

Domain reporting in systemic sclerosis-related Raynaud's phenomenon: An OMERACT scoping review

Nancy Maltez^{a,*}, Michael Hughes^{b,c}, Edith Brown^d, Virginia Hickey^e, Beverley Shea^a,
Ariane L. Herrick^c, Susanna Proudman^f, Peter A. Merkel^g, John D Pauling^{h,i}

^a Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

^b Northern Care Alliance NHS Foundation Trust, Salford Care Organisation, Salford, UK

^c Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

^d Manchester, United Kingdom

^e Adelaide, Australia

^f Discipline of Medicine, University of Adelaide and Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia

^g Division of Rheumatology, Department of Medicine, Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, PA, USA

^h North Bristol NHS Trust, Bristol, UK

ⁱ Bristol Medical School, University of Bristol, Bristol, UK

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ABSTRACT

Background: Raynaud's phenomenon (RP) is a cardinal feature of SSc and is associated with significant disease-related morbidity that impacts on quality of life. The assessment of SSc-RP is challenging. The aim of this scoping review was to evaluate the outcome domains studied and outcome measures used in clinical studies of SSc-RP. **Methods:** Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials were used to identify randomized control trials (RCTs), quasi-randomized studies, case-control studies, prospective and retrospective cohort studies, case series, and cross-sectional studies of adult participants with SSc-associated RP, written in English. A minimum of 25 participants for studies of imaging modalities and 40 participants for questionnaire-based studies was required for inclusion. Basic laboratory and genetic studies were excluded. No limitations were imposed based on intervention, comparator, or study setting. Study characteristics and primary and secondary target domains in each study were recorded.

Results: 58 studies (24 randomized clinical trials) were included in the final analysis. The commonest domains captured were severity of attacks (n=35), frequency of attacks (n=28), and duration of attacks (n=19). Objective assessments of digital perfusion were also commonly used in studies of SSc-RP.

Conclusion: The outcome domains and the associated outcomes used to assess the impact of SSc-RP in research studies are broad and have varied across studies. The results of this study will inform the OMERACT Vascular Disease in Systemic Sclerosis Working Group to establish a core set of disease domains encompassing the impact of RP in SSc.

Introduction

Systemic sclerosis (SSc) is a chronic disease characterized by vasculopathy, inflammation, and fibrosis. Raynaud's phenomenon (RP) affects >96% of those with SSc and is associated with significant impact on daily activities. [1,2] Results from a Canadian National Survey demonstrated that 78% of patients with SSc rated the impact of RP on daily activities as at least "moderate". [3]

Clinically, RP is a symptom complex which presents as intermittent episodes of digital ischemia (color change including cyanosis, pallor and erythema) and is often associated with other symptoms (e.g. pain and paraesthesias). These episodes are typically exacerbated by exposure to cold. [4] Patients with SSc exhibit a spectrum of digital vasculopathy ranging from reversible attacks of RP to permanent tissue damage (i.e. digital ulcers and gangrene). Although the pathogenesis of RP remains largely unknown, a combination of endothelial damage, structural

* Corresponding author.

E-mail address: nmaltez@toh.ca (N. Maltez).

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vascular remodeling, intravascular occlusion, neural control of vascular tone, and imbalances of circulating vasoactive factors has been described.[5]

Assessing symptoms related to SSc-RP in the context of clinical trials is challenging.[6,7] The episodic nature renders clinician assessment of RP problematic. Microvascular imaging methods, whilst useful for objectively quantifying digital perfusion, do not allow capture of the impact of SSc-RP on how patients feel and function. Patient-reported outcome (PRO) instruments are better placed for capturing the unique patient experience of RP. To date, PRO instruments for assessing SSc-RP have primarily focused on diary-based capture of the frequency and duration of attacks of RP. These may be susceptible to placebo response with a global assessment of SSc-RP severity and impact assessed using single-item scales such as the Raynaud's Condition Score [8–10].

The Outcome Measures in Rheumatology (OMERACT) collaboration works to improve harmonization of outcome domain collection for rheumatologic conditions. [11,12] Understanding and defining the essential outcome domains is a crucial step in the development of a core set of outcome measures specific to any disease. The focus of this scoping review is to evaluate the concepts, core areas and domains for outcome measurement of digital vasculopathy when evaluated in clinical studies of SSc-RP, with the range of instruments used to capture these domains also appraised.

Methods

Working group

The scoping review was conducted by the OMERACT Vascular Disease in Systemic Sclerosis Working Group which consists of 6 clinicians with an interest in SSc-RP, 1 methodologist, and 2 patient research partners. [13] This project adhered to the OMERACT domain selection process. [12,14,15]

Search strategy

A literature search strategy was developed and adapted for use in the following databases: EMBASE (OVID interface, 1947 onwards), MEDLINE (OVID interface, 1947 onwards), and Cochrane Central Register of Controlled Trials (OVID interface, 1947 onwards). These databases were searched for studies pertaining to participants with a clinical diagnosis of SSc-associated RP with no limitation by classification criteria used (given the various iterations in classification criteria for SSc utilized over the study period).

Eligibility criteria

There was no limitation by intervention, comparator, or study setting. To be included in the review, studies need to be a randomized control trial (RCT), quasi-randomized study, case-control study, cohort study (prospective and retrospective), case series, or cross-sectional study and written in English. Due to the anticipated high number of studies examining SSc-RP, this review was limited to studies with a minimum of 25 participants for studies of imaging modalities or 40 participants for questionnaire-based studies. Basic laboratory, genetic, or pre-clinical studies, and articles only available in abstract form were excluded.

Data extraction

Literature review sources were uploaded to a citation management software program (Covidence) and duplicates deleted. Two review authors (NM, MH) completed independent and duplicate screening for title/abstract and full text articles according to the inclusion criteria delineated above. Disagreements were resolved through consensus between the screening authors. Standardized data extraction forms were

developed and approved by all study authors. These forms were independently piloted by the review authors by extracting pertinent data for the first ten studies deemed eligible for inclusion. The remainder of data extraction was performed by one review author (NM).

Data analysis and interpretation

Data were extracted regarding study characteristics, including study design, sample size, intervention characteristics, and participant demographics. All primary and secondary outcomes measured, and associated instruments used in the included studies, were recorded. All review authors participated in identifying overarching outcome domains.

Results

Study selection

The electronic search strategy identified 4899 records after removal of duplicates, of which 146 were deemed potentially eligible and screened for inclusion (Fig. 1). Of the 146 records, 88 were excluded, mainly due to insufficient sample size (n=23 studies), full text not available (n=17), or being conference abstracts only (n=14 studies). Fifty-eight studies were included in the final data synthesis.

Study characteristics

Study characteristics for all included studies are delineated in Table 1. The studies were conducted between 1982 and 2019, with 23 studies published after 2010. The interventions included intravenous drug therapies (n=13), oral therapies (n= 13) and topical or injectable treatments (n=5). Sample sizes for the included studies ranged between 14 and 281 participants. Twenty-four studies were RCTs, of which 19 were placebo-controlled.

The outcome domains, and instruments to evaluate SSc-RP ascertained are listed in Table 2. Three overarching domains were ultimately identified: *Raynaud's phenomenon: clinical features and severity*, *Raynaud's phenomenon: impact on function and quality of life*, and *special tests*. Associated instruments used to assess these domains are presented in Supplementary Table 1.

Raynaud's phenomenon: clinical features and severity

The majority of studies assessed the severity of attacks of RP (n=35). Frequency of attacks and duration of attacks (number of attacks and their duration as determined by the participant) were measured in 28 and 19 studies, respectively. Pain was evaluated in 9 studies and physician global assessment of RP was gauged in 5 studies. A minority of studies assessed other patient experiences of SSc-RP including numbness (n=2), cold sensitivity (n=2), patient global assessment (n=1), tingling (n=1), and color changes (n=1).

Raynaud's phenomenon: impact on function and quality of life

The impact of RP on function was measured in 11 studies. Importantly, health-related quality of life was assessed in only one included study (Table 2).

Special tests

Objective measures of digital perfusion were assessed in 44 studies with thermography (n=16), laser Doppler imaging (n=15) and videocapillaroscopy (n=14) being the most common modalities employed. Serum biomarkers (n=13) were assessed in 6 studies.

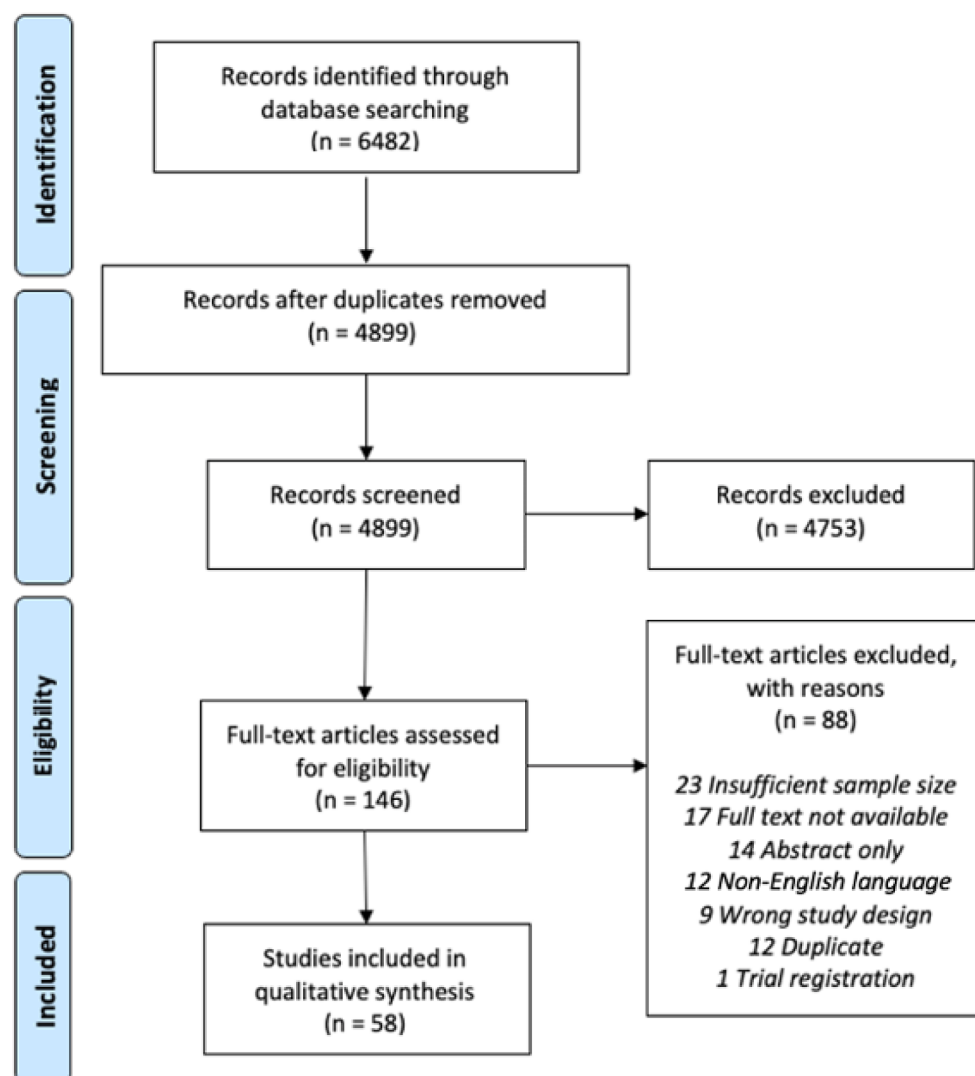


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing the search and study selection process.

Discussion

This scoping review identified outcome domains captured in the study of SSc-RP. The results were synthesized and summarized in three overarching domains: *Raynaud's phenomenon: clinical features and severity*, *Raynaud's phenomenon: impact on function and quality of life*, and *special tests*. There has been significant heterogeneity among the target domains used to date.

Interestingly, the more commonly reported outcome domains for SSc-RP in the included studies were overall impact and severity of RP ($n=35$), frequency of attacks ($n=28$), and duration of attacks ($n=19$). Although these outcomes may appear relatively intuitive, a broad range of instruments were employed to define them which, among other limitations, creates difficulty in comparing results between studies. Diary-based approaches to recording SSc-RP attack characteristics are unable to capture external factors that contribute to SSc-RP symptom worsening and the significant efforts taken by patients to avoid SSc-RP symptom worsening and/or ameliorate symptoms [16]. Symptoms of SSc-RP also appear to evolve over the course of the disease and not all patients identify with the concept of RP attacks [16,17,18]. Moreover, SSc-RP attack symptom diaries do not specifically capture other potentially important aspects of SSc-RP symptomatology such as pain, sensory symptoms, impact on function, emotional distress, social participation, and health-related quality of life [4,17]. Impact on function was only

assessed in a minority of studies identified in this review ($n=11$). Only 9 studies addressed the importance of pain, which is paramount to the patient experience of SSc-RP. Similarly, sensory symptoms have not been regularly assessed in studies of SSc-RP. [4,17] If these results reflect a perception among investigators that such experiences of SSc-RP are of less importance, then this would appear to be at odds with studies exploring the patient experience of SSc-RP. [17] A number of additional potentially important domains of SSc-RP were not identified in the present review as they have not been traditionally captured in studies and trials of SSc-RP. This does not negate the importance of these domains from a patient perspective. A pertinent example is the 'emotional impact' of SSc-RP which includes feelings of helplessness, anger, frustration, and embarrassment that have been identified as important to the patient experience. [4] This is also the case with adaptation and other self-management approaches which were not routinely captured in studies assessing severity of SSc-RP.

A variety of special tests predominantly assessing digital perfusion (n (studies) =44) have been utilized in studies to gauge severity of SSc-RP. Although these imaging modalities have been applied in clinical trials, they have not been sufficiently validated for use as surrogate measures in clinical trials of SSc-RP. [19,20] There have been many recent advances in these methods, collectively they are becoming more widely available, and validation studies are ongoing.[21] A few studies measured a variety of serum biomarkers ($n=6$) but additional studies are

Table 1
Characteristics of Studies of Raynaud's Phenomenon.

First author	Date of publication	RCT (Y/N)	Intervention	Comparator	Sample size Intervention	Comparator
Dowd [22]	1982	N	Iloprost		25	
Mohrland [23]	1985	Y	Prostaglandin	Placebo	16	15
Hawkins [24]	1986	Y	Nifedipine	Placebo	25*	
McHugh [25]	1988	Y	Iloprost	Placebo	24*	
Wigley [26]	1990	N			21	29
Torley [27]	1991	Y	Low-dose Iloprost	High-dose iloprost	28	27
O'Reilly [28]	1992	N			20	
Wigley [29]	1992	Y	Iloprost	Placebo	35	
TerBorg [30]	1994	N			22	
Wigley [31]	1994	Y	Iloprost infusion	Placebo	64	67
Belch [32]	1995	Y	Iloprost	Placebo	32	31
Black [33]	1998	Y	Iloprost	Placebo	33	35
Wigley [34]	1998	Y	Iloprost	Placebo	157	151
Clark [35]	1999	N			33	
Dziedzic [36]	1999	Y	Losartan	Nifedipine	14	13
Herrick [37]	2000	Y	Antioxidants / Allopurinol	Placebo	33*	
Coleiro [38]	2001	N	Fluoxetine	Nifedipine	27	
Gardinali [39]	2001	N	Prostaglandin		24	
Scorza [40]	2001	Y	Iloprost	Nifedipine		
Merkel [41]	2002	N			281	
Pucinelli [42]	2002	N			30	
Clark [43]	2003	N			33	
Foerster [44]	2005	N	Infrared-mediated hyperthermia		58	
Salsano [45]	2005	N	N-acetylcysteine		26	
Anderson [46]	2006	N			45	
Foerster [47]	2006	N			38	
Milio [48]	2006	Y	Iloprost	Iloprost (with dose adjustment)	30	30
Foerster [49]	2007	N			46	
Gliddon [50]	2007	Y	Quinapril	Placebo	91	95
Abou-Raya [51]	2008	Y	Atorvastatin	Placebo	56	28
Kawald [52]	2008	Y	High-dose Iloprost	Low-dose Iloprost	25	25
Chung [53]	2009	Y	Nitroglycerine	Placebo	67	64
Rosato [54]	2009	N	N-acetylcysteine		50	
Rosato [55]	2009	N			142	
Schiopu [56]	2009	Y	Tadalafil	Placebo	39*	
Correa [57]	2010	N			44	
Cutolo [58]	2010	N	Iloprost		34	
Rosato [59]	2010	N			105	
Shenoy [60]	2010	Y	Tadalafil	Placebo	23*	
Herrick [61]	2011	Y	Sildenafil	Placebo	30	27
Pauling [62]	2011	N			28	
Rosato [63]	2011	N			100	
Rosato [64]	2011	N			40	
Hummers [65]	2013	Y	Nitroglycerine gel	Placebo	24*	
Pauling [66]	2015	N			25	
Bellando-R. [67]	2016	N	Bosentan, Sildenafil		123	
Pavlov-D. [68]	2016	N			25	
Bello [69]	2017	Y	Botulinum toxin	Placebo	40	40
Denton [70]	2017	Y	Selexipag	Placebo	36	38
Dinsdale [71]	2017	N			26	
Motegi [72]	2017	Y	Botulinum toxin	Placebo	37	8
Wilkinson [73]	2018	N			159	
Dhaliwal [74]	2019	N	Botulinum toxin		40	
Frech [75]	2019	N			34	
Pauling [76]	2019	N			94	
Pauling [77]	2019	N			94	
Ruaro [78]	2019	N	Aminaphtone	Placebo	35	
Ruaro [79]	2019	N			68	

* Cross-over design

needed to define the role and validate circulating biomarkers in the evaluation of SSc-RP.

A major strength of this scoping review was the use of a broad search strategy which encompassed a variety of study types and settings, and was applied in multiple databases. One limitation is that the inclusion criteria restricted studies by language and sample size, which could have led to either underestimation or overestimation of the relative use of certain outcome domains. The sample size threshold may also have limited inclusion of qualitative studies examining the patient experience of SSc-RP, although such work was still considered as part of the broader appraisal of outcome domains in the study of SSc-RP. Additionally,

fewer than half the included studies were RCTs (n=24), and assessment of study quality was beyond the scope of this review.

This scoping review serves to highlight the broad-spectrum of relevant outcome domains in the study of SSc-RP. Next steps include further input from both patients, physicians, and other stakeholders, and achieving consensus on a core disease domain set as per the OMERACT framework.

Conclusion

In summary, this scoping review highlights the wide range of

Table 2

Broad Domains and Target Domains used in Clinical Research Studying Raynaud's Phenomenon in Systemic Sclerosis.

Broad Domain	Target Domain (number of studies)
Raynaud's phenomenon: Clinical features and severity	Severity and impact of attacks of Raynaud's phenomenon (35) Frequency of attacks of Raynaud's phenomenon (28) Duration of attacks (19) Pain (9) Physician global assessment (5) Numbness (2) Cold sensitivity (2) Patient global assessment (1) Tingling (1) Color changes (1)
Raynaud's phenomenon: Impact on function and quality of life	Function (11) Health-related quality of life (1)
Raynaud's phenomenon: Special tests	Objective assessment of digital perfusion (44) Serum biomarkers (6)

outcome domains used for the assessment of SSc-RP. These results will inform the OMERACT Vascular Disease in Systemic Sclerosis Working Group in the development of a core set of disease domains encompassing the impact of RP in SSc.

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Supplementary materials

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References

- [1] Walker, U.A., et al., Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR scleroderma trials and research group database. (0003-4967 (Print)).
- [2] Hughes, M., et al., Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. (1462-0332 (Electronic)).
- [3] Bassel M, et al. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a canadian national survey. *Rheumatology* 2011;50(4):762–7.
- [4] Pauling JD, et al. The patient experience of Raynaud's phenomenon in systemic sclerosis. *Rheumatology* 2018;58(1):18–26.
- [5] Herrick, A.L., Pathogenesis of Raynaud's phenomenon. (1462-0324 (Print)).
- [6] Pauling JD, 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(3):249–52.
- [7] Pauling JD. The challenge of establishing treatment efficacy for cutaneous vascular manifestations of systemic sclerosis. *Expert Rev Clin Immunol* 2018;14(5):431–42.
- [8] Gladue, H., et al., Evaluation of test characteristics for outcome measures used in Raynaud's phenomenon clinical trials. (2151-4658 (Electronic)).
- [9] Merkel PA, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002;46(9):2410–20.
- [10] Wigley FM, 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(4):670–7.
- [11] Boers, M.A.-O.X., et al., OMERACT Filter 2.1: Elaboration of the conceptual framework for outcome measurement in health intervention studies. (0315-162X (Print)).
- [12] Beaton, D.E.M.L., Grosskleg S, Shea B, Tugwell B eds., The OMERACT Handbook Version 2.1. <https://omeract.org/handbook/>. 2021.
- [13] Maltez N, et al. Developing a core set of outcome measure domains to study Raynaud's phenomenon and digital ulcers in systemic sclerosis: Report from OMERACT 2020. *Seminars in Arthritis Rheumat* 2021;51(3):640–3.
- [14] Maxwell LJ, et al. Core domain set selection according to OMERACT Filter 2.1: The OMERACT methodology. *J Rheumatol* 2019;46(8):1014–20.
- [15] Boers M, et al. OMERACT Filter 2.1: Elaboration of the conceptual framework for outcome measurement in health intervention studies. *J Rheumatol* 2019;46(8):1021–7.
- [16] 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(6):973–4.
- [17] Pauling JD, et al. Multinational qualitative research study exploring the patient experience of raynaud's phenomenon in systemic sclerosis. *Arthritis Care Res (Hoboken)* 2018;70(9):1373–84.
- [18] Hughes M, et al. The clinical relevance of Raynaud's phenomenon symptom characteristics in systemic sclerosis. *Clin Rheumatol* 2022.
- [19] Pauling JD, et al. Use of infrared thermography as an endpoint in therapeutic trials of Raynaud's phenomenon and systemic sclerosis. *Clin Exp Rheumatol Scleroderma Care Res* 2012;30(2):S103–15.
- [20] Pauling JD, et al. Performance of laser-derived imaging for assessing digital perfusion in clinical trials of systemic sclerosis-related digital vasculopathy: A systematic literature review. *Seminars in Arthritis Rheumat* 2020;50(5):1114–30.
- [21] Herrick AL, Dinsdale G, Murray A. New perspectives in the imaging of Raynaud's phenomenon. *Eur j rheumatol* 2020;7(Suppl 3):S212–21.
- [22] Dowd PM, Martin MFR, Cooke ED. Treatment of Raynaud's phenomenon by intravenous infusion of prostacyclin (PGI₂). *Br J Dermatol* 1982;106(1):81–9.
- [23] Mohrland JS, Porter JM, Smith EA. A multiclinic, placebo-controlled, double-blind study of prostaglandin E₁ in Raynaud syndrome. *Ann Rheumatic Dis* 1985;44(11):754–60.
- [24] Hawkins SJ, et al. Clinical and laboratory effects of nifedipine in Raynaud's phenomenon. *Rheumatol int* 1986;6(2):85–8.
- [25] McHugh NJ, et al. Infusion of iloprost, a prostacyclin analogue, for treatment of Raynaud's phenomenon in systemic sclerosis. *Ann rheumatic dis* 1988;47(1):43–7.
- [26] Wigley FM, et al. The post-occlusive hyperemic response in patients with systemic sclerosis. *Arthritis rheumat* 1990;33(11):1620–5.
- [27] Torley HI, et al. A double blind, randomised, multicentre comparison of two doses of intravenous iloprost in the treatment of Raynaud's phenomenon secondary to connective tissue diseases. *Ann rheumatic dis* 1991;50(11):800–4.
- [28] O'Reilly D, et al. Measurement of cold challenge responses in primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis. *Ann rheumatic dis* 1992;51(11):1193–6.
- [29] Wigley FM, et al. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. *J Rheumatol* 1992;19(9):1407–14.
- [30] Ter Borg EJ, et al. Serial nailfold capillary microscopy in primary Raynaud's phenomenon and scleroderma. *Seminars in Arthritis Rheumatism* 1994;24(1):40–7.
- [31] Wigley FM, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann int med* 1994;120(3):199–206.
- [32] Belch JJ, et al. Oral iloprost as a treatment for Raynaud's syndrome: a double blind multicentre placebo controlled study. *Ann rheumatic dis* 1995;54(3):197–200.
- [33] Black CM, et al. Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br j rheumatol* 1998;37(9):952–60.

- [34] Wigley FM, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis rheumatism* 1998;41(4):670–7.
- [35] Clark S, et al. Laser doppler imaging—a new technique for quantifying microcirculatory flow in patients with primary Raynaud's phenomenon and systemic sclerosis. *Microvasc res* 1999;57(3):284–91.
- [36] Dziadzio M, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis rheumatism* 1999;42(12):2646–55.
- [37] Herrick AL, et al. A double-blind placebo-controlled trial of antioxidant therapy in limited cutaneous systemic sclerosis. *Clin experimental rheumatol* 2000;18(3):349–56.
- [38] Coleiro B, et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology* 2001;40(9):1038–43.
- [39] Gardinali M, et al. Treatment of Raynaud's phenomenon with intravenous prostaglandin E1alpha-cyclodextrin improves endothelial cell injury in systemic sclerosis. *The J rheumatol* 2001;28(4):786–94.
- [40] Scorza R, et al. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. A randomized, controlled study. *Clin experimental rheumatol* 2001;19(5):503–8.
- [41] Merkel PA, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis rheumatism* 2002;46(9):2410–20.
- [42] Pucinelli MLC, Fontenelle S, Andrade LEC. Determination of fingertip lacticemia before and after cold stimulus in patients with primary Raynaud's phenomenon and systemic sclerosis. *The J rheumatol* 2002;29(7):1401–3.
- [43] Clark S, et al. Comparison of thermography and laser Doppler imaging in the assessment of Raynaud's phenomenon. *Microvascular res* 2003;66(1):73–6.
- [44] Foerster J, et al. Infrared-mediated hyperthermia is effective in the treatment of scleroderma-associated Raynaud's phenomenon [2]. *J Investigative Dermatol* 2005;125(6):1313–6.
- [45] Salsano F, et al. Significant changes of peripheral perfusion and plasma adrenomedullin levels in N-acetylcysteine long term treatment of patients with scleroderma Raynauds phenomenon. *Int j immunopathol pharmacol* 2005;18(4):761–70.
- [46] Anderson ME, et al. The 'distal-dorsal difference': a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. *Rheumatology (Oxford, England)* 2007;46(3):533–8.
- [47] Foerster J, et al. Infrared-monitored cold response in the assessment of Raynaud's phenomenon. *Clin experimental dermatol* 2006;31(1):6–12.
- [48] Milio G, et al. Iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis and the quality of life: a new therapeutic protocol. *Rheumatology (Oxford, England)* 2006;45(8):999–1004.
- [49] Foerster J, et al. A cold-response index for the assessment of Raynaud's phenomenon. *J dermatol sci* 2007;45(2):113–20.
- [50] Gliddon AE, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis rheumatism* 2007;56(11):3837–46.
- [51] Abou-Raya A, Abou-Raya S, Helmi M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *The J rheumatol* 2008;35(9):1801–8.
- [52] Kawald A, et al. Low versus high-dose iloprost therapy over 21 days in patients with secondary Raynaud's phenomenon and systemic sclerosis: a randomized, open, single-center study. *The J rheumatol* 2008;35(9):1830–7.
- [53] Chung L, et al. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. *Arthritis and rheumatism* 2009;60(3):870–7.
- [54] Rosato E, et al. The treatment with N-acetylcysteine of Raynaud's phenomenon and ischemic ulcers therapy in scleroderma patients: a prospective observational study of 50 patients. *Clin rheumatol* 2009;28(12):1379–84.
- [55] Rosato E, et al. Laser Doppler perfusion imaging is useful in the study of Raynaud's phenomenon and improves the capillaroscopic diagnosis. *The J rheumatol* 2009;36(10):2257–63.
- [56] Schiopu E, et al. Randomized placebo-controlled crossover trial of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis. *The J rheumatol* 2009;36(10):2264–8.
- [57] Correa MJ, Andrade LE, Kayser C. Comparison of laser Doppler imaging, fingertip lacticemia test, and nailfold capillaroscopy for assessment of digital microcirculation in systemic sclerosis. *Arthritis res therapy* 2010;12(4):R157.
- [58] Cutolo M, et al. Peripheral blood perfusion correlates with microvascular abnormalities in systemic sclerosis: a laser-Doppler and nailfold videocapillaroscopy study. *The J rheumatol* 2010;37(6):1174–80.
- [59] Rosato E, et al. The different photoplethysmographic patterns can help to distinguish patients with primary and scleroderma Raynaud phenomenon. *Am J Med Sci* 2010;340(6):457–61.
- [60] Shenoy PD, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology (Oxford, England)* 2010;49(12):2420–8.
- [61] Herrick AL, et al. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. *Arthr rheumat* 2011;63(3):775–82.
- [62] Pauling JD, et al. Influence of the cold challenge on the discriminatory capacity of the digital distal-dorsal difference in the thermographic assessment of Raynaud's phenomenon. *Microvascular res* 2011;82(3):364–8.
- [63] Rosato E, et al. The combination of laser Doppler perfusion imaging and photoplethysmography is useful in the characterization of scleroderma and primary Raynaud's phenomenon. *Scand j rheumatol* 2011;40(4):292–8.
- [64] Rosato E, et al. Laser Doppler perfusion imaging in systemic sclerosis impaired response to cold stimulation involves digits and hand dorsum. *Rheumatology (Oxford, England)* 2011;50(9):1654–8.
- [65] Hummers LK, et al. A multi-centre, blinded, randomised, placebo-controlled, laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine, in patients with Raynaud phenomenon. *Ann rheumatic dis* 2013;72(12):1962–7.
- [66] Pauling JD, et al. 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. *The J rheumatol* 2015;42(7):1163–8.
- [67] Bellando-Randone S, et al. Combination therapy with Bosentan and Sildenafil improves Raynaud's phenomenon and fosters the recovery of microvascular involvement in systemic sclerosis. *Clin rheumatol* 2016;35(1):127–32.
- [68] Pavlov-Dolijanovic S, et al. Diagnosis of Raynaud's phenomenon by 99mTc-per-technetate hand perfusion scintigraphy: a pilot study. *Rheumatol int* 2016;36(12):1683–8.
- [69] Bello RJ, et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated raynaud's phenomenon: a randomized, double-blind, placebo-controlled clinical trial. *Arthritis rheumatol (Hoboken, N.J.)* 2017;69(8):1661–9.
- [70] Denton CP, et al. Efficacy and safety of selexipag in adults with raynaud's phenomenon secondary to systemic sclerosis: a randomized, placebo-controlled, phase II study. *Arthritis rheumatol (Hoboken, N.J.)* 2017;69(12):2370–9.
- [71] Dinsdale G, et al. Quantitative outcome measures for systemic sclerosis-related Microangiopathy - Reliability of image acquisition in Nailfold Capillaroscopy. *Microvasc res* 2017;113(mwx, 0165035):56–9.
- [72] Motegi S-I, et al. Efficacy of botulinum toxin b injection for raynaud's phenomenon and digital ulcers in patients with systemic sclerosis. *Acta dermato-venereologica* 2017;97(7):843–50.
- [73] Wilkinson JD, 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. *Arthr rheumatol (Hoboken, N.J.)* 2018;70(6):903–11.
- [74] Dhaliwal K, et al. Optimisation of botulinum toxin type a treatment for the management of Raynaud's phenomenon using a dorsal approach: a prospective case series. *Clinical rheumatol* 2019;38(12):3669–76.
- [75] Frech TM, Murtaugh MA. Non-invasive digital thermal monitoring and flow-mediated dilation in systemic sclerosis. *Clin experimental rheumatol* 2019;37(4 Supplement 119):97–101.
- [76] Pauling JD, et al. Evolving symptom characteristics of raynaud's phenomenon in systemic sclerosis and their association with physician and patient-reported assessments of disease severity. *Arthritis care res* 2019;71(8):1119–26.
- [77] Pauling JD, et al. Factors influencing raynaud condition score diary outcomes in systemic sclerosis. *The J Rheumatol* 2019;46(10):1326–34.
- [78] Ruaro B, et al. Aminaphtone efficacy in primary and secondary raynaud's phenomenon: a feasibility study. *Front pharmacol* 2019;10(101548923):293.
- [79] Ruaro B, et al. Innovations in the Assessment of Primary and Secondary Raynaud's Phenomenon. *Front pharmacol* 2019;10(101548923):360.