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Factors influencing RCS-diary outcomes in SSc

## **Factors influencing Raynaud's condition score diary outcomes in systemic sclerosis**

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**Abstract (250 words)**

**Objectives:** Raynaud's 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 explored 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's Condition Score (RCS)-diary alongside collection of patient demographics, clinical phenotype, the Coping Strategies Questionnaire, Pain Catastrophisation Scale, Scleroderma Health Assessment Questionnaire (SHAQ) and both patient/physician visual analogue scale (VAS) assessments for RP, digital ulcer disease and global disease. Environmental temperature data was obtained at each site. A second RCS-diary was completed 6-months after enrolment.

**Results:** We enrolled 107 patients (baseline questionnaires returned by 94). There were significant associations between RCS-diary parameters and both catastrophisation and coping strategies. There were significant associations between RCS-diary outcomes and both environmental temperature and season of enrolment. 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, the SHAQ pain VAS and the SHAQ gastrointestinal VAS subscales as the strongest independent predictors of the RCS score.

**Conclusions:** Patient-reported assessment of SSc-RP severity is associated with a number of factors including pain, catastrophisation and coping strategies. The effects of seasonal variation in environmental temperature on SSc-RP burden has implications for clinical trial

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design. Treatments targeting SSc-RP pain and the development of behavioural interventions enhancing coping strategies may reduce the burden of SSc-RP.

## Introduction

Raynaud's phenomenon (RP) describes episodic excessive vasoconstriction of the digital microvasculature in response to cold exposure and/or emotional stress (1). It is the commonest manifestation of systemic sclerosis (SSc) and a major cause of disease-related morbidity (2-4). The severity of the underlying digital obliterative microangiopathy and relative efficacy of vasodilator medications are likely to contribute to the wide inter-individual variation in the severity and impact 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 impact of SSc-RP symptoms (4). The Raynaud's Condition Score (RCS) diary is currently the preferred endpoint for SSc-RP clinical trials (8). Captured over a 1-2 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 impact /severity of SSc-RP symptoms (applied as either an 11-point numeric rating scale [NRS] or 100mm visual analogue scale [VAS]). The mean daily frequency and duration of RP attacks during 2-week RCS diary collection has been relatively consistent across studies (between 3-4 attacks per day with a mean daily aggregate duration of 30-90 minutes/day; equating to average attack duration of ~15-20 minutes per attack (3). Similarly, the mean RCS score in SSc patients is typically ~4.4/10 on an 11-point NRS (3). Much of this data has been obtained in clinical trial settings; typically undertaken during Winter and often mandating a minimum threshold number of RP attacks in the period prior to study entry (3, 13). Establishing treatment efficacy using RCS diary parameters has been challenging with clinical trials of promising vasodilator therapies yielding negative or modestly positive findings at best (9-13). The high

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placebo response and poor agreement between RCS-diary parameters and objective assessments of digital perfusion have caused consternation (5, 14). Additional concerns about the RCS diary have been raised amongst 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's Symptom Study (RSS) is a multi-center longitudinal study designed to assess the nature 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, catastrophisation, and seasonal variation in environmental temperatures on patient-reported assessment of RP severity.

## **Patients 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, United Kingdom (UK) and Utah, United States (US) between April 2015 and January 2017. All patients were English speaking. 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 1<sup>st</sup> non-RP symptom), smoking history, clinical phenotype and

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autoimmune serology. The clinical phenotype sought documented evidence from the case notes of gastro-oesophageal reflux disease (GORD) symptoms, puffy fingers, sclerodactyly, digital ulcers (DU), digital pitting (DP), telangiectases, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) and autoantibody specificity. Relevant co-morbidities and vasoactive medication use were documented. Clinicians completed 100mm VAS scores physician global assessment, RP severity and DU severity.

### *Patient questionnaires*

Each participant received a RSS questionnaire containing the Scleroderma Health Assessment Questionnaire (SHAQ), comprising the HAQ-Disability Index and SSc-specific 150mm VAS subscales (18), the one-item coping skills questionnaire [CSQ] (19) (a validated abridged version of the original CSQ (20)), the pain catastrophisation scale [PCS] (21) and separate 100mm VAS assessments for SSc-RP severity, patient global assessment and DU severity (see supplementary material). The 7 items of the one-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: Diverting Attention , Reinterpreting Pain Sensations , Catastrophizing , Ignoring Sensations , Praying and Hoping , Coping Self-Statements and Increasing Behavioural Activities (19, 20). Patients were dichotomised 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 impacts on 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 cut-off of 30 applied to dichotomise the group into copers and catastrophizers (based on earlier work identifying a score of 30 as corresponding to the 75<sup>th</sup> percentile in samples of chronic pain patients) (21). Subscales for rumination (items 8-11), helplessness (items 1-5, 12) and magnification (items



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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 [of 14] had been completed satisfactorily). Participants completed a second RCS diary 6 months following enrolment.

#### *Weather data*

The daily maximum and minimum temperature from Bath, UK and Salt Lake City, Utah, weather stations was obtained using UK Meteorological Office data for April 2015 through to July 2017.

#### *Statistical analysis*

Descriptive statistics are defined where applicable. The Chi square test was used to compare observed frequencies across two 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 Rho 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 score 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 parameters were used for analyses examining associations with baseline questionnaire outcomes (e.g. relationship with CSQ and PCS). The impact of season was assessed by pooling RCS diary returns and categorising patients according to season of

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enrolment (Winter [1<sup>st</sup> December-February 28<sup>th</sup>], Spring [March 1<sup>st</sup> – May 31<sup>st</sup>], Summer [June 1<sup>st</sup> – August 31<sup>st</sup>] and Fall [September 1<sup>st</sup> – November 30<sup>th</sup>]). Local Meteorological Office data during the period of RCS diary collection was used to further explore 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*

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 baseline questionnaires. The patient demographics and clinical phenotype of the cohort are summarized in Table 1. The two cohorts were similar and we did not consider the lower age of the Utah cohort (mean of 56.4 years vs. 65.1 years) 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 one of the 3 RCS diary parameters 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 (70.2%) patients. A full breakdown of missing data is available as supplementary material online.

### *Associations between patient coping strategies on SSc-RP symptom burden*

Higher scores for “praying and hoping” and “catastrophisation” domains of the CSQ were associated with significantly higher RCS scores ( $p < 0.05$ , Table 2) indicating a relationship

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between these thoughts and higher burden of RP. Significantly higher RCS scores were also identified amongst participants reporting high utilisation of coping strategies to “re-interpret symptoms”, and “coping self-statements” (Table 2). Efforts to effectively “ignore sensations” was associated with lower RCS scores (not statistically significant). There was no significant relationship between “increased behaviours” (doing other activities despite symptoms) or “diverting attention” and the distribution of the RCS scores. 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 score (Table 2).

#### *Association between catastrophisation and SSc-RP symptom burden*

The relationship between catastrophisation and RCS diary outcomes was replicated using the PCS data. When dichotomising the group (< or > a composite score of 30), “copers” had significantly lower median mean daily RCS scores compared to the “catastrophisers” (1.5 [0.5-3.7] vs 4.9 [2.7-6.9],  $p < 0.01$ , 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 scores across the cohort (Spearman’s  $\rho$  0.42,  $p < 0.01$ , Table 3). This relationship was strongest for domains concerning “helplessness” ( $\rho$  0.47) and “magnification” ( $\rho$  0.43) when compared to “rumination” ( $\rho$  0.35). 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 sub-domains) and patient RP VAS ( $\rho$  0.35), patient DU VAS ( $\rho$  0.33), and patient global VAS ( $\rho$  0.47). A weak positive correlation was identified between the total PCS and *physician* RP VAS ( $\rho$  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 ( $\rho$

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0.42) and each of the SHAQ subscales with the exception of the SHAQ breathing VAS (Table 3). Across all of the analyses, the association between PRO outcomes 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 ( $\rho = -0.27$ ,  $p < 0.05$ ) 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 score and both mean daily maximum and minimum temperatures (Spearman’s  $\rho = -0.22$ ,  $p < 0.01$  for both analyses). There were weak negative correlations between the mean daily frequency of RP attacks and mean daily maximum and minimum temperatures (Spearman’s  $\rho = -0.27$ ,  $p < 0.01$  for both analyses). Similar trends were observed for mean daily duration of attacks ( $\rho = -0.26$  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 enrolment with significantly higher RCS diary parameters observed in Winter compared to Summer (Table 4).

#### *Overall determinants of the RCS score*

A multi-variate model was built to evaluate the relative contribution of all the relevant factors (weather, coping, other PRO outcomes, clinical features etc.) on the RCS score. A parametric approach was necessary for building the multivariate model, but the univariate findings were consistent with the non-parametric analyses presented earlier (Tables 2 and 3). Simple linear regression identified strongly significant associations ( $p < 0.01$ ) between the RCS score and the PCS, several of the CSQ domains (particularly “catastrophisation”

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[ $p < 0.001$ ] 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 scores 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 rho 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 sub-scores and the PCS sub-scores were highly correlated (Pearson’s correlation  $> 0.7$  for all pairs). The best fitting multivariate model only included the patient RP VAS, the SHAQ pain VAS and SHAQ 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 three predictors. The final multivariate model suggests increases in each of these PRO measures 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 two 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 relationship with the extent of digital vasoconstriction but the complex interplay of factors including, but not limited to, pain perception, coping strategies, catastrophisation and seasonal variation in weather.

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Our study is the first to examine the relationship between coping and patient-reported SSc-RP symptoms. Our findings confirm an earlier consensus amongst SSc experts in which 90% considered coping strategies to be an important determinant of RCS diary outcomes (15). Catastrophisation appears to be important with patients that report this behaviour (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 catastrophisation) could be used to develop novel behavioural approaches to by enhance resilience to reduce the impact 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 capitalise on these observations (4). Cognitive-behavioural interventions that modify catastrophisation (specifically concerning feelings of helplessness and tendency to symptom magnification) could be used to reduce the burden of SSc-RP. The direction of the relationship between the adoption of coping strategies around “re-interpretation” and “coping self-statements” and RCS diary outcomes was somewhat unexpected (with patients reporting a higher impact of SSc-RP despite the utilisation of coping strategies within these domains). Nonetheless, strategies to help patients to think about their RP symptoms in more neutral terms (“re-interpretation”), desist from catastrophisation thoughts (such as “I can’t stand it anymore”) or 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

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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-behavioural interventions targeting “ignoring sensations” and “increasing behavioural activities” might result in excessive exposure to activities that might exacerbate peripheral vasoconstriction (23). Previous behavioural interventions for RP have examined approaches such as biofeedback that from a modern perspective are deemed ineffective. Behavioural interventions focussing on the modification of catastrophisation 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 score. Whilst 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 scores within the univariate analysis. Similarly, the SHAQ breathing VAS was the only subscale not to correlate with PCS parameters. A complex non-linear relationship between the severity of digital vasculopathy and pain perception may explain the poor agreement between

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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 impact of SSc-RP symptoms. The original validation work of the RCS diary identified differences in RCS scores (but not mean daily frequency or duration of RP attacks) in patients with and without DU (26). This study utilised data from a clinical trial that only recruited patients during the Winter months, examined differences in RCS diary parameters in patients with “active” DU (rather than a history of DU) and, importantly, utilised RCS score item wording that encouraged patients to consider the impact of “digital sores” when choosing their RCS score (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 with respect to studies countenancing enrolment 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 one study identifying a >50% improvement in RCS scores in over a fifth of patients following placebo administration (5). The pooled analysis for this estimation was undertaken using data from 3 RCTs that enrolled at Northern-hemispheric sites during Winter with primary endpoint analysis in the Spring (5). Changes in environmental temperature could be an



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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 underway 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).

The present study benefits from being a comparatively large multi-centre study but being primarily a cross-sectional study and the lack of objective assessment limits the extent to which we can fully explore the determinants of RCS diary outcomes. Approximately 30% of participants did not return the 6-month RCS diary although study attrition in a longitudinal study of self-administered questionnaires was expected and the majority of our analyses utilised baseline data alone, for which there was little 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 towards the RCS diary as a clinical trial endpoint (7, 15). The 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, inform future clinical trial design and may help develop novel behavioural approaches for the management of SSc-RP.

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