient DU VAS (ρ 0.33), and patient global VAS (ρ 0.47). A weak positive correlation was identified between the total PCS and physician RP VAS (ρ 0.23, p < 0.05), but there were no other correlations with physician assessments. There was a positive correlation between the total PCS and the HAQ–DI (ρ 0.42) and each of the SHAQ subscales with the exception of the SHAQ breathing VAS (Table 3). Across all the analyses, the association between

patient-reported outcome (PRO) instruments and PCS was strongest for the domains concerning "helplessness." There was no relationship between total PCS and disease duration, although a weak negative correlation with age (ρ –0.27, $p < 0.05$) may indicate partially successful adaptation with advancing years.

Association between RCS diary responses and environmental temperature. Using pooled data from the 154 RCS diary returns (combined baseline and 6-month data), there was a weak negative correlation between the mean daily RCS and both mean daily maximum and minimum temperatures (Spearman ρ –0.22, $p < 0.01$ for both analyses). There were weak negative correlations between the mean daily frequency of RP attacks and mean daily maximum and minimum temperatures (Spearman ρ –0.27, $p < 0.01$ for both analyses). Similar trends were observed for mean daily duration of attacks (ρ –0.26 and –0.25, respectively, $p < 0.01$). The association between environmental temperatures and RCS diary outcomes was further supported when examining the distribution of RCS diary responses according to season of enrollment, with significantly higher RCS diary variables observed in winter compared to summer (Table 4).

Overall determinants of the RCS. A multivariate model was built to evaluate the relative contribution of all the relevant factors (weather, coping, other PRO instruments, clinical features, etc.) on the RCS. A parametric approach was necessary for building the multivariate model, but the univariate findings were consistent with the nonparametric analyses presented earlier (Table 2 and Table 3). Simple linear regression identified strongly significant associations ($p < 0.01$) between the RCS and the PCS, several of the CSQ domains [particularly "catastrophizing" ($p < 0.001$) and "coping self-statements" ($p = 0.0044$)], patient RP VAS, patient DU VAS, patient global VAS, HAQ-DI (and all SHAQ subscales other than breathing VAS). Univariate analysis did not identify significant relationships between RCS and physician assessments, age, disease duration, environmental temperatures, sex, smoking history, vasodilator use, history of DU, or disease subset (Table 5). The individual correlations between RCS and PCS scores were all significant using both Spearman ρ and simple linear regression. Only total PCS was incorporated into the multivariate model because the total PCS was perfectly collinear with the sum of the subscores and the PCS subscores were highly correlated (Pearson correlation > 0.7 for all pairs). The best-fitting multivariate model included only the patient RP VAS, the SHAQ pain VAS, and SHAQ gastrointestinal (GI) VAS when assessing all possible combinations of the variables found to be significant at the $p < 0.01$ level in the univariate analyses (Table 5). Other model selection techniques also identified these 3 predictors. The final multivariate model suggests increases in each of these PRO instruments were significantly associated with increases in mean daily RCS. None of the coping strategy scores were selected in the final model, indicating that we would expect 2 patients with similar SHAQ and RP VAS scores but different coping strategies to have similar RCS diary responses (Table 5).

DISCUSSION

We report the findings of a large study investigating the factors influencing self-report of RP in SSc. The overall burden of SSc-RP symptoms is not a simple linear relation-

Table 4. The relationship between season of enrollment, environmental temperature, and RCS diary returns.

Variables	Winter, Dec 1–Feb 28	Spring, Mar 1–May 31	Summer, Jun 1–Aug 31	Autumn, Sept 1–Nov 30
No. diaries (total cohort N = 154), (%)				
Total	40 (26.0)	48 (31.2)	44 (28.6)	22 (14.2)
Bath	25	16	25	9
SLC	15	32	19	13
Max temperature, °C, mean (SD)				
Total	7.1 (3.7)	18.6 (4.0)	27.8 (6.5)	16.0 (4.7)
Bath	8.9 (1.8)	15.5 (2.8)	21.4 (1.6)	14.3 (3.6)
SLC	3.9 (3.8)	20.2 (3.6)	33.7 (1.5)	17.3 (5.2)
Min temperature, °C, mean (SD)				
Total	0.1 (3.5)	7.9 (3.7)	16.3 (4.2)	6.5 (3.9)
Bath	1.6 (2.7)	5.0 (3.4)	12.3 (0.9)	5.5 (3.3)
SLC	–2.7 (2.8)	9.4 (2.8)	20.0 (1.7)	7.1 (4.2)
Mean daily RCS, median (IQR)	2.5 (1.2–4.1) **	1.6 (0.8–2.9)	0.9 (0.4–2.5)	1.9 (0.7–4.4)
Mean daily RP attack frequency, median (IQR)	1.8 (0.7–3.3) *	1.4 (0.6–2.2)	0.9 (0.3–1.6)	1.6 (0.7–3.0)
Mean daily RP attack duration, median (IQR)	33.6 (11.2–73.9) **	15.7 (4.5–43.2)	15.7 (4.5–43.2)	33.1 (7.6–42.2)

Distribution across groups assessed using Kruskal-Wallis test. * $p = 0.02$. ** $p = 0.01$. RCS: Raynaud Condition Score; SLC: Salt Lake City; IQR: interquartile range; RP: Raynaud phenomenon.

Table 5. Univariate and multivariate analysis of factors influencing mean daily RCS score (baseline).

Continuous Variables	N	Mean (SD)	Univariate		Multivariate	
			β/SD	p	β/SD	p
Total PCS	72	12.92 (11.34)	0.0077	< 0.001		
PCS rumination	76	4.54 (4.15)	0.0462	0.0038		
PCS magnification	76	2.78 (2.66)	0.1329	< 0.001		
PCS helplessness	75	5.79 (5.35)	0.0379	< 0.001		
Physician VAS RP	82	28.21 (22.58)	0.001	0.0432		
Physician VAS DU	82	10.02 (23)	0.0011	0.0213		
Physician VAS global	82	30.96 (24.11)	6×10^{-4}	0.2161		
Patient VAS RP	78	39.79 (28.31)	0.0019	< 0.001	9×10^{-4}	0.0082
Patient VAS DU	74	21.95 (32.09)	9×10^{-4}	< 0.001		
Patient VAS global	78	37.09 (26.87)	0.0013	< 0.001		
HAQ-DI	74	0.83 (0.71)	2.1849	< 0.001		
SHAQ pain	79	1.04 (0.9)	1.8683	< 0.001	1.1681	< 0.001
SHAQ gastrointestinal	78	0.79 (0.86)	1.8673	< 0.001	0.9006	0.0145
SHAQ breathing	79	0.7 (0.79)	0.8623	0.0492		
SHAQ RP	79	0.75 (0.82)	2.0874	< 0.001		
SHAQ DU	75	0.46 (0.77)	1.3512	0.0048		
SHAQ global	79	1.09 (0.9)	1.6875	< 0.001		
Age	82	61.8 (11.24)	–0.0036	0.0891		
Disease duration	82	9.55 (9.01)	0.0012	0.7111		
Mean daily max temperature	81	15.37 (9.09)	–0.004	0.2207		
Mean daily min temperature	80	6.25 (7.38)	–0.0056	0.2582		
Categorical Variables	**Level**	**Counts**	**β**	**p**	**β**	**p**
CSQ Diverting score	Low, 0–2	51	–	0.0163		
	High, 3–6	23	1.46			
CSQ Reinterpreting score	Low, 0–2	36	–	0.0267		
	High, 3–6	38	1.25			
CSQ Catastrophizing score	Low, 0–2	47	–	< 0.001		
	High, 3–6	27	2.20			
CSQ Ignoring score	Low, 0–2	29	–	0.0763		
	High, 3–6	43	–1.05			
CSQ Hoping and praying score	Low, 0–2	45	–	0.0221		
	High, 3–6	29	1.32			
CSQ Coping self-statement score	Low, 0–2	13	–	0.0044		
	High, 3–6	62	2.08			
CSQ Increased behavior score	Low, 0–2	19	–	0.0999		
	High, 3–6	56	1.06			
Sex	Female	71	–	0.6427		
	Male	11	0.36			
Site	Bath	42	–	0.3075		
	Utah	40	0.54			
Smoking	Current	7	–	0.162		
	Never	51	–1.71			
	Ex-smoker	21	–1.95			
Any vasodilators	No	23	–	0.1978		
	Yes	59	0.76			
History of DU	No	37	–	0.1915		
	Yes	45	0.69			
Clinical disease subset	lcSSc	68	–	0.717		
	ssSSc	2	–0.34			
	dcSSc	12	–0.61			

Estimates of the change in mean daily RCS score at baseline in simple and multiple linear regression model. The summary statistics and sample sizes are for the subset of the data where both mean daily RCS and the variable are complete. For continuous explanatory variables, the β/SD column shows the expected change in the RCS for a 1 SD increase in the predictor. For the categorical predictor, the estimated difference in RCS between each level and the reference level. PCS: Pain Catastrophizing Scale; VAS: visual analog scale; RP: Raynaud phenomenon; DU: digital ulcer; HAQ-DI: Health Assessment Questionnaire–Disability Index; SHAQ: Scleroderma HAQ; CSQ: 1-item Coping Skills Questionnaire; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous SSc; ssSSc: SSc sine scleroderma; RCS: Raynaud Condition Score.

ship with the extent of digital vasoconstriction but the complex interplay of factors including but not limited to pain perception, coping strategies, catastrophizing, and seasonal variation in weather.

To our knowledge, our study is the first to examine the relationship between coping and patient-reported SSc-RP symptoms. Our findings confirm an earlier consensus among SSc experts, in which 90% considered coping strategies to be an important determinant of RCS diary outcomes[15]. Catastrophizing appears to be important with patients who report this behavior (using both the CSQ and PCS instruments), consistently reporting a higher burden of SSc-RP symptoms. The direction of causality cannot easily be determined but the identified associations between SSc-RP severity and coping strategies (such as catastrophizing) could be used to develop novel behavioral approaches to enhance resilience to reduce the effect of RP. A recent large qualitative study of SSc-RP patients independently identified a diverse range of coping strategies (including diverting attention, ignoring sensations, and coping self-statements) that individuals with SSc report adopting to lessen the burden of RP symptoms[4]. These coping strategies formed an important component of an emergent theme around "adaptation" in the patient experience of SSc-RP, and future interventions could capitalize on these observations[4]. Cognitive-behavioral interventions that modify catastrophizing (specifically concerning feelings of helplessness and tendency toward symptom magnification) could be used to reduce the burden of SSc-RP. The direction of the relationship between the adoption of coping strategies around "reinterpretation" and "coping self-statements" and RCS diary outcomes was somewhat unexpected (with patients reporting a higher effect of SSc-RP despite the use of coping strategies within these domains). Nonetheless, strategies to help patients to think about their RP symptoms in more neutral terms (reinterpretation), to desist from catastrophizing thoughts (such as "I can't stand it anymore"), or to devise positive coping self-statements (such as "No matter how bad it gets, I can do it" or "It won't last much longer") may help lessen the burden of SSc-RP. A similar approach has been shown to modify pain endurance in patients with other forms of chronic pain[22]. Intriguingly, the method chosen for inducing experimental pain in this work (a cold pressor test involving the immersion of hands into cold-water baths) closely resembles the conditions and physiological responses accountable for SSc-RP symptoms. Other coping strategies might be less helpful in SSc-RP. For example, cognitive-behavioral interventions targeting "ignoring sensations" and "increasing behavioral activities" might result in excessive exposure to activities that might exacerbate peripheral vasoconstriction[23]. Previous behavioral interventions for RP have examined approaches such as biofeedback that from a modern perspective are deemed ineffective. Behavioral interventions focusing on the modification of catastrophizing and coping strategies could be a potentially effective but hitherto neglected area of therapeutics for RP symptoms. Resiliency training is being increasingly used as an intervention to modify quality of life and function in people affected by chronic disease[24].

Our findings also suggest that interventions targeting SSc-RP pain might be as important as efforts to promote peripheral vasodilation. Our multivariate analysis identified the patient pain VAS (from the SHAQ), the patient RP VAS, and the SHAQ GI VAS as independent determinants of the RCS. While the association with the SHAQ GI VAS might represent a genuine association between RP severity and GI involvement in SSc, it is also possible this reflects an important shared contribution of pain/illness perception in both RP and GI severity self-report. Indeed, the SHAQ breathing VAS (which has no conceptual associations with pain) was the only SHAQ subscale not associated with RCS within the univariate analysis. Similarly, the SHAQ breathing VAS was the only subscale not to correlate with PCS variables. A complex nonlinear relationship between the severity of digital vasculopathy and pain perception may explain the poor agreement between subjective (RCS diary) assessment of RP burden and objective assessment of digital vascular function in SSc[14,25].

In contrast, putative factors such as age, disease duration, disease subset, vasodilator use, smoking history, or history of DU do not appear to be associated with patient-reported severity and effect of SSc-RP symptoms. The original validation work of the RCS diary identified differences in RCS (but not mean daily frequency or duration of RP attacks) in patients with and without DU[26]. This study used data from a clinical trial that recruited patients only during the winter months, examined differences in RCS diary variables in patients with "active" DU (rather than a history of DU), and importantly, used RCS item wording that encouraged patients to consider the effect of "digital sores" when choosing their RCS[26].

Our findings raise additional issues relevant to the design and interpretation of SSc-RP clinical trials. We have confirmed a previously reported association between seasonal variation in environmental temperature and RP symptom burden, although our findings suggested a lower burden of RP symptoms in winter than those previously reported in a relatively smaller study of 18 patients with SSc[6]. Our findings might be of value for future clinical trial power calculations, particularly regarding studies countenancing enrollment outside winter. The influence of seasonal variation is not unexpected but has often been overlooked in RP clinical trial design and interpretation. For example, concerns are frequently raised about the magnitude of the placebo response in RP clinical trials with 1 study identifying a > 50% improvement in RCS in over one-fifth of patients following placebo administration[5]. The pooled analysis for this estimation was undertaken using data from 3 randomized

controlled trials that enrolled at Northern hemispheric sites during winter with primary endpoint analysis in the spring[5]. Changes in environmental temperature could be an important contributing factor to the placebo effect (a major hurdle to demonstrating efficacy within the treatment arm) and could be modified through the design of shorter RP clinical trials. Efforts under way to devise a novel PRO instrument for SSc-RP that is not reliant on diary collection may support novel clinical trial design that facilitates this[27].

Our present study benefits from being a comparatively large multicenter study, but being primarily a cross-sectional study and lacking objective assessment limit the extent to which we can fully examine the determinants of RCS diary outcomes. About 30% of participants did not return the 6-month RCS diary. Study attrition in a longitudinal study of self-administered questionnaires was expected and the majority of our analyses used baseline data alone, for which there were few missing data. Our study has highlighted a number of factors influencing RCS diary outcomes and builds on recent work examining the opinions of patients and experts toward the RCS diary as a clinical trial endpoint[7,15]. The present study has highlighted a number of factors contributing to SSc-RP symptom burden (such as seasonal variation in environmental temperature) that will help us better interpret RCS diary outcomes and inform future clinical trial design, and may help develop novel behavioral approaches for the management of SSc-RP.

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REFERENCES

1. Wigley FM, Flavahan NA. Raynaud's phenomenon. N Engl J Med 2016;375:556-65.
2. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian national survey. Rheumatology 2011;50:762-7.
3. Pauling JD, Saketkoo LA, Matucci-Cerinic M, Ingegnoli F, Khanna D. The patient experience of Raynaud's phenomenon in systemic sclerosis. Rheumatology 2019;58:18-26.
4. Pauling JD, Domsic RT, Saketkoo LA, Almeida C, Withey J, Jay H, et al. Multinational qualitative research study exploring the patient experience of Raynaud's phenomenon in systemic sclerosis. Arthritis Care Res 2018;70:1373-84.
5. Gladue H, Maranian P, Paulus HE, Khanna D. Evaluation of test characteristics for outcome measures used in Raynaud's phenomenon clinical trials. Arthritis Care Res 2013;65:630-6.
6. Watson HR, Robb R, Belcher G, Belch JJ. Seasonal variation of Raynaud's phenomenon secondary to systemic sclerosis. J Rheumatol 1999;26:1734-7.
7. Pauling JD, Saketkoo LA, Domsic RT. Patient perceptions of the Raynaud's condition score diary provide insight into its performance in clinical trials of Raynaud's phenomenon: comment on the article by Denton et al. Arthritis Rheumatol 2018;70:973-4.
8. Khanna D, Lovell DJ, Giannini E, Clements PJ, Merkel PA, Seibold JR, et al; Scleroderma Clinical Trials Consortium co-authors. Development of a provisional core set of response measures for clinical trials of systemic sclerosis. Ann Rheum Dis 2008;67:703-9.
9. Denton CP, Hachulla E, Riemekasten G, Schwarting A, Frenoux JM, Frey A, et al; Raynaud Study Investigators. Efficacy and safety of selexipag in adults with Raynaud's phenomenon secondary to systemic sclerosis: a randomized, placebo-controlled, phase II study. Arthritis Rheumatol 2017;69:2370-9.
10. Herrick AL, van den Hoogen F, Gabrielli A, Tamimi N, Reid C, O'Connell D, et al. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. Arthritis Rheum 2011;63:775-82.
11. Wigley FM, Korn JH, Csuka ME, Medsger TA Jr., Rothfield NF, Ellman M, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. Arthritis Rheum 1998;41:670-7.
12. Nguyen VA, Eisendle K, Gruber I, Hugl B, Reider D, Reider N. Effect of the dual endothelin receptor antagonist bosentan on Raynaud's phenomenon secondary to systemic sclerosis: a double-blind prospective, randomized, placebo-controlled pilot study. Rheumatology 2010;49:583-7.
13. Pauling JD. The challenge of establishing treatment efficacy for cutaneous vascular manifestations of systemic sclerosis. Expert Rev Clin Immunol 2018;14:431-42.
14. Pauling JD, Shipley JA, Hart DJ, McGrogan A, McHugh NJ. Use of laser speckle contrast imaging to assess digital microvascular function in primary Raynaud phenomenon and systemic sclerosis: a comparison using the Raynaud condition score diary. J Rheumatol 2015;42:1163-8.
15. Pauling JD, Frech TM, Hughes M, Gordon JK, Domsic RT, Anderson ME, et al. Patient-reported outcome instruments for assessing Raynaud's phenomenon in systemic sclerosis: A SCTC Vascular Working Group Report. J Scleroderma Relat Disord 2018;3:249-52.
16. Pauling JD, Reilly E, Smith T, Frech TM. Evolving symptoms of Raynaud's phenomenon in systemic sclerosis are associated with physician and patient-reported assessments of disease severity. Arthritis Care Res 2018 Aug 21 (E-pub ahead of print).
17. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, 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.
18. Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984-91.
19. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One- and two-item measures of pain beliefs and coping strategies. Pain 2003;104:453-69.
20. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low-back-pain patients - relationship to patient characteristics and current adjustment. Pain 1983;17:33-44.
21. Sullivan MJ, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. Psychol Assess 1995;7:524-32.
22. Roditi D, Robinson ME, Litwins N. Effects of coping statements on experimental pain in chronic pain patients. J Pain Res 2009; 2:109-16.
23. Haythornthwaite JA, Menefee LA, Heinberg LJ, Clark MR. Pain coping strategies predict perceived control over pain. Pain 1998;77:33-9.
24. Leppin AL, Bora PR, Tilburt JC, Gionfriddo MR, Zeballos-Palacios C, Dulohery MM, et al. The efficacy of resiliency training programs: a systematic review and meta-analysis of randomized trials. PLoS One 2014;9:e111420.

25. Wilkinson JD, Leggett SA, Marjanovic EJ, Moore TL, Allen J, Anderson ME, et al. A multicenter study of the validity and reliability of responses to hand cold challenge as measured by laser speckle contrast imaging and thermography: outcome measures for systemic sclerosis-related Raynaud's phenomenon. Arthritis Rheumatol 2018;70:903-11.
26. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, et al; Scleroderma Clinical Trials Consortium. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002;46:2410-20.
27. Baron M, Kahaleh B, Bernstein EJ, Chung L, Clements PJ, Denton CP, et al. An interim report of the scleroderma clinical trials consortium working groups. J Scleroderma Relat Disord 2019;4:17-27.