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How Do Patients Define Raynaud's Phenomenon? Differences Between Primary and Secondary Disease

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ABSTRACT

INTRODUCTION/ OBJECTIVES: To examine how people define Raynaud's Phenomenon (RP), based on their lived experiences and explore if differences exist depending on primary or secondary RP diagnosis.

METHOD: An international survey was sent to people with RP through health systems, foundations, and social media. Qualitative coding of responses to an open text question regarding one's own definition of RP was performed and themes were identified. Prevalence of themes among the sample and then comparisons between themes among people who self-reported primary versus secondary diagnosis of RP were performed.

RESULTS: There were 1345 respondents from 45 countries (mean age 51.5 years, 93% female) who defined RP in their own words; 17% reported primary RP and 83% reported secondary RP (69% of secondary RP was scleroderma-related, $n = 927$). Over half defined their RP by describing the body parts affected, color changes, pain, and triggers or situations in which an episode occurs. Patients with primary RP more frequently defined RP in terms of its impact on function/quality of life and pain compared to those with secondary RP (34.5% versus 25.3% respectively, $p=0.004$; 54.0% versus 46.8%, $p=0.05$). Patients with secondary RP more frequently included specific body parts, color change, the management of attacks and other digital vascular complications in their definition of RP.

CONCLUSIONS: We have identified differences in how people with primary and secondary RP define RP, in terms of how they feel and function. Our findings have implications for the domains of outcome measures for assessing RP within different patient populations.

Keywords: Raynaud's Phenomenon, Scleroderma, systemic sclerosis, qualitative analysis, connective tissue diseases.

Key messages:

- Pain is more often mentioned in primary RP and color change in secondary RP.
- Over 25% of patients included reduced quality of life as part of their RP definition.
- The concept of "attack" is used to define RP by only 2% of patients.

INTRODUCTION

Raynaud's Phenomenon (RP) is a vascular disorder characterized by painful episodes of digital discoloration and rapid blood flow back to the affected areas [1] which impacts about 5% of the population worldwide [2]. RP has no cure, so treatment is focused on strategies that enable people to better manage symptoms, such as vasodilator medication and strategies to adapt to or avoid common triggers of cold exposure and emotional stress. However, optimal management is challenging. A main problem in establishing appropriate treatments is that RP itself is a blanket term describing heterogeneous disorders with different etiologies [3, 4], and practice guidelines and research studies often fail to account for these differences [3]. Additionally, the RP experience is not well-characterized and may differ between individuals [5], which hinders the ability to optimize treatment strategies.

A better understanding of how patients define their RP and its impact can better diagnose, assess (through understanding relevant outcome measure domains) and optimize treatment. Further, treatment targets may differ according to RP classification; whether it is 'primary', a functional vasospastic disorder without underlying cause in an otherwise healthy person, or 'secondary' to another condition, such as systemic sclerosis (SSc) [6]. Despite shared use of the eponym, the pathophysiology of primary RP and SSc-RP differs markedly. Both are associated with macrovascular vasospasm of the digital arteries and arterioles, but in SSc, digital vasculopathy is also associated with an irreversible obliterative microangiopathy.

Differences in the lived experience of RP between primary and secondary RP has not been systematically studied, but could have implications for outcome measures and interventions. Previous studies have identified differences; with pain was a prominent feature of secondary (SSc-related) RP whereas numbness was more frequently associated with primary RP [7, 8]. We utilized a large international survey of people with RP (n = 1345) to examine and compare how patients defined their primary or secondary RP in their own words. Through a synthesis of qualitative data, we discuss experiences that may inform future research on RP management in these two patient populations.

METHODS

Data were taken from the PATient Survey of experiences of RAYnaud's Phenomenon (PASRAP) Survey Project. The study was approved with exempt status by the University of Michigan IRB (Study ID: HUM00175143; OHRP IRB Registration Number(s): IRB00000246). An online survey was sent through several methods to tap a sample with primary or secondary (SSc-related) RP:

social media (including Facebook and Twitter), a scleroderma self-management website, Scleroderma Foundation website, and Scleroderma Raynaud's UK. Written consent was not needed based on IRB determination. The overall project objective was to examine signs and symptoms of RP including nature of digital color change and sensory symptoms, such as digital vasculopathy severity. Participants (≥ 18 years old) were invited to complete the survey if they had clinician-diagnosed RP. All participants self-reported RP classification (primary-not associated with another condition-or secondary). For secondary RP, the underlying disorder was specified by patients.

Analysis

To characterize the sample, descriptive analyses such as means and frequency counts were used. T-Tests and chi-square tests were used to examine differences between primary and secondary RP. Participants were asked to "define RP in your own words". Responses in languages other than English (e.g., Portuguese, Danish, French, Spanish) were translated into English prior to coding. Qualitative data was analyzed using an open coding process. All raters (SLM, MA, AL) were blinded to patient RP classification and had no information concerning demographics and geographical origins of patients while coding. They were only provided with written responses of each patient's RP definition. Definitions varied in length from a few words to several sentences; most commonly, 1-2 sentences were provided. Two independent raters (clinician specialized in RP management and patient with SSc-related RP) independently coded each transcript and came together to reconcile discrepancies. In cases where agreement was not reached, co-author SLM provided final reconciliation. Throughout coding, the codebook was revised as needed in an iterative, collaborative process among the team. Once both raters completed coding independently (using a common version of the codebook), a single report of themes was created. Qualitative frequencies resulting from this coding were utilized to inform what domains were most salient to participants [9]. Frequencies of themes were compared across primary and secondary RP using chi-square tests and presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were performed using SPSS 20.0. All tests were performed with a significance level of $p \leq 0.05$.

RESULTS

The survey was completed by 1718 people between April and May 2020. Of those, 1345 supplied an RP definition and self-reported primary or secondary RP. This sample was 93% female,

mean age was 51.5 years (SD± 13.4; range 18-83), and participants were from 45 countries (across 6 continents). With regard to RP classification, 17% (n=226) reported primary RP, 69% (n=927) reported SSc-RP, and 14% (n=192) reported other non-SSc-related, non-primary RP. Participants with primary RP were younger than those with secondary RP in this sample (41.8 years ± 11.9 versus 53.3 years ± 12.9 respectively, $p < 0.0001$, $n = 1337$). Of people with primary RP, 48% felt that their RP was not well-controlled. Slightly less than one third of the sample (31%) saw a specialist for RP, whereas the rest received care from a primary care provider. Use of vasodilators such as sildenafil, tadalafil or riociguat, was more frequently reported in patients with secondary RP versus primary RP (18.0% versus 2.6% respectively). The secondary RP group also more frequently reported usage of Endothelin receptor antagonists compared to the primary RP group (3.7% versus 1.3%).

Table 1 shows themes and patient descriptions. Regardless of RP classification, most people defined their RP by specific body parts affected, fingers and toes most frequently. Change in color of fingers and toes, and pain were mentioned by nearly half of the sample. Of people who identified triggers ($n = 624$, 46%), most were able to identify triggers that caused an episode (e.g., cold, stress, environmental conditions), although some mentioned it was unpredictable. Only 29 patients defined RP using “attack” (2%), and “episode” was only mentioned 13 times. Patients nonetheless frequently reported a similar succession of episodic color changes and sensations such as: “fingers turn white then blue then red, with pain”. The impact on quality of life and function was described by over a quarter of the sample (27%). People mostly used negative descriptors such as “debilitating, life-changing, or embarrassing”. Some people provided descriptions that ranged in severity from “inconvenient”, “limiting activities” to “makes my life a living hell.”. Others provided more details such as: “It's horrible. My hands are always cold. I have to wear gloves most of the time.” Another person defined RP stating: “It affects my daily life. I am always cold, my hands feel it the most. It can be depressing. It's not easy to manage. I have many aches and pains. I often ache.”

Table 2 shows differences in how people define their RP based on primary or secondary classification. Of all themes identified, six were significantly different in proportions who endorsed each by group. People with primary RP more frequently mentioned RP's impact on function or quality of life compared to secondary (35% and 25% respectively, $p=0.004$). Pain was more frequently mentioned in primary compared to secondary RP (54% and 47% respectively, $p=0.05$). In contrast, patients with secondary RP more frequently cited specific body parts, color change, management of attacks and RP-related complications.

DISCUSSION

This large international study found patients defined RP most often by body parts involved, color change, and pain. Significant differences in frequency of these three main themes were found in patients with primary and secondary RP. Pain was more frequently mentioned in primary RP whereas color change and body parts involved were more frequent in secondary RP. These results suggest that the definition and perception of RP differ by classification. More than a quarter of the overall sample mentioned reduced quality of life as part of their definition.

The main themes identified are consistent with a previous focus group study of 40 patients with SSc-RP [5], although the findings of this survey are based on reports from a larger number of people with SSc across 6 continents. The core domains comprising the patient experience of RP were similar across primary RP and SSc, although the relative importance (based on frequency of reported themes) differs between these patient populations. For example, RP management was only mentioned by 7% of people with primary RP whereas 13% of patients with secondary RP mentioned this theme. The theme “Constant vigilance and self-management” previously identified in SSc-related RP would thus be less applicable to primary RP [5, 8].

Although all patients defined RP by its impact on quality of life, it was more frequently mentioned in primary RP. It may be that patients with secondary RP benefit from being more closely monitored by their provider for their primary condition or view RP as part of their overall disease. In patients with SSc-related RP, other symptoms, like digital ulcers or gastrointestinal involvement, may be more impactful on quality of life than RP itself [10-12]. Previous studies mentioned that pain was more frequently reported in SSc-associated RP, but our results show a trend for more pain in primary RP [7, 8]. Recent advances in management of RP-related complications such as digital ulcers may have helped to limit pain in secondary RP [13]. Many patients from both groups also reported an impact of RP on functioning. Several patients also mentioned the impact of how others reacted to their RP as “embarrassing” or “misunderstood”. For some patients, it may be important to consider other therapies such as use of psychologists to address mental health and mood issues that may coincide with RP. Others mentioned lack of clinician education concerning RP. Education of clinicians about RP and addressing its complications may help improve patient quality of life. This may include referral to rehabilitation services to help people learn adaptive strategies for situations where RP is triggered.

Only one third of patients with primary RP included color change in their definition whereas this theme was mentioned by more than half of patients with secondary RP. Such findings could have implications for outcome measure development. For example, including color change in a combined index or outcome measure may not have the same clinical relevance to patients with secondary and primary RP. Interestingly, the concept of “episode” or “attack” was only included in definitions by less than 5% of the sample. This result challenges the concept of discrete “attacks” and number of “attacks” that has formed the basis of previous clinician-derived outcome measures in RP trials (14). Our findings are consistent with previous studies highlighting that number of RP attacks may be unreflective of RP activity. Previous studies have observed that some patients are not “100% sure what an attack is” [5, 15]. Therefore, the concept of “attacks” may not properly reflect RP from the patients’ perspective.

Our study does have some limitations. Participants were recruited through RP-related patient associations or foundations which has the risk of inherent selection-bias of more severe and well-informed patients. Diagnosis and classification of RP as primary or secondary was based on self-report which may have led to misclassification. However, our data suggest that classifications were trustworthy as people with secondary RP more frequently reported cutaneous complications such as telangiectasia or digital ulcers which are frequently seen in secondary RP related to SSc. The qualitative analysis was only based on a single open-ended question and thus saturation of themes was not possible. However, a particular strength is that this study has much more generalizability given the size and international representation of the sample. Also utilization of a mixed qualitative & quantitative approach allowed analysis of themes derived from patient data instead of preconceived definitions of themes and domains.

To conclude, our study highlights differences in relative importance of themes used for RP definitions of patients with secondary and primary RP and suggests that these two populations may differ in terms of feeling or functioning regarding their condition.

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Table 1. Examples of Responses Under Each Theme

Defines RP by...

EFFECTS ON BODY PARTS

Stating number and/or type of body parts affected

- “Decreased circulation to extremities. For me it is fingertips.”
- “(it’s) like having all the blood drained from your fingers.”

Stating color change and/or describes how colors change

- “Hands and feet become very cold with redness, white and blue color.”
- “Finger gets cold, turns white, individually, maybe just one, and feel numb and can't be warmed up with warm water, etc. Eventually warm up, turn red and stung a little.”

SYMPTOMS

Reporting pain

- “Throbbing pain at night, particularly before starting medication.”
- “Irritating and painful”

Mentioning other symptoms such as numbness, cold, head, loss of sensation, cramps, spasms

- “Burning sensation in the fingers and/or toes from lack of blood flow”

Reporting tingling, pins and needles

- “Taking all the blood flow and replacing it with lava burning pins and needles”

TRIGGERS

Identifying a trigger/ situation(s) in which it occurs, or unpredictable nature of episodes

- “(RP) can be triggered by cold weather, opening freezer, a breeze...”
- “Mine is triggered by stress & cold...”

IMPACT AND EFFECTS ON QUALITY OF LIFE

Describing impact on quality of life, by expressing negative emotions, how others react to RP, or specific functional limitations, such as loss of hand function

- “Debilitating to so many different aspects of everyday life. It was become increasingly worse every year!”
- “Embarrassing around people who don't know what it is. Limiting to day to day life. Impacts me every day”
- “Horrible! It is triggered by more than just temperature. Often just using the bathroom or eating in the morning will set it off. And it feels like my whole body is impacted. Sometimes I have just give in and lie down under an electric blanket”

MECHANISM

Explaining the mechanism, pathogenesis, how the body works or doesn't work

- “My body's overreaction to cold temperatures, almost a faulty defense mechanism to protect against cold weather”
- “Restricted circulation which leads to episodes of discoloration & pain in the extremities”

ONSET/ DURATION

Discussing timing of an episode, whether it was gradual or sudden onset or duration

- “Sleeping fingers that turn white in color, and then go to purple. It usually lasts around 20-30 minutes.”
- “Fingers suddenly lose blood supply...”

MANAGE SYMPTOMS

Mentioning strategies to try to manage, prevent, or stop episodes

- “Hands will swell in size and is very uncomfortable. Have tried meds and creams nothing works. What I find that works are white cotton gloves at night.”
- “I have to run (my fingers) under warm water then they turn purplish blue before returning to their normal color. I keep gloves/ mittens with me at all times and hand warmers...”

COMPLICATIONS

Reporting complications of RP, such as chilblains, telangiectasias, digital ulcers, sores, cracking, or infections

- “...Now in my feet with occasional chilblains”
- “...The ulcers are the most painful side effect.”

INFLUENCE OF WEATHER

Discussing differences in RP due to seasons or weather

- “(White freezing fingers and toes) happens more in winter but also spring if I'm outside and not moving”
 - “Winter very difficult, summer air conditioning a nightmare”
-

Table 2. Differences in RP Definition based on Primary or Secondary Diagnosis (n = 1345)

Themes from RP	Primary RP (N = 226)		Secondary RP (N = 1119)		OR	95% CI	P value
	n	(%)	n	(%)			
EFFECTS ON BODY PARTS							
Number and types of body parts affected	140	(61.9)	788	(70.4)	0.684	0.508-0.921	0.01
Color change	81	(35.8)	615	(55.0)	0.458	0.34-0.62	0.0001
SYMPTOMS							
Pain	122	(54.0)	524	(46.8)	1.33	1.00-1.77	0.05
Other symptoms	19	(8.4)	109	(9.7)	0.85	0.51-1.42	0.53
Tingling, Pins and Needles	56	(24.8)	248	(22.2)	0.86	0.62-1.21	0.39
TRIGGERS							
Identifying triggers	94	(41.6)	530	(47.4)	0.79	0.59-1.06	0.11
IMPACT AND EFFECTS ON QUALITY OF LIFE							
Impact on function or Quality of Life	78	(34.5)	283	(25.3)	1.56	1.14-2.11	0.004
MECHANISM							
Explaining Mechanism	63	(27.9)	307	(27.4)	1.02	0.74-1.41	0.89
ONSET/DURATION							
Timing/Onset of Episodes	51	(22.6)	270	(24.1)	0.92	0.65-1.29	0.62
MANAGE SYMPTOMS							
Strategies to manage and prevent episodes	15	(6.6)	148	(13.2)	0.466	0.27-0.81	0.006
COMPLICATIONS							
Complications	11	(4.9)	111	(9.9)	0.465	0.25-0.88	0.02
INFLUENCE OF WEATHER							
Season or Weather	19	(8.4)	79	(7.1)	1.21	0.72-2.04	0.48

RP=Raynaud's Phenomenon, OR=Odds Ratio; CI=Confidence interval

Univariable associations assessed through Chi² square test, level of significance P<0.05