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Concise report

Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception

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Abstract

Objective. To evaluate whether patients can predict attacks of RP (if so, this would have implications for developing new treatments) and to evaluate the impact of RP attacks on quality of life (QoL).

Methods. Individuals with RP were invited through international patient associations to participate in an online survey.

Results. Responses from 443 subjects with self-reported RP from 15 countries were evaluable. The mean age of subjects was 41 years (91% female). Fifty-eight per cent of subjects reported they could predict at least 51% of RP attacks, and 57% could predict attack severity either fairly well or better [with 43% predicting severity only poorly (30%) or very poorly (13%)]. Sixty-four per cent of subjects reported a poor or very poor current ability to prevent/control RP attacks. One hundred and eighty-two subjects (41%) reported current or previous use of medications for RP: 82% reported at least one currently used medication being tolerated, but only 16% reported at least one current medication being effective. Most subjects (78%) reported making at least one life adjustment due to RP, with more in subjects with secondary RP compared with primary RP (87% *vs* 71%, $P = 0.001$). Current QoL with RP was impaired [mean = 6/10 (10 best imaginable)] and secondary RP subjects reported a greater absolute improvement when asked to imagine their QoL without RP (2.3 *vs* 3.3 $P = 0.0002$).

Conclusion. Subjects' ability to predict RP attacks is limited. Treatments were generally considered tolerable but seldom fully effective. Our results confirm an unmet need for new treatments. RP significantly impacts on QoL in all subjects.

Key words: Raynaud's phenomenon, systemic sclerosis, quality of life, impact, predict, severity.

Rheumatology key messages

- Subjects had a limited ability to predict the occurrence and severity of RP attacks.
- There is an unmet need to develop new treatments for RP.
- Quality of life is significantly reduced in all subjects with RP.

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Introduction

RP is a common vasospastic disorder characterized by colour change of the digits of the hands (and often the feet) in response to cold and/or emotional stressors [1, 2]. In most patients RP is idiopathic [primary RP (PRP)], but less commonly may be secondary (SRP) to an underlying disease process, e.g. SSc [1, 2]. SRP (unlike PRP) may progress to irreversible tissue damage resulting in digital ulceration or digital loss [1, 2], especially

in patients with SSc [3]. Currently licensed treatments for RP are far from ideal and are often associated with significant side effects [4, 5]. One possible solution would be to develop treatments to be taken immediately before or after the onset of RP rather than on a continuous basis. We wondered if patients could anticipate an upcoming RP attack based on previous life experiences with exposure to cold or emotional stress triggers. Little is known about whether patients can predict either the occurrence or severity of future RP attacks and there is very little literature relating to patients' quality of life (QoL) with RP [6, 7], thus determining the impact of RP on the patient's daily life is another area requiring further research. The specific objectives of the study were to explore whether subjects could predict the occurrence and severity of RP attacks, to determine the subjects' current ability to prevent/control RP attacks, and to determine the impact of RP attacks on QoL.

Methods

Study design

A survey was developed to inform a drug development programme for the treatment of RP. Three international patient associations—the Federation of European Scleroderma Associations, the Raynaud's and Scleroderma Association and the Raynaud's Association—were asked to distribute a link to the online survey to their members. The link was posted on the association's website or on social media pages; one association also included the link in a printed monthly letter to its members. The survey (see supplementary data, available at *Rheumatology* Online) comprised 19 questions that included basic demographic information, the background of the responders' RP, whether they can predict RP attacks, how they control their RP and its impact on QoL. The first question filtered the responders: Do you suffer from RP (colour changes of your fingers, usually in response to cold. Typical colour changes are white and/or blue and/or red)? Responders who selected no or I do not know were not eligible to progress further. Ethical approval was deemed unnecessary because identifiable information was not collected and the online questionnaire system was set not to collect any information on the responder.

Statistical analysis

All statistical analyses on the data were performed using STATA version 13 (StataCorp, College Station, TX, USA). The Mann–Whitney test was used to make comparisons of ordinal responses between subjects with PRP and those with SRP. Chi-square tests were used to compare binary variables and *t*-tests were used to compare continuous variables. Linear regression was performed to explore the association between current QoL and type of RP while adjusting for age. A *t*-test of the differences between the actual and imagined QoL scores was preferred to linear regression, as the assumptions underlying the regression were found to be untenable. Respondents who did not know or did not report whether their RP was primary or secondary were excluded from comparisons between individuals with PRP and those SRP, but were included in overall summaries of the cohort.

Results

Responders' demographics

A total of 487 responses to the online survey were submitted, of which 443 were from responders with RP (as self-reported) and evaluable. The mean age of responders (henceforth termed subjects) (not reported for two subjects) was 41.3 years [range 18–83 (S.D. 13.8)]; subjects with SRP were slightly older than those with PRP (46.3 *vs* 38 years). The majority (91%) of subjects were female (not reported for four subjects). Responders were asked to state the country of winter residence; of the 15 separate countries reported, most (85%) lived in either in the UK or the USA.

RP characteristics

Subjects were asked to indicate whether they suffered from PRP (43%) or SRP (34%). Approximately one quarter (23%) did not know whether they had PRP or SRP (not reported for seven subjects). The majority of subjects with SRP (59%) indicated that their RP was due to SSc, and 58% of subjects with SSc reported a history of digital ulceration. The self-reported duration of RP was >10 years in 50%, 5–10 years in 16%, 2–5 years in 23% and <2 years in 11%, with no evidence of a difference between subjects with PRP and those with SRP ($P = 0.4$).

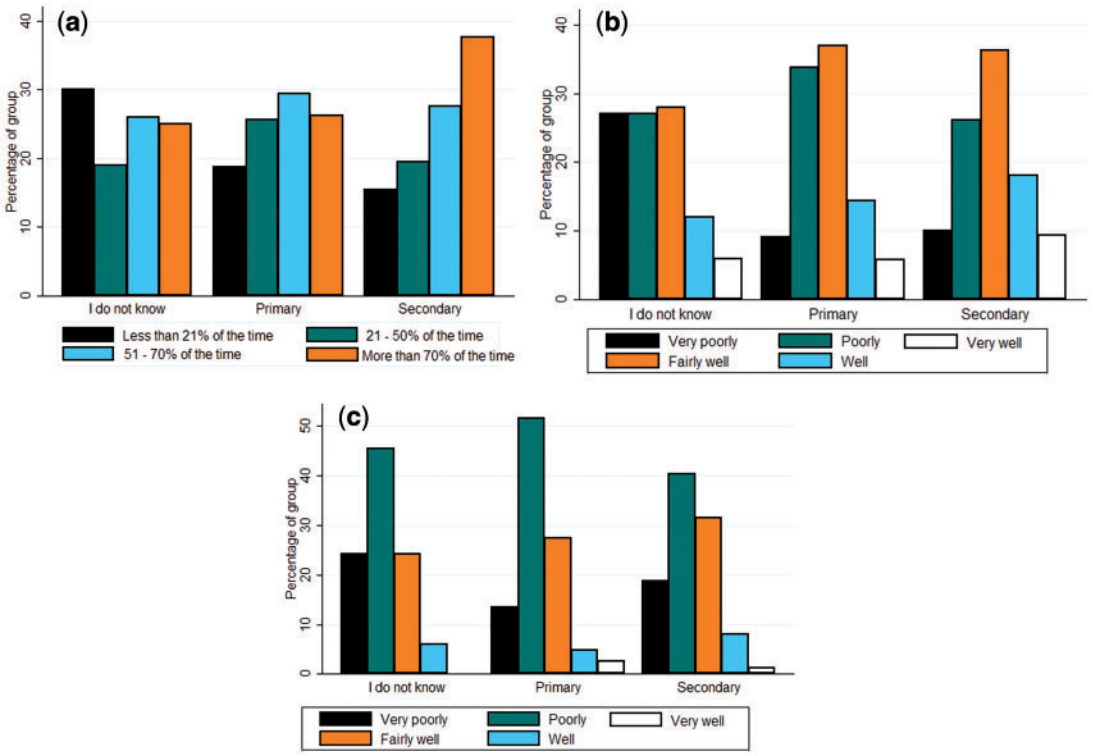
Prediction of attacks

Subjects were asked to report their ability to predict the occurrence (Fig. 1a) of RP attacks on an ordinal scale (<21%, 21–50%, 51–70% and >70% of the time). Fifty-eight per cent reported that they could predict at least 51% of RP attacks (66% SRP *vs* 56% PRP, $P = 0.03$). Subjects were also asked whether they could predict the severity (Fig. 1b) of RP attacks on an ordinal scale (very poorly, poorly, fairly well, well and very well). Fifty-seven per cent reported that they could predict attack severity either fairly well or better (64% SRP *vs* 58% PRP, $P = 0.16$), with 43% predicting severity only poorly (30%) or very poorly (13%). The majority of subjects (91%) reported that cold sensitivity was a trigger for RP, with approximately one-third (30%) reporting emotional stress. SRP subjects were more likely than PRP subjects to report an emotional trigger (30% *vs* 17%, $P = 0.007$), with no evidence of a difference in cold sensitivity (95% *vs* 91%, $P = 0.12$).

Prevention and treatment of attacks

Subjects were asked to report how well they could currently prevent/control the occurrence of RP attacks on an ordinal scale (very poorly, poorly, fairly well, well and very well). Sixty-four per cent reported either a poor or very poor current ability to prevent/control the occurrence of

FIG. 1 Prediction of the occurrence/severity and the ability to prevent/control RP attacks

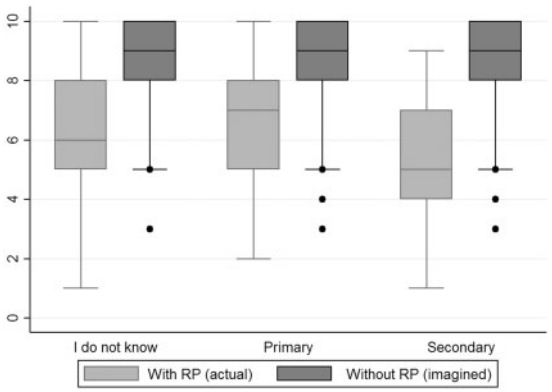


Subject-reported ability to predict (**a**) the occurrence and (**b**) the severity of RP attacks. (**c**) Current ability to prevent/control RP attacks, by RP subtype. Subjects were subdivided into those with primary RP, those with secondary RP and those who did not know whether their RP was primary or secondary (I do not know).

RP attacks (Fig. 1c). There was insufficient evidence to suggest that the overall patterns of self-perceived prevention ability were different between SRP and PRP populations ($P = 0.77$).

Of all subjects, 182 (41%) reported either current or previous medication use for their RP, with higher use reported in SRP subjects compared with PRP (64% *vs* 33%, $P < 0.001$). Subjects were asked to list up to three of the medications that they have used to control their RP. One hundred and twenty-one subjects (27%) reported currently taking medication/s for RP: 86 (71%) one medication, 27 (22%) two medications and 8 (7%) three medications. Vasodilators were most commonly used (88% of those currently taking medication for RP), with the majority of these subjects taking calcium channel blockers (75%). Subjects were asked to grade the effectiveness of the medication they reported on an ordinal scale (not effective, fairly effective and effective). Most subjects reported that at least one of their current medications was at least fairly effective for RP (85%) or was tolerated (82%). However, only 16% of subjects reported that one or more of their medications was effective. A greater proportion of SRP subjects than PRP subjects believed at least one of their current medications to be at least fairly effective (91% *vs* 79%, $P = 0.09$) or effective (21% *vs* 12%, $P = 0.29$), whereas more PRP subjects

FIG. 2 Quality of life (QoL) in subjects with RP



Current reported QoL in subjects with primary and secondary RP, and an assessment of what QoL would be without RP, by RP subtype. Subjects were subdivided into those with primary RP, those with secondary RP and those who did not know whether their RP was primary or secondary (I do not know). Medians and interquartile ranges are displayed (boxes) together with the ranges (whiskers). Potentially outlying values are plotted separately.

reported at least one of their current medications was tolerated (85% *vs* 81%, $P = 0.58$).

Impact of attacks

The perceived impact of RP attacks on patients' QoL is shown in Fig. 2. Most subjects (78%) reported making at least one adjustment to their life due to RP, more so for SRP than PRP (87% *vs* 71%, $P = 0.001$). Subjects were asked to assess their QoL with RP (on a 0–10 scale, where 10 is the best imaginable QoL). The mean QoL for all subjects with RP was 6.0 (S.D. 2.1, range 1–10). PRP subjects' current QoL was higher than SRP subjects [mean QoL 6.5 and 5.2, respectively; difference in mean 1.21 (95% CI 0.76, 1.66); $P < 0.001$] after adjusting for age, sex and duration of RP using linear regression. When asked to imagine their QoL without RP, SRP subjects imagined a greater absolute improvement from their current QoL [2.3 *vs* 3.3; difference in means −0.9 (95% CI −1.4, −0.4); $P = 0.0002$].

Discussion

This is the first study, to our knowledge, to explore whether subjects can predict the occurrence and severity of RP attacks. A key finding of the study is that subjects have a limited ability to predict these. Only approximately half of the subjects could predict the occurrence of RP attacks on at least 51% of occasions or predict the severity fairy well or better, with SRP subjects predicting better than PRP subjects. The difference was statistically significant for the prediction of occurrence of RP attacks, but not for the prediction of severity.

The limited ability of subjects to predict RP attacks must be considered in the development (including clinical trial design) of future novel, *pro re nata* (PRN, as required) treatments. For example, in a recent study of a novel formulation of glyceryl trinitrate for RP, the study drug was provided to participants in a pouch to be used immediately before or up to 5 min after the onset of an RP attack [8]. Our results suggest that almost half of patients would not be able to anticipate attacks and therefore would not initiate treatment before an attack. Thus preventive therapy is best given at some regular pre-set interval determined by the expected duration of benefit of the agent to be studied.

Almost half of all subjects reported either current or previous treatment for RP. Although >80% of subjects currently taking medication for their RP reported that at least one current medication was at least either fairly effective or was tolerated, only 16% reported currently taking a medication that they described as effective. More than 60% of subjects reported either a very poor or poor ability to prevent or control RP attacks. These data support the idea that there is an unmet clinical need to develop new additional treatments and to re-examine the existing strategy for treating RP.

Our results confirm a perceived detrimental impact of RP on subjects' QoL [6, 7, 9–11], including in subjects with PRP [4, 7]. Most subjects reported making at least one adjustment to their life due to RP, and most thought there would be a significant improvement in QoL when asked to imagine life without RP. As one might expect, SRP subjects' QoL due to RP was more severely impacted and the potential perceived improvement in the absence of RP was greater than for PRP subjects. There is a very limited literature base directly exploring QoL in patients with PRP [7] and SRP [6], although several studies examining drug treatment involving SRP patients have confirmed an improvement in QoL with RP treatment, including calcium channel blockers [9], iloprost [10] and phosphodiesterase type 5 inhibitors [11].

Our study does have several limitations. Subjects were recruited through RP-related international patient associations, therefore it could be argued that those subjects who participated might have had more severe RP, or conversely, some may just be cold sensitive. Consequently our findings might not be generalizable to all patients with RP. Twenty-three per cent of respondents did not know whether they had PRP or SRP and had to be excluded from comparisons between disease subtypes. Results based on these comparisons might be biased if those who did not know their diagnosis differ systematically from those who did. In addition, we used a simple, pragmatic, non-validated scale for patients to report perceived QoL both with and without RP. Climate data were only available for approximately half of respondents (and therefore these data were not shown), the majority of whom were located in temperate climates, e.g. north-western Europe. In future studies, the impact of climate on patient-perceived RP should be explored.

In conclusion, our findings suggest that subjects with RP have a limited ability to predict both the occurrence and the severity of RP attacks, and thus this must be considered in the development and design of clinical trials of future treatments for RP. Subjects reported a poor ability to prevent/control RP attacks, and in those who currently took medication for RP, only 16% reported that at least one current medication was effective, a finding consistent with an unmet area of clinical need. Our data confirm the significant burden of PRP as well as SRP on QoL.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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