

Use of infrared thermography as an endpoint in therapeutic trials of Raynaud's phenomenon and systemic sclerosis

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ABSTRACT

Objective. To perform a systematic review evaluating the use of infrared thermography (IRT) as an endpoint in clinical trials of Raynaud's phenomenon (RP).

Methods. Articles reporting the use of IRT and Raynaud's phenomenon were identified following systematic searches of PubMed, EMBase, MEDLINE and AMED databases. Articles incorporating IRT as an endpoint in a therapeutic trial were selected for full text analysis. Data extracted from articles included study design, study size, intervention, clinical and thermographic endpoints, and outcomes. Studies were scored on their methodological quality. Data analysis involved a descriptive analysis of the studies, along with a secondary analysis focusing on agreement between clinical and thermographic outcomes in the larger, better-described studies.

Results. Thirty-two studies evaluating 654 patients with RP were assessed. Significant heterogeneity between studies precluded any attempt at formal meta-analysis. Most studies were small (median 15.5 patients) and open-label design (19/32, 59.4%). The majority of studies (18/32, 56.3%) reported improvements in both clinical and thermographic endpoints. Thermographic parameters showing agreement with clinical endpoints in therapeutic trials included baseline hand/finger absolute temperature and parameters derived following local cold challenge, including longitudinal thermal gradients and percent re-warming.

Conclusion. No single thermographic parameter has emerged as the preferred endpoint for clinical trials of RP. Objective microvascular imaging tools such as IRT have the potential to overcome the limitations of self-report assessment of RP. Future studies should

continue to evaluate IRT, alongside recommended self-reports, in an attempt to validate objective microvascular assessment tools in therapeutic trials of RP.

Introduction

Raynaud's phenomenon (RP) is characterised by excessive peripheral vascular reactivity to cold exposure and emotional stress leading to intermittent episodes of digital ischaemia (1). Episodes are frequently associated with pain and impaired motor and sensory function. For the majority of patients, RP occurs as an isolated phenomenon (termed primary Raynaud's) however in a minority it can herald the onset of potentially life threatening diseases such as systemic sclerosis (SSc) in which vascular dysfunction can lead to irreversible morphological vascular changes and digital necrosis (1, 2). Treatments are available to reduce the impact of the disorder by altering the balance of vascular resistance in favour of vasodilatation. Objective quantification of peripheral vascular dysfunction in RP is challenging but essential to allow evaluation of response in therapeutic trials.

The episodic nature of RP attacks has led to a dependence on self-report assessment of the frequency, duration and severity of Raynaud's symptoms. These tools are subjective, sensitive to placebo effect, time consuming, require a prolonged period of assessment and influenced by seasonal variation in environmental temperature. Furthermore, the frequency, duration and severity of RP attacks are intrinsically linked with the effectiveness of coping strategies adopted by patients to avoid the conditions responsible for an attack. Due in part to these problems and despite the many therapeutic pharmacological and non-pharmacological studies in RP,

Competing interests: none declared.

only di-hydropyridine calcium antagonists (usually nifedipine) and intravenous prostanoids are currently recommended for the treatment of RP as part of SSc (3).

A major limiting factor of studies assessing efficacy in therapeutic studies of Raynaud's phenomenon is the lack of validated objective outcome tools for the assessment of digital vascular function. Currently, only patient self-reports and physician global assessments of RP severity are recommended for use in therapeutic trials of Raynaud's phenomenon (4). Of the methods that have been evaluated to attempt to objectively assess digital vascular function, the most widely assessed has been infrared thermography (IRT). IRT has the advantage of providing sensitive, quantifiable and responsive data regarding vascular function. Thermographic protocols for RP assessment often incorporate a local cold stress test (CST) to allow dynamic assessment of vascular function in an attempt to simulate the conditions responsible for an attack of Raynaud's *in vivo*. However, there is no consensus on the duration, magnitude of the challenge or the exact thermographic endpoints. In this systematic review we have identified studies that have incorporated IRT as an endpoint in therapeutic trials of RP. We shall describe and critique the various thermographic protocols and endpoints used previously and highlight potential areas for future research.

Methods

Study selection

To ensure comprehensive study identification, our search criteria extended to all articles reporting the use of IRT in the context of Raynaud's phenomenon and scleroderma spectrum disease. Initial searches indicated this was necessary to capture all studies using IRT as an outcome measure, despite identifying a large number of diagnostic or unrelated studies. A systematic search of the literature, limited to the English language and articles published between 1975 and the present day, was performed using the MEDLINE, EMBASE, AMED databases accessed via the NHS National Health Resources on March 9th 2011. The search terms used

were: (Thermography) AND (CREST OR Scleroderma OR systemic sclerosis OR Raynaud's).

An additional search was undertaken using PubMed on 21st October 2011. The following keywords and medical subject heading (MeSH) terms were used: (Thermography [all fields] OR Thermal [all fields]) AND (Raynaud's [all fields] OR CREST [all fields] OR sclerosis, progressive systemic [all fields] OR scleroderma [all fields]). An additional hand search of relevant articles cited in these papers was also performed. The study selection process comprised two rounds. The first was based on the titles and abstracts of the studies identified following the preliminary searches. Diagnostic studies, or those investigating conditions other than RP or SSc (such as morphoea) or paediatric assessment were excluded. Similarly, review articles, editorials, comments, conference abstracts and individual case reports were excluded from analysis unless they reported the findings of a clinical trial. Studies incorporating methods other than non-contact IRT for the measurement of cutaneous temperature (such as contact thermistors) were also excluded. The full text of each article identified for further assessment in the first round was reviewed. Studies fulfilling the above exclusion criteria, or those lacking sufficient information to facilitate further analysis were subsequently excluded.

Data extraction

One investigator (JDP) was responsible for selecting and reviewing articles based on title and abstract. The full text studies selected for further consideration were reviewed by 2 investigators (JDP and JAS). Data was systematically extracted using a pre-designed proforma to record year of publication, study design, study size, patient characteristics, intervention, clinical endpoints and outcome, together with thermographic endpoints and outcome. In addition, each study was scored independently by 2 investigators (JDP and JAS) for methodological quality using the well-described Jadad scoring method (scale 0–5) (5). Where agreement was not present following independent as-

essment, the full text was reviewed by both assessors and a consensus reached. In particular, studies were only awarded a point for describing withdrawals and dropouts if this was explicitly stated in the text, even if the results presented would suggest no patients had dropped out of the trial. In accordance with previous studies, Jadad scores of 0–2 and 3–5 were considered low and high quality, respectively.

Study analysis

An analysis of all studies was undertaken to describe their key characteristics in terms of study design, intervention and clinical/thermographic parameters used. Relatively small study numbers and significant variation in study design, therapeutic intervention, imaging protocols and thermographic endpoints precluded any useful attempt at statistical pooling of results as part of a formal meta analysis. Nonetheless, some indication of the utility of specific thermographic parameters can be derived from evaluating agreement between the outcomes of clinical and thermographic endpoints of digital vascular function following intervention. A secondary analysis was therefore undertaken focusing on agreement between clinical and thermographic outcomes within studies. Studies failing to adequately report the outcome of clinical and/or thermographic endpoints, or those with small sample sizes ($n \leq 13$), were excluded from the secondary analysis to ensure this targeted the larger, better described studies with greater informative value.

Results

Article selection

Of the 294 articles identified from the original searches, 37 were deemed appropriate for full text analysis. Of these publications, a further 6 were excluded on review of the full text; four due to the use of contact thermocouples rather than IRT (6–8), one review article (9), and one which failed to report the methods or outcome of thermal imaging (10). We could not obtain the manuscript for one study using either our institutional subscriptions or inter-library loans service (which included access to all journals held within the British

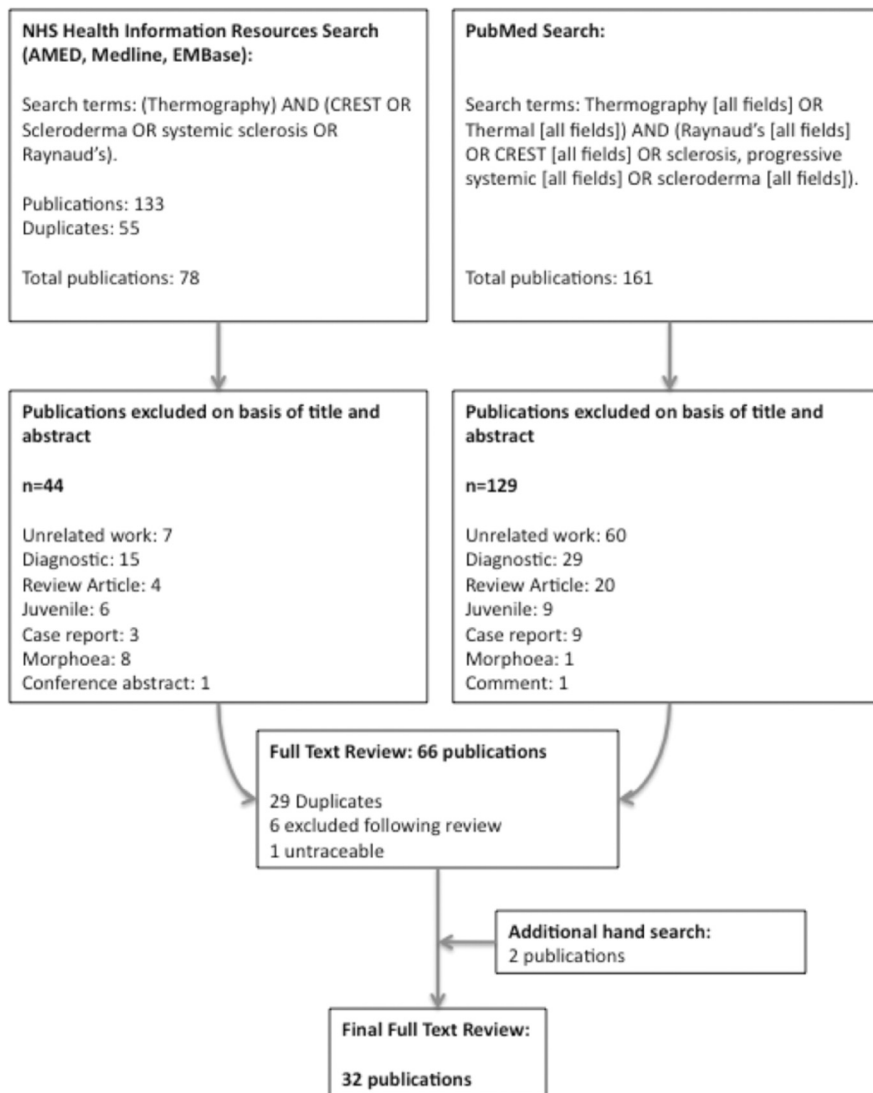


Fig. 1. Literature search strategy and identification of relevant publications.

Library) (11). Two additional publications were identified following a subsequent hand search prompted by citations identified in the full-text of other selected articles and were included in subsequent analysis. This resulted in a full-text review of 32 studies. A flowchart summarising the outcome of the search process used to identify publications for final analysis is presented in Figure 1. Twenty studies were excluded from the secondary analysis (evaluating agreement between clinical and thermographic endpoints) due to small sample size ($n \leq 13$) and/or an insufficient description of clinical and/or thermographic endpoints (12–31). The key characteristics and findings of the twelve studies included in the secondary analysis are summarised in Table

I. A more comprehensive summary of the key characteristics of all 32 studies reviewed is available as supplementary material (Supplementary Table I).

Study population

The 32 publications identified following the literature search represent the study of 654 patients with Raynaud's phenomenon, the majority of whom had a diagnosis of SSc (326, 49.8%) or primary RP (230, 35.2%). The remaining patients (98, 15%) had RP associated with other conditions, typically other rheumatic diseases such as rheumatoid arthritis, mixed connective tissue disease and systemic lupus erythematosus. Many studies incorporated a heterogeneous mix of RP patients, and within these studies we did not identify sub-

analyses that specifically compared groups. Other studies used either solely primary RP (*e.g.* (32–34)) whereas others use solely SSc (*e.g.* (35)). IRT did not appear to perform better in one disease group than the other although the small number of studies incorporating a homogenous disease cohort, and the range of interventions, precluded any useful comparison along these lines.

Study size

Study size was generally small with a median participant number of 15.5 (inter-quartile range 8.75 to 26.75). Fifty percent of the studies consisted of greater than 15 subjects whilst ten studies (31.3%) consisted of fewer than 10 subjects.

Study design

A variety of methodological approaches were used, although the majority of studies were open-label in design (19/32, 59.4%). There were 10 (31.3%) randomised double-blind, placebo-controlled (or cross-over studies), 2 single-blind studies and one retrospective study.

Study quality

The majority of studies (22/32, 68.8%) would be considered of low quality according to the Jadad score (0–2). Seven studies had a Jadad score of 3 and three had a Jadad score of 4.

Date of publication

The studies are evenly distributed in terms of date of publication with 1 study in the 1970s, 12 studies in the 1980s, 8 studies in 1990s and 11 studies since 2000.

Intervention

A large variety of interventions had been assessed including pharmacological treatments (22/32, 68.7%), complementary therapies (6/32, 18.7%), surgical intervention (2/32, 6.3%) and autologous blood product transfusions (2/32, 6.3%). The most commonly evaluated pharmacological agent was exogenous prostanoid therapy (9/32, 28.1%). Most classes of pharmaceutical drug commonly used in the management of Raynaud's phenomenon have been

Table 1. Summary of major studies reporting the use of infrared thermography (IRT) as an endpoint in clinical trials of Raynaud's phenomenon (a comprehensive summary of all studies identified following literature searches is available as an online supplement)

Author, year	Study design	Jaddad Score	No of patients (All/PRP/SSs)	Intervention	Clinical endpoint	Clinical improvement	IRT protocol	IRT endpoint	Thermographic Response
Clifford, 1980 (36)	Open-label	0	26/2/18	72 hours IV PG-E ₁ qds for 36 weeks	Patient rated RP better, same or worse. Pain assessed using 10cm VAS and a 4-point scale. Ulceration and ischaemic changes documented	25/26 improved during infusion. 17/26 improved at 2 weeks and 6 weeks Significant improvement in pain VAS at 2 weeks. Healing occurred in most patients with ulcers.	IRT at baseline, during, immediately after and at 2 and 6 weeks post treatment One hand subjected to CST with assessments before and at 4 and 10 minutes post-CST (20°C for 60s)	Average T values from spot measurements with an infra red radiometer of 6 areas of dorsum of fingers and 5 areas of dorsum of hands	Significant increase in hand/finger T during, after, at 2 weeks, and at 6 weeks No change in response to CST
Ring, 1981 (42)	Open-label	1	20/2/0	Inositol nicotinate 1g qds for 36 weeks	VAS scores (0-100) for coldness, pain, numbness, burnings. Approximate duration of attacks (self report)	Significant improvement in coldness, pain and numbness VAS scores, and reported duration of attacks post-treatment	IRT at -1, 0, 1, 3, 5, 12, 24 & 36 weeks. IRT pre and 10 minutes post CST (20°C for 60s).	TG (T of fingers – dorsum of hands) at baseline and 10 minutes post-CST	Significant reduction in the magnitude of the post-CST TG following treatment. No change in baseline TG.
Dowd, 1982 (38)	Open-label	1	25/0/25	IV prostacyclin over 72 hours	Subjective 3 point scale (better, same, worse) for warmth, cold intolerance and stiffness Pain (10cm VAS) Frequency and duration of attacks	Significant improvement in pain VAS. Response to treatment in 21/24 participants. Effects lasted from 4-28 weeks.	Both IRT (n=14) and radiometry (n=10) performed at baseline, during infusion, immediately after and 2 weeks post treatment. CST (20°C for 60s) of one hand undertaken as part of thermographic and radiometric assessment with assessments prior to, immediately following and at 1 minute intervals until 10 minutes post-CST.	Radiometry used spot measurements (6 dorsum of fingers, 5 dorsum of hands) IRT Mean hand and finger T at baseline and following CST with calculation of "Thermographic index" to quantify vascular response to CST.	Significant increase in T of hands and fingers during, immediately after and at 2 weeks post infusion using IRT. Radiometry revealed increased hand and finger T during, but not after infusions. Improvement in Thermographic Index only reported in 2/14 patients.
McHugh, 1988 (41)	Double-blind cross over trial	3	29/3/26	Infusions of iloprost or placebo over 6 hours on 3 consecutive days. 6 weeks between treatments arms	Frequency, duration and severity (1-3 scale) of RP attacks Pain (1-2 scale) Patient global assessment on effectiveness Active lesions on hands and feet recorded at each assessment.	Sig improvement in frequency, severity and patient global assessment of effectiveness following iloprost compared to placebo. No difference in lesion healing between the iloprost and placebo.	IRT (radiometry or thermography) assessments of the dorsum of both hands at baseline and 10 minutes post-CST (20°C for 60s). Assessments undertaken before, immediately following 3 rd infusion, 2 weeks and 6 weeks.	Mean T of dorsum of hands and fingers. Calculation of TG at baseline and 10 minutes post-CST. Combined thermal index calculated by adding TG at baseline with TG at 10 minutes post-CST	Significant difference between placebo and iloprost was for the change in thermal gradient following CST the day after the 3 rd infusion.
Teh, 1995 (43)	Randomised, double-blind, placebo-controlled, cross-over study	3	32/17/15	7 days transdermal Glyceryl Tri-Nitrate (0.2mg/hr) vs. placebo	Frequency of RP attacks Severity of RP attacks (separate assessments of pain, numbness and colour change scored as none, mild, moderate or severe) Severity of RP (0-10 VAS) at baseline and following treatment periods	Improvement in frequency and severity of RP attacks	IRT images at baseline and following treatment periods. Dorsum of hands 2 hours after application of patch, and following CST (15°C for 60s)	DDD (dorsum of hands and distal regions of index, middle, ring and little fingers). Distal inter-phalangeal joint measurements used to calculate: Mean T immediately following CST Lag period before the onset of re-warming Maximum % recovery over 10 minutes post-CST	No significant differences

Author, year	Study design	Jadad Score	No of patients (All/PRP/SSe)	Intervention	Clinical endpoint	Clinical improvement	IRT protocol	IRT endpoint	Thermographic Response
Dziedzic, 1999 (39)	Open-label, randomised, parallel group study	1	52/25/27	Losartan 50mg od vs. nifedipine 20mg bd, 6 weeks	Frequency and severity of RP attacks (0-10 VAS)	Significant reduction in frequency and severity of attacks following losartan only	IRT at weeks 0 and 6 weeks. IRT images at baseline, immediately following CST (15°C 60s), 5 and 10 minutes post-CST	Mean fingertip T at baseline, immediately following cold stress and 5 minute and 10 minutes post-CST	No improvement in recovery 10 minutes after cold challenge following either drug
Herrick, 2000 (35)	Randomised placebo-controlled double-blind cross-over	3	33/0/33	10 week combination anti-oxidants and allopurinol vs. placebo	Frequency of RP attacks Duration of RP attacks Subjective report of RP severity (better, same or worse)	No improvement	Dorsal aspect of hands at baseline and following CST (15°C for 60s) Measurement over DIP joints of index, middle and ring fingers over 15 minute re-warming	Mean T at baseline, Max. T recovery gradient Lag period before the onset of re-warming Maximum % recovery over 15 minutes post-CST	No improvement
Coleiro, 2001 (40)	Open-label randomised cross over study	2	53/26/27	6-week treatment periods with fluoxetine 20mg OD vs. nifedipine LA 40mg OD, 6 weeks	Frequency and severity of RP attacks (0-10 VAS)	Significant reduction in frequency and severity of attacks following fluoxetine only	IRT at weeks 0 and after each 6-week treatment period. IRT images at baseline, immediately following CST (15°C 60s) and 10 minutes post-CST	Mean T of hands at baseline, immediately following CST (15°C 60s) and 10 minutes post-CST % re-warming at 10 minutes.	No difference at baseline Significant improvement in % re-warming for PRP following treatment with fluoxetine
Hirschi, 2002 (34)	Randomised, double-blind, placebo-controlled, cross-over study	3	18/18/0	LLLT vs. placebo (5 sessions per week for 3 weeks)	Frequency of RP attacks Intensity of RP attacks (1-5 VAS)	Improvement in intensity but not frequency of RP attacks	IRT images of the dorsal aspect of both hands at baseline and following CST (20°C for 60s) at beginning of the study and following each treatment period	Mean TG between MCP and fingertip for all fingers 20 minutes post -CST Number of fingers with TG <1°C 10 minutes post-CST	TG significantly reduced post-CST following LLLT compared to placebo. No significant difference in the number of fingers with gradient <1°C 10 minutes post CST between placebo and LLLT group
Al-Awami, 2004 (37)	Randomised, double-blind, placebo-controlled	4	47/18/5	10 sessions of LLLT vs. sham laser placebo	Frequency of RP attacks Severity of RP attacks (0-10 VAS)	Significant improvement in frequency and severity of RP following both LLLT and placebo (more pronounced improvement in the LLLT group)	IRT at baseline and 6 weeks a) Baseline b) Immediately after 1 minute warm challenge (immersion of gloved hands in water at 39°C) c) Measurements immediately post-CST (20°C for 60s) d) Measurements 10 and 20 minutes post-CST	Change in basal fingertip skin T 20 minutes post-CST	Significantly reduced change in fingertip T post-CST following LLLT but not placebo
Hirschi, 2004 (33)	Double-blind randomised, placebo-controlled cross-over	3	48/48/0	3 weeks LLLT vs. placebo	Frequency and intensity (5 point VAS) of RP attacks	Significant decreases in frequency and intensity of RP attacks following LLLT compared to placebo	IRT assessments at baseline and following treatment periods. IRT image of dorsal hands taken pre and for 20 minutes post-CST (20°C for 60s)	The mean TG of all fingers, the maximum TG and number of fingers with DDD <1°C at 20 minutes post CST	Non significant trend towards improvement following LLLT compared with placebo
Shlager, 2011 (32)	Open-label	0	26/26/0	Auricular electroacupuncture (6 sessions over 6 weeks)	Frequency (diary monitoring) and severity (0-10 VAS) of RP attacks	Significant improvement in frequency and severity of attacks at 3, 6 and 24 weeks	IRT assessments of volar aspect of patient hands at baseline, 3, 6 and 24 weeks.	Fingertip skin T before and following CST (20°C for 60s).	No change.

DU: digital ulceration; CREST: calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasia; CST: cold stress test; PRP: primary Raynaud's phenomenon; SSe: systemic sclerosis; RP: Raynaud's phenomenon; T: temperature; VAS: Visual Analogue Scale; PG-E₁: Prostaglandin E₁; SHAQ: Scleroderma Health Assessment Questionnaire; PG-I₂: Prostaglandin I₂; CGRP: Calcitonin Gene Related Peptide; TG: Thermal Gradient; LLLT: low level laser therapy; 5-HT: 5-hydroxytryptamine; SHAQ: scleroderma health assessment questionnaire.

Supplementary Table I. Summary table of the studies reporting the use of infrared thermography (IRT) as an endpoint in clinical trials of Raynaud's phenomenon.

Author, year	Study design	Jadad Score	No of patients (All/PP/SSc)	Intervention	Clinical endpoint	Clinical improvement	IRT protocol	IRT endpoint	Thermographic Response
Ring, 1977 (17)	Open-label	0	6/0/0	Inositol nicotinate 3g daily for >2 months	Not assessed		IRT at baseline, week 1, week 3, week 7 and 9 months	"Thermographic index" of dorsal aspect of three middle fingers and dorsum of hands	Trend for improvement after 7 weeks treatment
Clifford, 1980 (36)	Open-label	0	26/2/18	72 hours IV PG-E ₁	Patient rated RP better, same or worse Pain assessed using 10cm VAS and a 4-point scale. Ulceration and ischaemic changes documented	25/26 improved during infusion, 21/26 improved at 2 weeks and 17/26 improved at 6 weeks Significant improvement in pain VAS at 2 weeks. Healing occurred in most patients with ulcers.	IRT at baseline, during, immediately after and at 2 and 6 weeks post treatment One hand subjected to CST with assessments before and at 4 and 10 minutes post-CST (20°C for 60s)	Average T values from spot measurements with an infra red radiometer of 6 areas of dorsum of fingers and 5 areas of dorsum of hands	Significant increase in hand/finger T during, after, at 2 weeks, and at 6 weeks No change in response to CST
Martin, 1981 (20)	Single-blind cross over trial	0	12/0/12	3 day treatment period with PG-E ₁ vs. placebo	Patients rated hand symptoms as better, same or worse, Pain (10cm VAS) in 7 patients.	Marked improvement in hand symptoms following PG-E ₁ Pain VAS improved following PG-E ₁	IRT assessments at baseline, daily during treatment period and at 2 weeks post treatment. CST (20°C for 60s) pre and post infusion, with images taken at baseline, 4 and 10 minutes post-CST	T of dorsum of hand and proximal interphalangeal joints used to calculate "thermographic index" (method of calculating TI not reported)	Significant improvement in mean thermographic index during therapy and at 2 weeks. Effects of cold challenge not altered following PG-E ₁
Wesseling, 1981 (13)	Double-blind randomised placebo-controlled cross-over	3	7/4/2	Acute effects of sublingual and oral isoxsuprine vs. placebo	Not assessed		IRT at baseline and during 20 minutes cooling (hands placed on cooling plate at 6°C) and every 5 minutes during subsequent 30 minutes re-warming	% change in T over cross-section of all fingers of left hand during cooling after treatment	Significantly decreased cooling following sublingual and oral therapy compared with placebo
Ring, 1981 (42)	Open-label	1	20/2/0	Inositol nicotinate 1g qds for 36 weeks	VAS scores (0-100) for coldness, pain, numbness, burnings. Approximate duration of attacks (self report)	Significant improvement in coldness, pain and numbness VAS scores, and reported duration of attacks post-treatment	IRT at -1, 0, 1, 3, 5, 12, 24 & 36 weeks. IRT pre and 10 minutes post CST (20°C for 60s).	TG (T of fingers - dorsum of hands) at baseline and 10 minutes post-CST	Significant reduction in the magnitude of the post-CST TG following treatment. No change in baseline TG.
Dowd, 1982 (38)	Open-label	1	25/0/25	IV prostacyclin over 72 hours	Subjective 3 point scale (better, same, worse) for warmth, cold intolerance and stiffness Pain (10cm VAS) Frequency and duration of attacks	Significant improvement in pain VAS. Response to treatment in 21/24 participants. Effects lasted from 4-28 weeks.	Both IRT (n=14) and radiometry (n=10) performed at baseline, during infusion, immediately after and 2 weeks post treatment. CST (20°C for 60s) of one hand undertaken as part of thermographic and radiometric assessment with assessments prior to, immediately following and at 1 minute intervals until 10 minutes post-CST.	Radiometry used spot measurements (6 dorsum of fingers, 5 dorsum of hands) IRT Mean hand and finger T at baseline and following CST with calculation of "Thermographic index" to quantify vascular response to CST.	Significant increase in T of hands and fingers during, immediately after and at 2 weeks post infusion using IRT. Radiometry revealed increased hand and finger T during, but not after infusions. Improvement in Thermographic Index only reported in 2/14 patients.
Kyle, 1985 (22)	Open-label	1	10/2/6	3 consecutive day infusions of PG-E ₁ (12 week assessment period)	Pain (0-10 VAS) Subjective description of change in frequency of RP attacks and temperature of hands	Non-significant reduction in VAS Improvement in 9/10	IRT at baseline and 2 week intervals following treatment. Pattern of 15 minutes equilibration at room temperature (20°C), 3 minute warming of right hand at 37°C followed by CST (20°C for 60s) to right hand, with IRT images acquired pre and post equilibration, post CST and at 5 min intervals for subsequent re-warming	Discriminant function value (DFV) obtained by comparing mean temperature change of the index finger 10 minutes following CST and mean longitudinal TG along index finger during re-warming	Improvement in DFV in majority of patients with sustained improvement at 12 weeks in 4 patients

Author, year	Study design	Jadad Score	No of patients (All/PRP/SSc)	Intervention	Clinical endpoint	Clinical improvement	IRT protocol	IRT endpoint	Thermographic Response
Gush, 1987 (28)	Placebo-controlled double blind cross over study	1	9 / 0 / 0 (5 <i>antoinimune</i> RP)	Acute effects of sub-lingual nifedipine 20mg vs. placebo	Not assessed		IRT images of right index finger at 30 minutes and 15 minutes prior to, and at 15 minute intervals (up to 90 minutes) following nifedipine	Right index finger mean T and TG	No change
Yamaoka, 1987 (12)	Open-label	0	9/0/3	2 hours IV prostacyclin derivative (CS-570) BD for 2-4 weeks	Subjective 3 point scale (better, same, worse) changes to digital ulceration, skin ulceration an ischaemic changes	7/9 "better" with improvement in frequency, severity and duration of attacks skin ulcers markedly improved	IRT of hands and feet at baseline, and following treatment	T of fingers and toes	No change.
Meloni, 1987 (19)	Open-label	1	11/3/3	10 day placebo cycle followed by 21 day Ketanserin (5-HT receptor antagonist) 60mg increasing to 120mg/day	Subjective response (length, number, severity of attacks) following treatment presence of ulcers	10/11 "good or excellent effects" 4/5 healing of digital ulcers	IRT at baseline and post-CST (17°C for 3 minutes), before and after treatment	Time to re-establish basal surface temperature following CST	Improvement in 7/11 patients
McHugh, 1988 (41)	Double-blind cross over trial	3	29/3/26	Infusions of iloprost or placebo over 6 hours on 3 consecutive days. 6 weeks between treatments arms	Frequency, duration and severity (1-3 scale) of RP attacks Pain (1-2 scale) Patient global assessment on effectiveness /Active lesions on hands and feet recorded at each assessment.	Sig improvement in frequency, severity and patient global assessment of effectiveness following iloprost compared to placebo. No difference in lesion healing between the iloprost and placebo.	IRT (radiometry or thermography) assessments of the dorsum of both hands at baseline and 10 minutes post-CST (20°C for 60s). Assessments undertaken before, immediately following 3 rd infusion, 2 weeks and 6 weeks.	Mean T of dorsum of hands and fingers. Calculation of TG at baseline and 10 minutes post-CST. Combined thermal index (TI) calculated by adding TG at baseline with TG at 10 minutes post-CST	Significant difference between placebo and iloprost was for the change in thermal gradient following CST the day after the 3 rd infusion.
Rademaker, 1989 (18)	Double-blind, placebo-controlled randomised group comparison study	4	23/0/23	3 days iv iloprost at baseline and additional single infusion at 8 weeks, or nifedipine 30mg for 4 weeks followed by 60mg for 8 weeks	Number, duration and severity of RP attacks Skin lesions	Significant improvement following both treatments during study.	RT assessment at baseline, 1 weeks 4, 8, 12 and 16	Mean hand temperature for 15 minutes after CST (20°C 60s).	Increase in mean finger T following iloprost reported but no data presented
Klimiuk, 1989 (24)	Open-label	1	11/0/11	Treatment with IV followed by oral ketanserin	Digital pain score (10cm VAS) on entry and 1 week VAS (10cm) for warmth and sensory symptoms in affected limb, and body warmth Grading of number of digits affected by digital ulceration, calcinosis and digital pitting, on entry, 2 hrs, 7 days	Improvement in VAS scores for pain, limb and body warmth Ulcer healing in all 6 patients with active DU at entry into study.	Bolometric and thermographic assessments at baseline, 24 hours and 1 week	Mean index finger T (thermography) Mean finger pulp temperature (bolometry)	Significant improvements in finger temperatures at 24hrs and 1 week
Shawket, 1991 (15)	Double-blind cross-over	3	6/6/0	Single 3 hour infusion of α -CGRP vs. PG-I ₂	No clinical endpoints described in methods	It is reported that thermographic data correlated well with subjective improvements from patient reports of the number and severity of attacks	IRT at baseline, following warming (37°C for 3 minutes) and following CST (20°C for 60s) at time points 0, 1, 5, 10, 15, 20 minutes. CST analysis done before, immediately after, day 3 and day 14 post treatment	Total change in T compared with immediately post-CST of the five digits of the right hand during 20-minute re-warming period.	No difference in re-warming seen immediately post infusion. Significant improvement in extent of re-warming 3 days post CGRP but not PG-I ₂
Kyle, 1992 (23)	Double-blind cross over	4	13/8/4	IV iloprost over 6 hours on 3 consecutive days vs. placebo	Frequency of RP attacks Duration of RP attacks Severity (1-3 scale) of RP attacks Patient global assessment of RP response to treatment at each assessment.	Significant improvement in frequency but not duration or severity of RP attacks for iloprost vs. placebo No significantly improvement in global assessment	Baseline, day 4, 2 weeks and 6 weeks. Fifteen minutes acclimatisation at ambient 20°C followed by 3 minute warming of both hands at 37°C, followed by 1 minute CST (20°C for 60s) to right hand with images collected immediately after and at 5 min intervals during subsequent re-warming	Mean hand re-warming scores calculated by averaging the re-warming that occurred at 4 time points over 20 minutes post-CST relative to hand temperature within 1 minute of CST	No significant differences between baseline and subsequent assessments for placebo vs. iloprost

Author, year	Study design	Jaded Score	No of patients (AII/PRP/SSc)	Intervention	Clinical endpoint	Clinical improvement	IRT protocol	IRT endpoint	Thermographic Response
Katch, 1992 (25)	Open-label	0	40/1	Acute and short term effects of multiple infusions of IV PG-E ₁	Pain and colour score of worst lesion (1-5 scale)	Improvement in scores at 6, 24, 48, 72, 168 hours reported.	IRT of hands at baseline, 10, 30 and 60 minutes	T of "worst lesion"	Significant increase in T 60 minutes following lipo-PG-E ₁ infusion
Teh, 1995 (43)	Randomised, double-blind, placebo-controlled, cross-over study	3	32/17/15	7 days transdermal GTN (0.2mg/hr) vs. placebo	Frequency of RP attacks Severity of RP attacks (separate assessments of pain, numbness and colour change scored as none, mild, moderate or severe)	Improvement in frequency and severity of RP attacks	IRT images at baseline and following treatment periods. Dorsum of hands 2 hours after application of patch, and following CST (15°C for 60s)	DDD (dorsum of hands and distal regions of index, middle, ring and little fingers). Distal interphalangeal joint measurements used to calculate: Mean T immediately following CST Lag period before the onset of re-warming Maximum % recovery over 10 minutes post-CST	No significant differences
Stratton, 1997 (14)	Retrospective study	0	13/0/13	Digital sympathectomy	Retrospective questionnaire assessments of digital pain score (0-4 VAS), presence of digital ulcers and pitting scars count, and global outcome score (0-3) pre and post surgery	Significant improvement in pain score, ulcer score and global outcome score, but not in digital pitting scars.	IRT at baseline, 5 and 10 minutes post-CST (no details of nature of cold challenge)	Baseline wrist to fingertip TG Mean change in gradient 5 minutes post cold challenge Mean change in gradient 10 minutes post cold challenge	Improvement in mean change in TG 10 minutes post-CST only ($p < 0.06$)
Cooke, 1997 (29)	Open-label	0	4/4/0	Autologous blood transfusions following <i>ex vivo</i> heating, ozonation and UV light therapy	Subjective improvement in severity and duration of attacks	Improvement persisting for at least 3 months post treatment reported	IRT images of hands at baseline and immediately following autologous blood transfusion prior to, day after and 3-4 weeks post	Mean hand T	Non significant increase in all patients immediately post-therapy
Maeda, 1998 (21)	Open-label	0	24/0/17	Acute effects of electrical acupuncture	Not assessed		IRT assessments at baseline, 10, 45 and 60 minutes following electrical acupuncture	Surface T of dorsum of hands/fingers	Insufficient data reported to quantify response
Dzadzio, 1999 (39)	Open-label, randomised, parallel group study	1	52/25/27	Losartan 50mg od vs. nifedipine 20mg bd, 6 weeks	Frequency and severity of RP attacks (0-10 VAS)	Significant reduction in frequency and severity of attacks following losartan only	IRT Ax at weeks 0 and 6 weeks. IRT images at baseline, immediately following CST (15°C 60s), 5 and 10 minutes post-CST	Mean fingertip T at baseline, immediately following cold stress and 5 minute and 10 minutes post-CST	No improvement in recovery 10 minutes after cold challenge following either drug
Herrick, 2000 (35)	Randomised placebo-controlled double-blind cross-over	3	33/0/33	10 week combination anti-oxidants and allopurinol vs. placebo	Frequency of RP attacks Duration of RP attacks Subjective report of RP severity (better, same or worse)	No improvement	Dorsal aspect of hands at baseline and following CST (15°C for 60s) Measurement over DIP joints of index, middle and ring fingers over 15 minute re-warming	Mean T at baseline. Max. T recovery gradient Lag period before the onset of re-warming Maximum % recovery over 15 minutes post-CST	No improvement
Coleiro, 2001 (40)	Open-label randomised cross over study	2	53/26/27	6-week treatment periods with fluoxetine 20mg OD vs. nifedipine LA 40mg OD, 6 weeks	Frequency and severity of RP attacks (0-10 VAS)	Sig reduction in frequency and severity of attacks following fluoxetine only	IRT Ax at weeks 0 and after each 6-week treatment period. IRT images at baseline, immediately following CST (15°C 60s) and 10 minutes post-CST	Mean T of hands at baseline, immediately following CST (15°C 60s) and 10 minutes post-CST % re-warming at 10 minutes	No difference at baseline Significant improvement in % re-warming for PRP following treatment with fluoxetine.
Al-awami, 2001 (31)	Open-label	0	40/11/11	10 sessions of LLLT over 6 weeks	Frequency and severity of RP attacks (0-10 VAS)	Significant improvement in VAS scores at 6 weeks and 3 months	Baseline and 6 weeks and 3 months a) basal fingertip skin T b) challenge (immersion of gloved hands in water at 39°C), and c) measurements immediately after CST (20°C for 60s). Recovery temperatures were measured 10 and 20 minutes later.	Recovery T after cold exposure	Significant improvement at 6 weeks reported in all 40 patients but data not presented

Author, year	Study design	Jaded Score	No of patients (AII/PRP/SSc)	Intervention	Clinical endpoint	Clinical improvement	IRT protocol	IRT endpoint	Thermographic Response
Hirschi, 2002 (34)	Randomised, double-blind, placebo-controlled, cross-over study	3	18/18/0	LLLT vs. placebo (5 sessions per week for 3 weeks)	Frequency of RP attacks Intensity of RP attacks (1-5 VAS)	Improvement in intensity but not frequency of RP attacks	IRT images of the dorsal aspect of both hands at baseline and following CST (20°C for 60s) at beginning of the study and following each treatment period	Mean TG between MCP and fingertip for all fingers 20 minutes post-CST Number of fingers with TG <1°C 10 minutes post-CST	TG significantly reduced post-CST following LLLT compared to placebo. No significant difference in the number of fingers with gradient <1°C 10 minutes post CST between placebo and LLLT group
Balogh, 2002 (30)	Open-label	1	7/7/0	Adventitial stripping of radial and ulnar arteries	Questionnaire 1-year post surgery. Qualitative assessment of pain, frequency and duration of RP attacks; QoL 0-10 VAS. Questionnaire assessment of ulcers, use of gloves and fridge/cold tolerance	Reduction in severity of all parameters reported. Improvement in QoL VAS in all subjects.	IRT assessment at baseline, 3 and 6 months following surgery.	Qualitative assessment of thermographic appearances of dorsum of hands at baseline, immediately post-CST (20°C 60s), and 5 and 10 minutes post-CST.	Reduced vasoconstriction reported in 3/5 patients and enhanced re-warming post-CST reported in 3/5 patients.
Kan, 2002 (26)	Open-label	0	25/0/25	Nitro-glycerine (NTG) patch applied to one wrist	Nil	N/A	IRT assessment of the dorsal aspect of both hands at baseline.	Change in the fingertip T of the coldest digit on each hand at baseline and one hour following application of NTG patch	Significant improvement in fingertip T following NTG tape in patients with SSc
Al-Awami, 2004 (37)	Randomised, double-blind, placebo-controlled	4	47/18/5	10 sessions of LLLT vs. sham laser placebo	Frequency of RP attacks Severity of RP attacks (0-10 VAS)	Significant improvement in frequency and severity of RP following both LLLT and placebo (more pronounced improvement in the LLLT group)	IRT at baseline and 6 weeks a) Baseline b) Immediately after 1 minute warm challenge (immersion of gloved hands in water at 39°C) c) Measurements immediately post-CST (20°C for 60s) d) Measurements 10 and 20 minutes post-CST	Change in basal fingertip skin T 20 minutes post-CST	Significantly reduced change in fingertip T post-CST following LLLT but not placebo
Hirschi, 2004 (33)	Double-blind randomised, placebo-controlled cross-over	3	48/48/0	3 weeks LLLT vs. placebo	Frequency and intensity (5 point VAS) of RP attacks	Significant decreases in frequency and intensity of RP attacks following LLLT compared to placebo.	IRT assessments at baseline and following treatment periods. IRT image of dorsal hands taken pre and for 20 minutes post-CST (20°C for 60s)	The mean TG of all fingers, the maximum TG and number of fingers with DDD <1°C at 20 minutes post-CST	Non significant trend towards improvement following LLLT compared with placebo
Selenko-Gebauer, 2006 (16)	Open-label	0	3/0/2	Bosentan 62.5mg bd weeks 0-4, 125mg bd weeks 5-12	Frequency, duration and severity (1-3) of RP attacks. The SHAQ and pain VAS (0-10 VAS)	Descriptive analysis of improvement in RP activity, pain VAS and number/severity of RP attacks.	IRT Ax at weeks 0 and 16. IRT images of dorsum of hands at baseline and 20 minutes post-CST (20°C, ?duration)	No specific IRT endpoint	IRT images presented for subjective analysis. No quantifiable thermographic endpoints reported.
Ishigatsubo, 2010 (27)	Open-label	0	8/0/8	Autologous transplantation of bone-marrow-derived cells	Pain VAS (0-10) and ulcer size	Descriptive report of pain VAS and ulcer size responses over 24 weeks post-transplantation. Pictorial examples of ulcer healing presented	IRT protocol not reported	IRT endpoints not reported	Thermal images demonstrating increased perfusion post-transplantation from one patient presented. Thermographic improvement reported in 5 of 8 patients.
Shlager, 2011 (32)	Open-label	0	26/26/0	Auricular electroacupuncture, 6 sessions over 6 weeks	Frequency (diary monitoring) and severity (0-10 VAS) of RP attacks	Significant improvement in frequency and severity of attacks at 3, 6 and 24 weeks	IRT assessments of volar aspect of patient hands at baseline, 3, 6 and 24 weeks.	Fingertip skin T before and following CST (20°C for 60s).	No change.

DU: digital ulceration; CREST: calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasia; CST: cold stress test; PRP: primary Raynaud's phenomenon; SSc: systemic sclerosis; RP: Raynaud's phenomenon; T: temperature; VAS: Visual Analogue Scale; PG-E₁: Prostaglandin E₁; SHAQ: Scleroderma Health Assessment Questionnaire; PG-I₂: Prostaglandin I₂; CGRP: Calcitonin Gene Related Peptide; Ax: assessment; TG: Thermal Gradient; NS: non-significant; LLLT: low level laser therapy; 5-HT: 5-hydroxytryptamine; DDD: dorsal-distal difference.

evaluated thermographically in clinical trials, the only notable exception being phosphodiesterase inhibition.

Technical aspects

As anticipated, a wide variety of brands and models of infrared camera were used in the studies, precluding any evaluation of study quality on the basis of equipment used.

Clinical endpoints

The majority of studies incorporated clinical endpoints. Many early studies adopted categorical descriptions from patients regarding RP severity following intervention (*e.g.* much better, better, no change, worse etc.) or visual analogue scales (VAS) scores assessing pain levels associated with RP attacks (20, 36). More recent studies have incorporated quantitative assessments of RP severity using VAS and RP diaries recording attack frequency, duration and severity. Interestingly, none of the studies had used the recommended Raynaud's Condition Score (RCS) proposed in 1992 and recommended for use in clinical trials of RP since 2003 (4). Modified versions of the RCS, collecting information on the frequency and duration of RP attacks have been used, presumably for practical reasons relating to study design.

Thermographic protocol

The majority of studies incorporated a period of acclimatisation in a quiet temperature-controlled laboratory prior to thermographic assessment. Temperature measurement of the dorsum of the hands was undertaken in most studies although measurement of the volar aspect of the fingers has also been described (32). The majority of thermographic protocols incorporated a CST (22/32, 68.8%), usually achieved through the submersion of gloved hands into a water bath. The conditions of the CST varied, although the most commonly used protocol involved a cold challenge of 20°C for 60s (14/32, 43.8%). The use of cooled contact plates to promote vasoconstriction has also been evaluated (13). Several studies incorporated an additional period of digital warming prior to evaluation of the CST (23, 22, 15, 31, 37).

Thermographic endpoints

Two principle methods have emerged for the reporting of thermographic endpoints; absolute temperature values of the hands and/or fingers from distinct regions of interest, and/or thermal gradients derived from either the difference between the mean temperatures of the dorsum of the hand and of the fingers, or the longitudinal thermal gradient along individual digits. Studies with thermographic protocols incorporating a local cold challenge were able to report additional thermographic parameters describing digital vascular responses to cold exposure and the characteristics of the re-warming process. These included absolute temperature values before and after cold challenge (36, 38, 18, 39, 40, 31, 37, 32), percent recovery indices (*e.g.* maximum percent recovery during 10 minutes re-warming period post-CST) (40) or thermal gradients at specific time-points following cold challenge (34, 33, 23, 41, 17, 42, 14). If sufficient thermographic measurements are made following the cold challenge, attempts can be made to quantify the characteristics of the re-warming curve using parameters such as the lag-time to re-warming and maximum percent recovery (35, 43). Additional thermographic parameters derived from the re-warming curve characteristics such as area under the curve and maximum gradient of re-warming that have been successfully applied in diagnostic studies have not been evaluated as endpoints in these therapeutic trials of RP. A small number of studies, notable for their small sample sizes, used a qualitative assessment of the appearances of the thermal images alone to attempt to demonstrate response to therapy (16, 27, 30).

Agreement between clinical and thermographic endpoints – Improvement in both clinical and thermographic endpoints

The majority of studies (18/32, 56.3%) reported improvements in both clinical and thermographic outcome measures. Eleven of these studies were characterised by either small patient numbers ($n \leq 13$) (14, 16, 19, 20, 24, 25, 29, 30, 22) and/or failed to substantiate evidence for thermographic improvement

with supportive data (18, 31). The extent to which one can critically appraise the thermographic parameters used in these studies is questionable. The remaining 7 studies shall be considered further and are included within Table I (42, 41, 34, 38, 40, 36, 37). Three studies (1 blinded) evaluated the use of prostanoids such as prostacyclin (PG-I₂) and prostaglandin E₂ (PG-E₂) in studies of greater than 20 patients (41, 38, 36). These parenterally administered agents are amongst the most potent vasodilators and recommended for use in severe RP or for the emergency management of ischaemic complications in SSc (3). Clinical endpoints in these studies included pain VAS, subjective categorical variables (better, same, worse), ulcerative complications, and the frequency, duration and severity of RP attacks. Two of these studies used the average temperature of hands/fingers at baseline to demonstrate improved peripheral vascular function following therapy, but failed to demonstrate a significant change in the parameters derived following the CST (38, 36). In contrast, McHugh *et al.* did not identify improvements in baseline thermal imaging following iloprost therapy but did identify a reduced thermal gradient (dorsum of fingers – dorsum of hands) 10 minutes post-CST indicative of a suppressed vasospastic response to cold exposure (41). The remaining 4 studies evaluated a range of interventions including inositol nicotinate, serotonin re-uptake inhibition and low level laser therapy (LLLT) (42, 34, 40, 37). Ring *et al.* identified significant improvements in VAS scores for coldness, pain and numbness VAS scores, and a significant reduction in the estimated duration of vasospastic incidents post-treatment (42). This was accompanied by a significant reduction in the magnitude of the thermal gradient 10 minutes post-CST (the same thermographic endpoint used in the aforementioned study by McHugh *et al.*) (41, 42). Coleiro *et al.* used an open-label randomised cross over study design to demonstrate a reduction in the frequency and severity of RP attacks following fluoxetine therapy (40). This was accompanied by a significant improvement in percent re-warm-

ing 10 minutes post-cold challenge. There was no improvement in baseline hand temperature following treatment (40). A double-blind study of LLLT undertaken by Hirschl *et al.* demonstrated improvement in the intensity of RP attacks accompanied by an improvement in the mean longitudinal temperature gradient across all fingers at 20 minutes post-CST (34). The number of digits with a pathological thermal gradient of $<-1^{\circ}\text{C}$ 10 minutes post-CST was not affected by LLLT (34). A similarly designed study, also evaluating LLLT, demonstrated significant improvements in the frequency and severity of RP attacks in both the LLLT and placebo arms (37). The thermographic improvement, assessed using fingertip skin temperature post-cold challenge, was only demonstrated in the LLLT arm of the study (37).

– Improvement in clinical endpoints alone

Six studies (6/32, 18.8%) identified improvements in clinical endpoints that were not accompanied by improvements in thermographic parameters (12, 39, 33, 23, 32, 43). Two studies were excluded from further analysis due to small study numbers ($n \leq 13$) (12, 23). Two of the studies were double-blind RCTs, one evaluating transdermal glycerine tri-nitrate (GTN) (43), and the other LLLT (33). Thermographic endpoints in these studies included distal-dorsal gradients, number of digits with a DDD of $<-1^{\circ}\text{C}$, characteristics of re-warming curves and mean fingertip temperature following cold challenge. Interestingly, the study evaluating LLLT was undertaken by the same group that had demonstrated improvements of both clinical and thermographic parameters in an earlier similarly designed study involving fewer patients (34, 33). The remaining 2 studies (evaluating losartan therapy and auricular electroacupuncture) were open-label study design and improvement in clinical endpoints may have been achieved by placebo effect alone (39, 32).

The remaining studies

Six studies failed to report any clinical endpoints, often those studies evaluat-

ing the acute digital vascular effects of therapeutic intervention (28, 26, 21, 17, 15, 13). Another small study failed to undertake statistical analysis of clinical or thermographic outcomes, instead providing pictorial examples of ulcer healing and figures presenting the evolution of ulcer size and pain VAS for each patient during the study period (27). A well-designed study by Herrick *et al.*, failed to identify improvements in either clinical or thermographic endpoints, possibly reflecting true inefficacy of the intervention (combination antioxidants and allopurinol) (35). No studies reported an improvement in thermographic parameters without also demonstrating an improvement in clinical endpoints.

Discussion

The present paper is the first to systematically review the previous therapeutic studies of Raynaud's phenomenon that have incorporated IRT as an outcome measure. Comparison between studies is limited by variation in study design, intervention, IRT protocols and endpoints, precluding any attempt at formal meta-analysis. Nonetheless, we have been able to provide a detailed description of the various methods incorporated in previous studies that can help influence the design of future work. No single method has emerged as the preferred thermographic parameter for use in clinical trials. We have attempted to highlight promising thermographic parameters by reporting those studies in which agreement was present between subjective clinical endpoints and thermographic parameters. Thermographic parameters including absolute temperature measurements at baseline, and longitudinal thermal gradients and percent re-warming following cold challenge, have been successfully applied in studies reporting agreement between clinical and thermographic endpoints. The major limitation of this approach is that subjective self-reports and thermographic assessment may provide differing information on peripheral vascular function.

IRT, along with other non-invasive microvascular imaging modalities, is not currently included in the proposed

core set of outcome measures of vascular dysfunction in clinical trials of RP and SSc, although the urgent need for useful markers of biological vascular activity has been highlighted (4). The outcome measures currently recommended for use in clinical trials are patient self-reports or physician global assessments. There are obvious limitations to a reliance on subjective endpoints. Patient self-reports of RP severity, usually taking the form of a diary of frequency, duration and severity of attacks carry several limitations. They are subjective, time consuming, poorly completed, and influenced by seasonal variation in environmental temperature and strategies adopted by patients to avoid conditions necessary for an attack of RP. It is our experience that patients with profound peripheral vascular dysfunction, as is commonly seen in SSc, have a tendency to under-report RP severity in self-reports. This may be the result of habituation and difficulty discerning discreet RP attacks from chronic basal vascular compromise associated with progressive structural microvascular dysfunction. Furthermore, psychosomatic testing has revealed distinct personality traits between patients with primary and secondary RP which could influence self-report measures of RP severity between the 2 groups (44). The extent of placebo effect noted in previous therapeutic studies highlights a major disadvantage to self-reports of RP severity. Large randomised controlled studies incorporating diary cards have reported statistically significant improvements in the Raynaud's Condition Score (RCS), duration and frequency of RP attacks of up to 60% in placebo arms (45-47). It is possible that "diary fatigue" could contribute to a lower rate of self-report as studies progress. Whatever the cause, it becomes increasingly difficult to identify differences in between-group comparisons in the presence of such stark responses following sham therapy. Non-invasive microvascular assessment tools, such as IRT, have the advantage of providing a rapid, quantitative, objective measure of digital vascular dysfunction upon which to guide diagnostic and therapeutic de-

cisions. Any placebo effect might be expected to be lower using objective microvascular imaging tools compared with self-reports. Furthermore, the use of standardised microvascular imaging protocols, incorporating an acclimatisation period prior to assessment, may help negate the influence of seasonal variation in environmental temperature and the coping strategies adopted by patients to avoid cold, which influence self-reports. Several other non-invasive microvascular imaging techniques such as laser Doppler, plethysmography, digital artery pressure have been used in therapeutic trials of RP. We have not attempted to consider such methods as it would have greatly extended the scope of the review, rendering it increasingly difficult to compare and contrast previous work.

Conclusions

To date, no single thermographic parameter has emerged as a preferred endpoint for clinical trials. We would encourage the ongoing evaluation of microvascular imaging tools such as IRT in clinical trials of RP, alongside recommended self-report tools such as the RCS, noting the potential advantages of objective microvascular imaging tools over self-report. Such work should attempt to define the true nature of what each outcome measure actually informs us regarding digital vascular function. We would recommend the creation of a consensus panel of experts to form recommendations on a standardised approach to the use of IRT in future clinical trials of RP. This would encourage the use of high quality thermographic protocols and endpoints, and facilitate easier comparison of the outcomes of therapeutic studies of RP.

Author contributions

The study selection process was undertaken by JDP. The full text of each article selected was reviewed and scored independently by JDP and JAS. All authors contributed to drafting the article and had access to all of the data used in the study. All authors approved the final version to be submitted for publication.

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References

1. LEROY EC, MEDSGER TA, JR.: Raynaud's phenomenon: a proposal for classification. *Clin Exp Rheumatol* 1992; 10: 485-8.
2. LEROY EC, BLACK C, FLEISCHMAJER R *et al.*: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
3. KOWAL-BIELECKA O, LANDEWÉ R, AVOUAC J *et al.*: EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009; 68: 620-8.
4. MERKEL PA, CLEMENTS PJ, REVEILLE JD, SUAREZ-ALMAZOR ME, VALENTINI G, FURST DE: Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. *J Rheumatol* 2003; 30: 1630-47.
5. JADAD AR, MOORE RA, CARROLL D *et al.*: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1-12.
6. BELCH JJ, NEWMAN P, DRURY JK *et al.*: Successful treatment of Raynaud's Syndrome with prostacyclin. *Thromb Haemost* 1981; 45: 255-6.
7. RANIERI G, DE MITRIO V, PETRUZZELLIS V, SCARAGGI FA, QUARANTA D, DAMMACCO F: Defibrotide in the treatment of Raynaud's phenomenon in patients with progressive systemic sclerosis or essential mixed cryoglobulinemia. *Curr Ther Res Clin Exp* 1993; 53: 48-58.
8. AROSIO E, MONTESI G, ZANNONI M, PERBELLINI L, PALUANI F, LECHI A: Efficacy of ketanserin in the therapy of Raynaud's phenomenon: thermometric data. *Angiology* 1991; 42: 408-13.
9. WOUDA AA: Methods of evaluating Raynaud's phenomenon for the purpose of pharmacotherapeutic research. *Vasa Suppl* 1987; 18: 32-9.
10. LUKAC J, ROVENSKY J, TAUCHMANNOVA H, ZITNAN D: Long-term ketanserin treatment in patients with systemic sclerosis and Raynaud's phenomenon. *Curr Ther Res Clin Exp* 1991; 50: 869-77.
11. MERLA A, ROMANI GL, DI LUZIO S *et al.*: Raynaud's phenomenon: Infrared functional imaging applied to diagnosis and drugs effects. *Int J Immunopathol Pharmacol* 2002; 15: 41-52.
12. YAMAOKA K, MIYASAKA N, SATO K, NISHIOKA K, OKUDA M: Therapeutic effects of CS-570, a chemically stable prostacyclin derivative, on Raynaud's phenomenon and skin ulcers in patients with collagen vascular diseases. *Int J Innumotherapy* 1987; 3: 271-7.
13. WESSELING H, DEN HEETEN A, WOUDA AA: Sublingual and oral isoxsuprine in patients with Raynaud's phenomenon. *Eur J Clin Pharmacol* 1981; 20: 329-33.
14. STRATTON R, HOWELL K, GODDARD N, BLACK C: Digital sympathectomy for ischaemia in scleroderma. *Br J Rheumatol* 1997; 36: 1338-9.
15. SHAWKET S, DICKERSON C, HAZLEMAN B, BROWN MJ: Prolonged effect of CGRP in Raynaud's patients: a double-blind randomised comparison with prostacyclin. *Br J Clin Pharmacol* 1991; 32: 209-13.
16. SELENKO-GEBAUER N, DUSCHEK N, MINIMAIR G, STINGL G, KARLHOFFER F: Successful treatment of patients with severe secondary Raynaud's phenomenon with the endothelin receptor antagonist bosentan. *Rheumatology (Oxford)* 2006; 45 (Suppl. 3): iii45-48.
17. RING EF, BACON PA: Quantitative thermographic assessment of inositol nicotinate therapy in Raynaud's phenomena. *J Int Med Res* 1977; 5: 217-22.
18. RADEMAKER M, COOKE ED, ALMOND NE *et al.*: Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; 298: 561-4.
19. MELONI F, TRANSI MG, SCIACCA V, DE FELICE C, BAGARONE A, SCIACCA A: Therapeutic efficacy of ketanserin, a selective antagonist of the serotonin (5-HT₂) receptors, in primary and secondary Raynaud's phenomenon. *Angiology* 1987; 38: 530-6.
20. MARTIN MF, DOWD PM, RING EF, COOKE ED, DIEPPE PA, KIRBY JD: Prostaglandin E1 infusions for vascular insufficiency in progressive systemic sclerosis. *Ann Rheum Dis* 1981; 40: 350-4.
21. MAEDA M, KACHI H, ICHIHASHI N, OYAMA Z, KITAJIMA Y: The effect of electrical acupuncture-stimulation therapy using thermography and plasma endothelin (ET-1) levels in patients with progressive systemic sclerosis (PSS). *J Dermatol* 1998; 17: 151-5.
22. KYLE V, PARR G, SALISBURY R, THOMAS PP, HAZLEMAN B: Prostaglandin E1 vasospastic disease and thermography. *Ann Rheum Dis* 1985; 44: 73-8.
23. KYLE MV, BELCHER G, HAZLEMAN BL: Placebo controlled study showing therapeutic benefit of iloprost in the treatment of Raynaud's phenomenon. *J Rheumatol* 1992; 19: 1403-6.
24. KLIMIUK PS, KAY EA, MITCHELL WS *et al.*: Ketanserin: an effective treatment regimen for digital ischaemia in systemic sclerosis. *Scand J Rheumatol* 1989; 18: 107-11.
25. KATOH K, KAWAI T, NARITA M, UEMURA J, TANI K, OKUBO T: Use of prostaglandin E1 (lipo-PGE1) to treat Raynaud's phenomenon associated with connective tissue disease: thermographic and subjective assessment. *J Pharm Pharmacol* 1992; 44: 442-4.
26. KAN C, AKIMOTO S, ABE M, OKADA K, ISHIKAWA O: Preliminary thermographic evaluation of new nitroglycerine tape on the peripheral circulatory disturbance in systemic sclerosis. *Ann Rheum Dis* 2002; 61: 177-9.
27. ISHIGATSUBO Y, IHATA A, KOBAYASHI H *et al.*: Therapeutic angiogenesis in patients with systemic sclerosis by autologous transplantation of bone-marrow-derived cells. *Mod Rheumatol* 2010; 20: 263-72.

28. GUSH RJ, TAYLOR LJ, JAYSON MI: Acute effects of sublingual nifedipine in patients with Raynaud's phenomenon. *J Cardiovasc Pharmacol* 1987; 9: 628-31.
29. COOKE ED, POCKLEY AG, TUCKER AT, KIRBY JD, BOLTON AE: Treatment of severe Raynaud's syndrome by injection of autologous blood pretreated by heating, ozonation and exposure to ultraviolet light (H-O-U) therapy. *Int Angiol* 1997; 16: 250-4.
30. BALOGH B, MAYER W, VESELY M, MAYER S, PARTSCH H, PIZA-KATZER H: Adventitial stripping of the radial and ulnar arteries in Raynaud's disease. *J Hand Surg Am* 2002; 27:1073-80.
31. AL-AWAMI M, SCHILLINGER M, GSCHWANDTNER ME, MACA T, HAUMER M, MINAR E: Low level laser treatment of primary and secondary Raynaud's phenomenon. *Vasa* 2001; 30: 281-4.
32. SCHLAGER O, GSCHWANDTNER ME, MLEKUSCH I *et al.*: Auricular electroacupuncture reduces frequency and severity of Raynaud attacks. *Wien Klin Wochenschr* 2011; 123: 112-6.
33. HIRSCHL M, KATZENSCHLAGER R, FRANCESCONI C, KUNDI M: Low level laser therapy in primary Raynaud's phenomenon – results of a placebo controlled, double blind intervention study. *J Rheumatol* 2004; 31: 2408-12.
34. HIRSCHL M, KATZENSCHLAGER R, AMMER K, MELNIZKY P, RATHKOLB O, KUNDI M: Double-blind, randomised, placebo controlled low level laser therapy study in patients with primary Raynaud's phenomenon. *Vasa* 2002; 31: 91-4.
35. HERRICK AL, HOLLIS S, SCHOFIELD D *et al.*: A double-blind placebo-controlled trial of antioxidant therapy in limited cutaneous systemic sclerosis. *Clin Exp Rheumatol* 2000; 18: 349-56.
36. CLIFFORD PC, MARTIN MF, SHEDDON EJ, KIRBY JD, BAIRD RN, DIEPPE PA: Treatment of vasospastic disease with prostaglandin E1. *Br Med J* 1980; 281: 1031-4.
37. AL-AWAMI M, SCHILLINGER M, MACAT, POL-LANZ S, MINAR E: Low level laser therapy for treatment of primary and secondary Raynaud's phenomenon. *Vasa* 2004; 33: 25-9.
38. DOWD PM, MARTIN MF, COOKE ED *et al.*: Treatment of Raynaud's phenomenon by intravenous infusion of prostacyclin (PGI₂). *Br J Dermatol* 1982; 106: 81-9.
39. DZIADZIO M, DENTON CP, SMITH R *et al.*: Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum* 1999; 42: 2646-55.
40. COLEIRO B, MARSHALL SE, DENTON CP *et al.*: Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)* 2001; 40: 1038-43.
41. MCHUGH NJ, CSUKA M, WATSON H *et al.*: Infusion of iloprost, a prostacyclin analogue, for treatment of Raynaud's phenomenon in systemic sclerosis. *Ann Rheum Dis* 1988; 47: 43-7.
42. RING EF, PORTO LO, BACON PA: Quantitative thermal imaging to assess inositol nicotinate treatment for Raynaud's syndrome. *J Int Med Res* 1981; 9: 393-400.
43. TEH LS, MANNING J, MOORE T, TULLY MP, O'REILLY D, JAYSON MI: Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; 34: 636-41.
44. BAYLE O, CONSOLI SM, BAUDIN M, VAYSSAIRAT M, FIESSINGER JN, HOUSSET E: [Idiopathic and secondary Raynaud's phenomenon. A comparative psychosomatic approach]. *Presse Med* 1990; 19: 741-5.
45. BLACK CM, HALKIER-SORENSEN L, BELCH JJ *et al.*: Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br J Rheumatol* 1998; 37: 952-60.
46. BELCH JJ, CAPELL HA, COOKE ED *et al.*: Oral iloprost as a treatment for Raynaud's syndrome: a double blind multicentre placebo controlled study. *Ann Rheum Dis* 1995; 54: 197-200.
47. NGUYEN VA, EISENDLE K, GRUBER I, HUGL B, REIDER D, REIDER N: Effect of the dual endothelin receptor antagonist bosentan on Raynaud's phenomenon secondary to systemic sclerosis: a double-blind prospective, randomized, placebo-controlled pilot study. *Rheumatology (Oxford)* 2010; 49: 583-7.