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REVIEW ARTICLE

# Raynaud's phenomenon—an update on diagnosis, classification and management

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## Abstract

Raynaud's phenomenon (RP) is used to describe a symptom complex caused by digital vascular compromise. RP is a clinical diagnosis. The typically episodic nature of RP has resulted in a reliance upon patient self-report for diagnosis. The term 'primary RP' is generally applied when no underlying pathology can be demonstrated. Whilst 'primary RP' is currently considered a distinct disorder, there is evidence that the term may comprise several entities that include a functional vasospastic disorder, a physiologically appropriate thermoregulatory response, subclinical atherosclerosis and 'cold intolerance'. Optimal management may differ depending on cause. The term 'secondary RP' encompasses a broad range of rheumatological, haematological, endocrinological and vascular pathology. RP can range from relatively benign but intrusive vasospasm, to the progressive obliterative microangiopathy of systemic sclerosis (SSc), in which severe digital ischaemia can threaten tissue viability. SSc has formed the focus of much of the research into RP but, consistent with most medical symptom complexes, the aetiopathogenesis of RP varies greatly dependent on cause. Vasospasm within the digital macro- and microvasculature occurs in SSc, but digital ischaemia is further compounded by a progressive obliterative microangiopathy. Recent work exploring the patient experience of SSc-RP is challenging the 'episodic' paradigm of 'Raynaud's', with important implications for clinical trials utilising diary-based patient-reported outcome instruments for assessing Raynaud's symptoms. This review shall examine the causes, pathogenesis, clinical features, classification and management of RP. A practical approach to the evaluation and management of RP is outlined, highlighting important knowledge gaps and unmet research needs where applicable.

**Key Points**

- *Raynaud's phenomenon is a symptom complex related to digital vascular compromise secondary to broad-ranging pathology.*
- *Raynaud's phenomenon, as currently classified, likely encompasses a number of aetiopathogenic processes.*
- *Raynaud's phenomenon causes significant disease-related morbidity in autoimmune rheumatic diseases such as systemic sclerosis.*

**Keywords** Assessment · Classification · Management · Pathogenesis · Raynaud's phenomenon · Systemic sclerosis

## Introduction

The term Raynaud's phenomenon (RP) is used to describe a symptom complex relating to digital vascular compromise, typically aggravated by the vasoconstrictive effects of cold exposure and other sympathomimetic drivers. This review provides an overview of RP, highlighting the breadth and burden of pathology associated with Raynaud's symptoms alongside implications for management. A practical approach to the evaluation and management of RP shall be outlined, highlighting important knowledge gaps and unmet research needs.

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## Search strategy and selection criteria

Many valuable reviews have been prepared on the subject of Raynaud's phenomenon. To ensure the present review provided a comprehensive update on recent developments in this field, the following search strategies were adopted in accordance with recommendations for narrative reviews [1]. Data was identified within the National Institutes of Health's National Library of Medicine (PubMed) using the following search criteria (01 January 2015–20 March 2019):

(Raynaud*) AND ((pathogenesis) OR (assessment) OR (classification) OR (clinical trial) OR (impact) OR (burden) OR (imaging) OR (treatment) OR (clinical) OR (management) OR (features))

Original research articles (excluding abbreviated reports, case reports and reviews) identified were scrutinised for data relating to the major subheadings of this review. An additional search for 'Raynaud*' (custom date range limited to 01 January 2015–20 March 2019) within the Cochrane Database of Systematic Reviews was also undertaken to support management aspects. A grey search of manuscripts cited within these articles was undertaken, alongside the inclusion of earlier seminal and influential work on the subject of Raynaud's phenomenon.

## What is Raynaud's phenomenon

Unlike many medical eponyms that assemble a constellation of clinical features pertaining to a single disease entity, the term 'Raynaud's' is applied across a broad range of disparate pathology. This curious position can be directly traced to Raynaud's original treatise that included a young woman (case I) who [2],

> Under the influence of a very moderate cold…she sees her fingers become ex-sanguine, completely insensible, and of a whiteish yellow colour. This phenomenon happens often without reason, lasts a variable time and terminates by a period of very painful reaction, during which the circulation is re-established.

Raynaud described 25 cases of increasing severity, culminating in a published report of bilateral upper limb gangrene (case XXV) that had presented to the academy 150 years earlier [2]. Raynaud also described probable cases of systemic sclerosis (SSc), characterised by digital ulceration and visceral fibrosis fibrosis [2]. Barlow supplemented his translation of Raynaud's thesis with additional cases of likely SSc, alongside cases of cold-induced haemolysis that he considered within the same disease spectrum. From these origins, the eponym rapidly became associated with a wide breadth of disparate pathology associated with digital vascular compromise, leading to confusion over classification. The issue of what actually constituted 'RP' vexed early twentieth century clinicians who questioned [3]:

> Should the diagnosis be reserved for a carefully defined condition, with characteristics sufficiently common to all cases for the condition to be designated as a disease, or should its boundaries be so extended as to include the larger and more inclusive group of vasospastic disturbances?

Disagreement amongst experts of the essential prerequisites of Raynaud's persists to this day [4]. Putting to one side the clinical features and classification (discussed later), RP may be best summarised as a symptom complex arising from varying degrees of digital vascular compromise.

## Conditions associated with RP

The functional vasospastic disorder, in an otherwise healthy person, described by Raynaud (and now termed 'primary RP'), represents the commonest form of RP. This fully reversible and episodic nature of this phenomenon (alongside its relationship with cold exposure) has led to reliance upon self-report of cold sensitivity and digital colour changes to diagnose RP, particularly primary disease in which objective microvascular imaging and serological studies are typically negative [4–7]. There is large variation in prevalence estimates for RP (ranging from 2.1–22.4%) of primary RP [8], highlighting the limitations of diagnostic approaches but also questioning the appropriateness of categorising RP as a distinct disorder. Digital vasoconstriction is an appropriate thermoregulatory response to cold exposure. Inevitably, wide inter-individual variation in basal sympathetic tone, vascular reactivity and the thresholds at which people experience digital ischaemic symptoms exists, prompting observations that 'we are all subjects of Raynaud's phenomena to a greater or lesser degree' [9] and others to question the very existence of primary RP [10].

The first major study of 'primary RP' identified a high incidence (24%) of 'functional disturbances' (noting that 'vague aches and pains, constipation and headaches are frequently complained of') [11]. Differences in psychological phenotype between primary and secondary RP have been reported [12]. Other factors associated 'primary RP' include female gender (likely secondary to the vasoactive influence of female sex hormones), colder climate, low weight, smoking, manual occupation, atherosclerotic disease and psychological impairment, observations that themselves suggest distinct pathophysiological mechanisms resulting in

symptoms of digital vascular compromise [3, 5, 8, 11]. Raynaud's symptoms have been reported in 18–53% of patients with fibromyalgia syndrome (FMS) [13, 14]. Comparatively normal digital vascular responses to local cold challenge in FMS compared with patients with primary RP suggests 'cold intolerance' may account for Raynaud's-like symptoms amongst some patients with FMS [15]. A 20-year analysis of patients enrolled into a community-based study capturing RP symptoms identified a 1.5-fold increase in the risk of cardiovascular disease-related morbidity in people reporting blanching RP symptoms (but not when in conjunction with cyanosis) suggesting that, amongst some patients at least, RP symptoms could represent pre-clinical cardiovascular disease [16]. It has been noted that subtle nailfold capillary abnormalities in primary RP are more pronounced in younger people, consistent with the possibility that proximal vessel atherosclerotic disease may account for 'primary' RP symptoms presenting in older people [17]. What we currently term primary RP may therefore encompass a broad spectrum that includes a true vasospastic disorder, physiologically appropriate homeostatic thermoregulatory digital vasoconstriction, subclinical atherosclerosis and cold intolerance, each concealed behind a potentially misleading eponym that may impede more targeted therapeutic intervention (Fig. 2).

The term secondary RP is applied to a similarly broad range of conditions associated with recognised digital vascular compromise (Table 1). The high prevalence of RP within autoimmune rheumatic diseases (ARDs, particularly SSc and mixed connective tissue disease [MCTD]) has resulted in rheumatologists adopting an important role in the assessment and management of RP. Clinicians must consider a broad range of potential pathology when assessing a patient with RP symptoms. Virtually, all pathology associated with impaired digital vascular perfusion can result in RP symptoms, whether this relates to external arterial compression, intravascular occlusion, altered sympathetic tone or structural abnormalities within the vessel wall. Whilst ARD-related RP is commonly identified in the rheumatology setting, a detailed clinical assessment is necessary to exclude large-vessel (compressive and obstructive), iatrogenic, occupational, haematological and neurological disorders that may impair digital perfusion leading to Raynaud's symptoms (Table 1). Clinical features of underlying pathology are generally present at the time of assessment, although this may not be the case in ARDs such as SSc, in which RP symptoms are often the first clinical manifestation, sometimes predating other clinical features by several years [18–20]. The identification of SSc-associated autoantibodies and structural microvascular abnormalities are valuable predictors of likely evolution to SSc (see later) [21]. Whereas RP occurs in > 96% of patients with SSc [22], the prevalence of RP is lower in systemic lupus erythematosus (SLE, ~ 30%), primary Sjogren's syndrome (pSS, ~ 30%) and myositis-spectrum disorders (MSD, ~ 40% particularly patients with anti-synthetase autoantibodies). The precise role of anti-nuclear autoantibodies in the aetiopathogenesis of secondary RP has not been elucidated but autoimmune serology is a useful predictor of RP symptoms in ARDs. RP is less frequently identified in dermatomyositis associated with anti-TIF1γ compared with other antibody specificities [23]. The presence of anti-U1-RNP and anti-Smith antibodies increases the likelihood of RP symptoms in SLE [24, 25]. Unsurprisingly, the presence of SSc-specific autoantibodies (particularly anti-centromere) increases the likelihood of RP across the spectrum of ARDs including SLE [26], rheumatoid arthritis [27] and pSS [28, 29]. Potentially 'agonistic' anti-endothelial cell (and receptor) and angiotensin II receptor antibodies are reported to be more prevalent at high titres in people with SSc-spectrum disorders and associated with a more severe vascular phenotype, strengthening the interrelationship between autoimmunity and vasculopathy in ARD [30–32]. Efforts to identify autoantibodies targeting putative antigens responsible for increased cold sensitivity have been unsuccessful to date [33].

## Clinical features and impact of Raynaud's

Given the broad range of pathology associated with Raynaud's symptoms, it is unsurprising that differences in clinical features and impact of Raynaud's may exist between different patient populations.

### Digital colour changes

Perhaps owing to Raynaud's initial description, there has been a tendency to focus on digital colour changes when diagnosing/classifying RP [4]. White (blanching secondary to vasoconstriction/occlusion of the pre-capillary arterioles), blue/purple (cyanosis secondary to deoxygenation of sequestered blood following vasoconstriction/occlusion of the post-capillary venules) and red (post-ischaemic hyperaemia) are the digital colour changes commonly associated with Raynaud's symptoms (Fig. 1). Not all colour changes are necessary for diagnosis, although there has been a tendency to mandate the presence of at least 2 colour changes ('biphasic') before diagnosing or classifying RP [4]. Whether such distinctions accurately reflect the digital vascular symptoms of conditions purported to be associated with RP such as thoracic outlet syndrome or hypothyroidism is questionable and has not formed the basis of sufficient enquiry. The term acrocyanosis is often preferentially applied in vaso-occlusive disorders such as cold agglutinin disease, perhaps reflecting a predominance of cyanosis over other digital colour changes within certain diseases.

Cyanosis (without blanching) appears commoner in SSc than amongst people with primary RP, whereas reactive

**Table 1** The secondary causes of Raynaud's phenomenon

| Cause of RP | Underlying aetiology | Clinical findings/investigations aiding diagnosis |
|---|---|---|
| Large vessel (usually proximal large-vessel disease, often unilateral symptoms) | Compressive (e.g. cervical rib)<br>Neurogenic (thoracic outlet obstruction)<br>Inflammatory vascular disease (e.g. thromboangiitis, obliterans [Buerger's disease] or large-vessel vasculitis)<br>Atherosclerosis | Careful clinical examination of the peripheral pulses<br>Large-vessel imaging (e.g. angiography) |
| Occupational | Hand–arm–vibration syndrome (vibration white finger) | Obtaining a detailed occupational history (e.g. use of vibratory tools) |
| Autoimmune rheumatic diseases | Systemic sclerosis<br>Systemic lupus erythematosus<br>Sjogren's syndrome<br>Mixed connective<br>tissue disease/overlap syndromes<br>Undifferentiated connective<br>tissue disease<br>Idiopathic inflammatory myopathies<br>Vasculitis | History and careful physical examination<br>Targeted investigations as indicated by clinical assessment (e.g. autoantibodies and nailfold capillaroscopy) |
| Drug/chemical-related | Amphetamines<br>Beta-blockers<br>Bleomycin<br>Cisplatin<br>Clonidine<br>Cyclosporine<br>Interferons<br>Methysergide<br>Polyvinyl chloride | Eliciting a relevant drug/medication history including exploring chemical exposures |
| Vaso-occlusive disease | Cold agglutinin disease<br>Cryoglobulinaemia<br>Cryofibrinogenaemia<br>Paraproteinaemia<br>Malignancy (including as a paraneoplastic phenomenon) | Clinical assessment and targeted investigations as appropriate toward any suspected cause of vaso-occlusive disease (e.g. detection of of cryoglobulins or cryofibrinogen) |
| Other causes and associations | Carpal tunnel syndrome<br>Frostbite<br>Hypothyroidism<br>POEMS syndrome<br>Fibromyalgia syndrome | Clinical assessment and investigation to identify other causes and associations (e.g. nerve conduction studies for carpal tunnel syndrome) |

hyperaemia appears to be less common in SSc [34, 35]. A recent study reported uniphasic digital colour changes (blanching in 91%, cyanosis in 9%) in over half of patients with SSc, which could significantly influence disease classification in early disease if rigorously applied (and may account for the reported 4% of SSc patients without Raynaud's symptoms) [36]. Recent reports suggests bi- or triphasic digital colour changes of RP are actually more common in SSc, reassuring for classification purposes, but confirming significant heterogeneity and possible geographic variation in RP symptomatology amongst SSc patients [37]. Specific self-reported digital colour changes are not associated with distinct clinical phenotypes [37]. Cold-induced digital colour changes focus on the reversible vasospastic aspects of RP. More persistent digital vascular compromise secondary to the irreversible and often progressive obliterative microangiopathy also contributes to digital vascular symptoms in SSc.

## Symptoms of digital ischaemia

Tissue ischaemia associated with digital vascular compromise leads to pain, numbness, feeling cold and impaired function irrespective of cause and it is these clinical features that typically prompt patients to seek medical assistance [38]. Recent work exploring the patient experience of SSc-RP suggests physical symptoms of RP are more persistent in nature for many patients and not restricted to Raynaud 'attacks', challenging the episodic paradigm of RP [37–39]. More persistent symptoms of digital vascular compromise in SSc appear to be associated with longer disease duration and may reflect progression of the underlying obliterative microangiopathy [37]. Pain appears to be a more important physical symptom in SSc (perhaps due to more pronounced tissue ischaemia) than in primary RP, in which numbness/tingling feature more prominently as subjective symptoms of RP [5, 36, 40]. RP can result

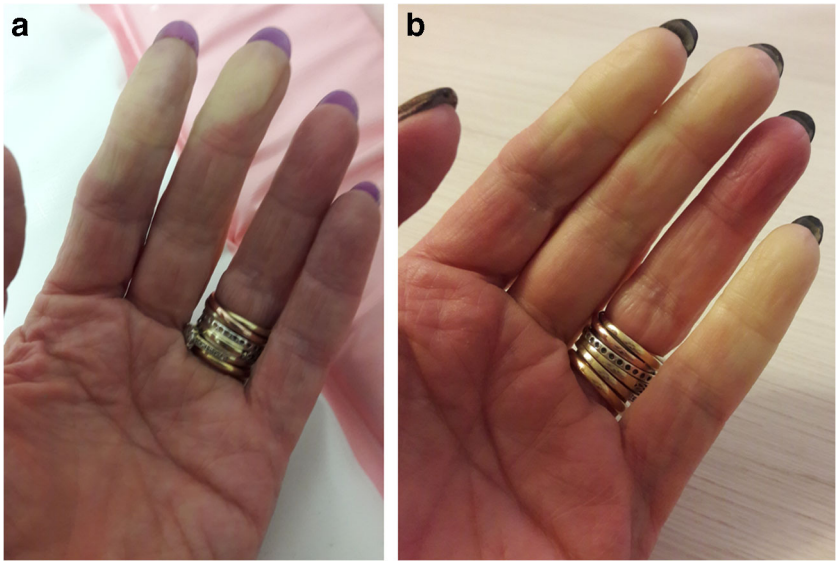


**Fig. 1** Digital colour changes associated with Raynaud's phenomenon. There is blanching (pallor of the fingers) with sparing of the thumb in keeping with primary Raynaud's phenomenon. The attacks may be associated with pain, numbness and negatively impact on hand function

in significant emotional distress, social isolation and body image dissatisfaction in SSc [38, 40]. The overall burden of RP symptoms is influenced by the effectiveness of efforts made to avoid or ameliorate RP symptoms when they occur [38, 41]. This may contribute to discordance between patient-reported evaluation of RP activity and objective assessment of digital cutaneous perfusion in SSc [42, 43]. Adaptation and habituation may lessen the burden of RP symptoms despite progression of the digital vasculopathy. Indeed, the effectiveness of coping strategies appears to be an important determinant of RP severity [44], although there remains a limited capacity amongst patients to predict or control RP symptoms [45].

### Aggravating factors

Cold exposure is an important aggravating factor in all forms of RP, whereas emotional distress appears to be a more important trigger in primary compared with secondary Raynaud's [40, 45–47]. The importance of cold exposure is reflected in seasonal variation in RP burden, although (unlike the majority of primary RP) people with SSc experience symptoms throughout the year [44, 46, 48]. The relationship between cold exposure and RP burden is, however, complex. For example, clinical trial data suggests a similar burden of SSc-RP symptoms over winter in patients enrolled to trials in India and North America, despite differences in average daily temperatures of > 20 °C between the 2 regions [49].

### Body parts affected by Raynaud's

The fingers are virtually always affected, although other body parts can be affected including the toes, ears, nose and areolar tissue. Recent work examining body areas affected by SSc-RP identified finger involvement in 98% of patients with the thumbs (62%), toes (67%), nose (28%), ears (19%) and nipples (0%) being less often affected by SSc-RP [37]. Relative sparing of the thumb occurs in both primary and secondary RP, but is more pronounced in primary RP [50].

### Impact of RP on health-related quality of life

RP is a major cause of disease-related morbidity in SSc [40] and was ranked highest disease-specific manifestation of SSc for frequency and impact of symptoms in a large survey of SSc patient experiences [51]. Other surveys of patient priorities in SSc have highlighted the major impact that RP has on health-related quality of life and negative perception of illness severity, although such findings, in part, reflect the much higher prevalence of RP over less common severe manifestations such as progressive ILD or PAH in this heterogenous disease [52]. Association between RP severity and both hand function [53] and the presence of digital ulceration [54] has been reported in SSc.

## Aetiopathogenesis of RP

As previously discussed, the term RP describes a symptom complex rather than a disease entity. Any attempt to describe the aetiopathogenesis of RP must therefore focus on individual causes, in the same manner that would need to be applied to describing the pathogenesis of other medical symptoms, e.g. 'breathing problems'. A detailed appraisal of RP pathogenesis is beyond the scope of this review. Much of the research into RP pathogenesis has focussed on the endothelial damage, impaired endothelial dilatation, obliterative microangiopathy and intravascular factors (such as impaired

fibrinolysis, cryofibrinogenaemia and excessive platelet activation) each contributing to digital vascular compromise in SSc [55]. These may be less relevant contributory pathologenic factors for RP symptoms in hypothyroidism (possibly exaggerated thermoregulatory response), cytotoxic therapy–induced Raynaud's symptoms (local vascular injury) or thoracic outlet obstruction (proximal compressive vascular and neural factors impairing distal perfusion). This could have important implications for classification and management. For example, the correlation between BMI and digital perfusion in primary RP suggests treatment may be best focussed on core temperature control [56]. Similarly, the association between primary RP and cardiovascular disease may indicate an important need to address conventional cardiovascular risk factors with treatments such as statins and anti-platelet therapy in patients labelled as primary RP in whom atherosclerotic disease is identified. The identification of an association between RP symptoms and a polymorphism in the NOS1 provides an intriguing explanation for vasospastic tendency and supports the presence of a functional vasospastic disorder at the heart of some cases of primary Raynaud's symptoms [57]. Future genetic association studies may be further served by carefully phenotyping patient cohorts of primary RP according to possible aetiopathogenic/aggravating factors.

## Classification of RP

A number of approaches have been proposed for classification and diagnosis of RP (Table 2). Each relies on self-report, sometimes incorporating colour charts, and each focusses on an episodic paradigm of RP requiring cold sensitivity and vasospastic episodes manifest as digital colour changes (mono- or biphasic). This approach can be useful in patient-organisation-led initiatives designed to raise awareness about RP and encourage people to seek medical advice where 'red flags' exist [37, 59]. Our existing approach to classifying Raynaud's amalgamates all disease entities associated with digital vascular compromise under the umbrella term 'secondary' RP with the remaining patients being labelled primary disease. Proposed classification criteria for primary RP are primarily designed to exclude recognised important secondary causes of RP such as SSc (Table 2). As outlined above, it is possible that what is currently termed primary RP actually constitutes a number of clinical entities including physiologically healthy thermoregulatory response to threatened core temperature, subclinical atherosclerotic disease and cold intolerance. Future work should examine the suitability of existing classification definitions across a broader range of disorders known to be associated with RP and there may be a need to re-appraise the existing taxonomy around primary RP to determine whether a primary functional vasospastic disorder ('true primary RP') exists alongside other clinical entities also capable of precipitating symptoms of digital vascular compromise (Fig. 2). This could have important implications for future clinical trials of 'primary RP' and the investigation and management of Raynaud's generally.

## Assessment of Raynaud's symptoms

The principal objectives for the assessing clinician are to recognise the symptom complex of RP and then establish potential reasons *why*. The assessment of RP symptoms requires a combination of careful history and examination, laboratory investigations and imaging studies. These mutually exclusive but complementary assessment tools are of equal importance in the broader assessment of RP symptoms.

### History and examination

A thorough history and physical examination is necessary, enquiring about the nature and character of digital vascular symptoms. This should include establishing a history of cold intolerance, the nature of digital discolouration and other symptoms. Secondary RP should be considered in people developing symptoms over the age of 30 years, RP in males and for unilateral symptoms (particularly with asymmetrical pulses). Primary Raynaud's typically develops between 15 and 25 years. There may be other relevant clues from the history (e.g. occupational exposure to vibrating tool use, recent weight loss, changes to drug therapy). Systems enquiry should seek features consistent with ARD such as puffy fingers, involvement of the thumbs, gastro-oesophageal reflux, inflammatory arthralgia, mucocutaneous manifestations and digital ischaemic lesions (seldom a feature of primary RP). A family history can be relevant (even for primary disease where familial clustering has been noted) [60]. RP is also more prevalent in the families of people with SSc [61].

A thorough physical examination should be performed with a particular focus on the hands (sclerodactyly, telangiectasia, calcinosis, macroscopic nailfold capillary abnormalities and digital ischaemic lesions such as pitting scars/ulcers). These clinical features may not be present in early SSc and it is hoped the concept of 'Very Early Diagnosis of SSc' (VEDOSS; based on the presence of RP, puffy fingers, anti–nuclear antibody [ANA] and is confirmed by the presence of nailfold capillaroscopic abnormalities and/or SSc-associated autoantibodies) will reduce diagnostic delay in SSc and help investigators better understand natural history and aetiopathoigenesis of RP within the ARDs [18–20].

Peripheral pulses should be assessed for evidence of proximal (large) vessel disease and provocation tests performed if

**Table 2** Classification and diagnostic approaches for Raynaud's phenomenon. Adapted from Maverakis et al. [4]

| Classification | Classification criteria |
|---|---|
| Classification criteria based on clinician's assessment (Brennan et al.) [7] | Negative:<br>Absence of episodes of colour change (pallor, cyanosis, erythema), or symptoms (parasthesia, numbness) on exposure to cold<br>Possible:<br>Episodes of uniphasic change (one of pallor, cyanosis, erythema), and/or paraesthesia or numbness<br>Definite:<br>Repetitive episodes of biphasic colour (at least two of pallor, cyanosis, erythema), in either cold or normal environments<br>Severe:<br>Repetitive episodes of biphasic colour (at least two of pallor, cyanosis, erythema), in addition to paraesthesia or numbness, occurring in both cold and normal environments. |
| Based upon screening questions (Wigley) [58] | 1. Are your fingers unusually sensitive to cold?<br>2. Do your fingers change colour when they are exposed to cold temperatures?<br>3. Do they turn white, blue or both?<br>The diagnosis of Raynaud's phenomenon is confirmed by a positive response to all three questions.<br>If positive for diagnosis of Raynaud's phenomenon, further criteria for the distinction of Primary versus Secondary RP are then evaluated for. |
| Criteria for the diagnosis of primary Raynaud's phenomenon (LeRoy and Medsger) [6] | - Vasospastic attacks precipitated by cold or emotional stress<br>- Symmetrical attacks involving both hands<br>- Absence of issue necrosis or gangrene<br>- No history or physical findings suggestive of a secondary cause<br>- Normal nailfold capillaries<br>- Normal erythrocyte sedimentation rate<br>- Negative serologic findings, particularly negative test for anti-nuclear antibodies |
| Classification scheme based on colour charts and questionnaire (Maricq and Weinrich) [34] | Questionnaire:<br>Are your fingers sensitive to cold?<br>Do your fingers show unusual colour changes, and if 'Yes,' do they become white, blue, red or purple?<br>Negative:<br>No blanching by hand photograph or colour scale<br>Possible:<br>Blanching by hand photograph and/or colour scale but insufficient for definite<br>Definite:<br>At least three of the following:<br>Blanching by hand photograph<br>Blanching by colour scale<br>Yes to question (a)<br>Yes to question (b) |
| Three-step approach to diagnosis of RP (Maverakis et al.) [4] | Step 1: Ask screening question<br>Are your fingers unusually sensitive to the cold?<br>Yes, proceed to step 2<br>Step 2: Assess colour changes<br>Occurrence of biphasic colour changes during the vasospastic episodes (white and blue)<br>Yes, proceed to step 3<br>Step 3: Calculate disease score<br>(a) Episodes are triggered by things other than cold (i.e. emotional stressors)<br>(b) Episodes involve both hands, even if the involvement is asynchronous and/or asymmetric<br>(c) Episodes are associated by numbness and/or parasthesias<br>(d) Observed colour changes are often characterised by a well-demarcated border between affected and un-affected skin<br>(e) Patient provided photograph(s) strongly support a diagnosis of RP<br>(f) Episodes sometimes occur at other body sites (e.g. nose, ears, feet and areolas)<br>(g) Occurrence of triphasic colour changes during the vasospastic episodes (white, blue and red)<br>If 3 or more criteria met from step 3 (a–g), then the patient has RP |

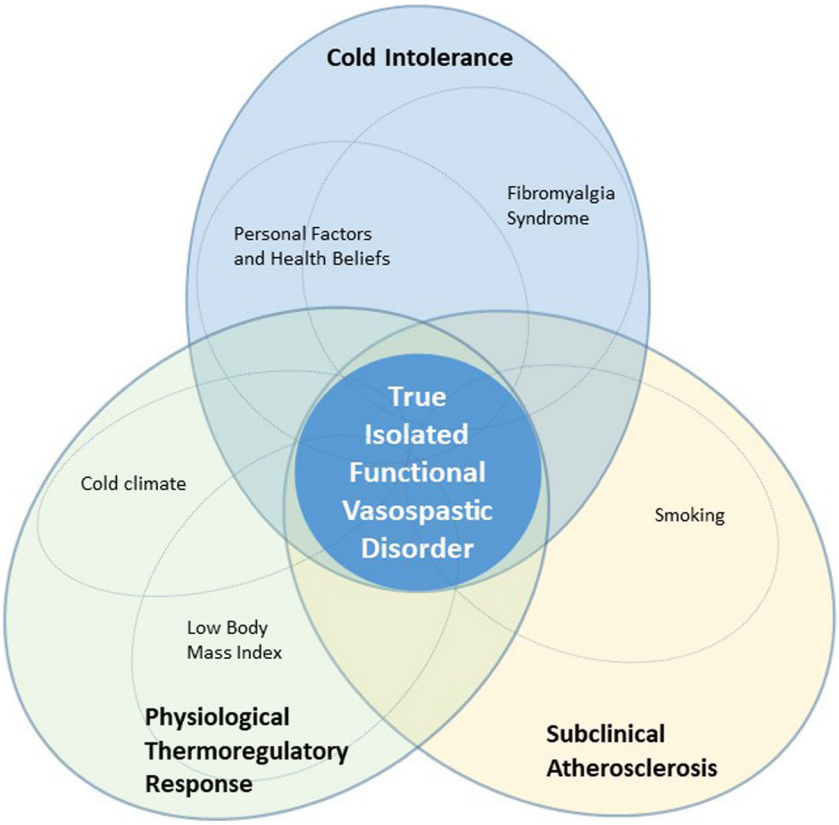


**Fig. 2** The potential complexity of primary Raynaud's phenomenon and factors that may be considered in future re-classification. A primary isolated functional vasospastic disorder exists at the heart of primary Raynaud's phenomenon and may be the sole source of digital vascular compromise. A number of additional factors may be the sole cause or exacerbate symptoms of digital vasculopathy. For example, 'cold intolerance' may result in Raynaud's symptoms in fibromyalgia syndrome in the absence of an isolated functional vascular disorder. A person with low BMI moving to a cold climate may experience Raynaud's symptoms without having an underlying functional vasospastic disorder. In those with a true functional vasospastic disorder, any one of the additional factors may exacerbate the severity and impact of Raynaud's symptoms

thoracic outlet obstruction suspected. There can be asymmetry in the digital vasculopathy of SSc but radial pulses should be of normal volume and character.

## Laboratory investigations

The investigations should be tailored to the clinical findings. The basic repertoire of laboratory investigations should comprise a full blood count, inflammatory markers, thyroid function and ANA testing by indirect immunofluorescence (supplemented by ELISA or solid-phase immunoassays to establish antigen specificities where possible). ANA immunofluorescence (with a description of pattern) should always be performed in the assessment of RP. A negative ANA with cytoplasmic stain may indicate the presence of anti-synthetase antibodies such as anti-Jo-1 or rarer SSc-specific autoantibodies such as anti-EIF2B [62]. If clinical features warrant, laboratory testing of creatinine kinase, complements (SLE and cryoglobulinaemia), immunoglobulins with protein electrophoresis and fasting lipid profile (in patients at risk of atherosclerosis) may be considered [63].

## Imaging

Nailfold capillaroscopy (NC) is a useful investigation for excluding SSc (Fig. 3). Characteristic SSc-type capillaroscopic abnormalities are typically evident in SSc-spectrum disorders at diagnosis (and other CTDs such as dermatomyositis) [64]. Definitions to describe abnormal capillary morphology in SSc have been developed and tested [65]. The characteristic NC changes of SSc include the presence of giant capillaries and microhaemorrhages (often categorised as 'early' changes in the early stages of SSc). The presence of avascular areas (with capillary drop out) and aberrant neoangiogenesis ('bizarre' or 'bushy' capillaries) are more frequently found in established disease (and categorised as 'late' NC changes) [66]. More subtle NC changes can be found in SLE [67], pSS [68] and primary RP [69]. Scleroderma-like nailfold capillary abnormalities occur in ~35% of anti-synthetase syndrome patients, but only half experience RP symptoms [70]. Nailfold capillaroscopy can be performed using low- and high-magnification (× 200) wide-field microscopy or

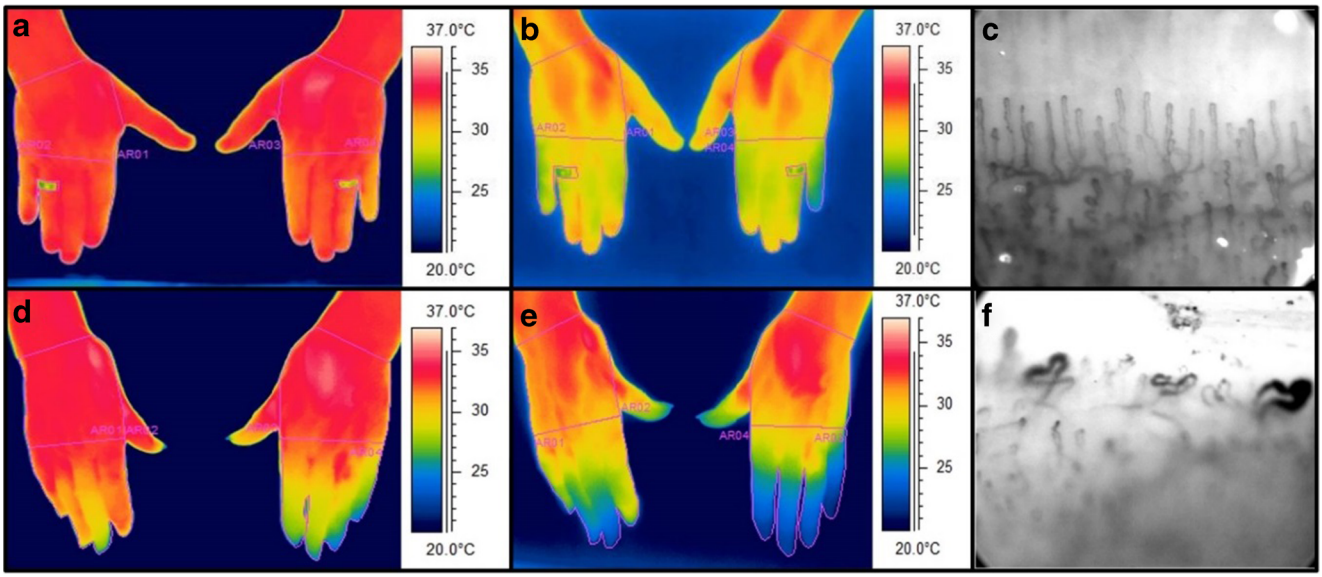


**Fig. 3** Non-invasive imaging illustrates important functional and morphological vascular differences between clinically indistinguishable primary and secondary 'Raynaud's phenomenon'. **a**–**c** Primary Raynaud's phenomenon. **a** Baseline thermograph revealing normal resting digital perfusion. **b** Thermograph 10 min following local cold challenge demonstrating delayed re-perfusion following local cold challenge. **c** Uniformly sized and spaced nailfold capillaries. **d**–**f** Early systemic sclerosis. **d** Baseline thermograph highlighting reduced perfusion of the fingertips under ambient conditions. **e** Pronounced delayed re-perfusion following local cold challenge. **f** Significantly reduced capillary density on nailfold capillaroscopy with giant capillaries and aberrant neovascularisation

videocapillaroscopy. Low-magnification (× 10) assessment using a dermatoscope [71], ophthalmoscope or USB–microscope should facilitate adequate visualisation of nailfold capillaries to determine whether normal/abnormal but may miss more subtle capillary abnormalities in early SSc. Primary care providers can be trained to identify capillaroscopic abnormalities that may indicate the presence of underlying SSc. Formal angiography may be required to exclude compressive/obstructive macrovascular disease such as thrombangiitis obliterans (Buerger's disease) or thoracic outlet obstruction. Functional assessment of digital perfusion using non-invasive methods such as infrared thermography or laser-derived methods (often incorporating a provocation test such as local cold exposure, post-occlusive analysis or iontophoresis of vasoactive substances) are primarily used in the research setting but have been used to differentiate primary from secondary RP [15, 42, 72]. Finger systolic pressure measurements and plethysmography have been used to evaluate digital vasculopathy in RP but are not generally used in routine clinical practice.

## Assessment of RP severity and treatment response

The decision to initiate treatment and assessment of treatment response is typically based upon clinician-patient discussions around symptom severity and effectiveness of intervention. The recommended endpoint for RP clinical trials is the Raynaud's Condition Score (RCS) diary. The RCS diary allows quantification of the mean daily frequency, duration and severity/impact of RP symptoms over 1–2 weeks. Establishing treatment efficacy has been challenging and there have been negative clinical trials of promising vasodilator therapies in SSc-RP [73]. The RCS diary is not typically used in routine clinical practice and limitations of the RCS diary have been identified amongst SSc experts and patients [39, 41]. Symptom diaries, such as the RCS diary, based on the episodic paradigm of RP, may be ill-suited to capturing the persistent digital vascular compromise of SSc, possibly contributing to the poor agreement with objective assessment of digital perfusion [42, 43]. Intriguingly, clinical trials incorporating mixed populations of primary and secondary RP (a curious approach stemming from shared use of the eponym 'Raynaud's') have consistently identified better treatment responses within primary RP subgroups [74, 75]. This might reflect lack of responsiveness of the obliterative microangiopathy of SSc to vasoactive therapy but may also reflect the need for bespoke clinical trial endpoints within distinct patient populations such as SSc. Non-invasive microvascular imaging methods such as infrared thermography and laser-derived imaging may provide a valuable tool for assessing treatment efficacy in the future and have been used as an explorative endpoint within a number of previous RP clinical trials [76]. The reliability and validity of such methods is the focus of ongoing work [77].

## Management of RP

Management should be tailored to the underlying diagnosis and aetiopathogenic drivers. Occasionally, a reversible cause is identified and treatment initiated accordingly, e.g. cold agglutinin disease. Patients should be educated about their condition and sign-posted to patient organisations for advice and support.

### General approaches

Self-management advice on cold avoidance and keeping warm is important although there is little evidence to support behaviour change interventions for RP [78]. Patients should be supported in their efforts to stop smoking (which promotes vasoconstriction).

### Pharmacological management

Treatment with vasodilator therapies is generally considered when lifestyle adaptions are ineffective. In general, drug therapies are started at low dose and increased gradually depending on tolerability and efficacy. Specific reference should be made to potential vasoactive adverse effects such as hypotensive symptoms (often necessitating dose modification or treatment cessation) and vasoactive headache (often responsive to simple analgesic use and likely to resolve with repeat dosing). A detailed appraisal of the mode of action and clinical trial data to support individual classes of vasodilator drugs is beyond the scope of this review but is presented elsewhere. Calcium channel blockers (CCBs) are generally considered first-line drug treatment for the management of RP [79–81]. A recent Cochrane meta-analysis suggests treatment of RP with CCBs reduces the number of RP attacks by around one third, with higher doses likely to be more effective, and primary RP appears more responsive than SSc-RP [82]. An overview of the positioning of other classes of vasodilator therapy for SSc-RP adapted from recently published expert consensus and evidence-based guidelines is presented in Fig. 4 [63, 79, 81]. A description of commonly used drugs for RP and recommended dosing is described elsewhere [63]. These recommendations are often based on fairly modest reported treatment benefits in clinical trials, but this may reflect limitations in clinical trial design and outcome measures rather than the treatment effects themselves. For example, phosphodiesterase inhibitors command a prominent role in the recommended management of SSc-RP despite a meta-analysis of 6 trials reporting a pooled reduction in the daily frequency and duration of RP attacks of only 0.49 attacks/day and 14.6 min respectively [83]. Vasodilator drugs not routinely advocated for RP management include endothelin receptor antagonists and oral prostanoid therapies. A recent clinical trial of selexipag (an oral selective IP prostacyclin receptor agonist licenced for use in pulmonary arterial hypertension) did not identify any reduction in the number of RP attacks or other RCS diary parameters [84]. There are geographic differences in pharmacological management of RP, possibly owing to variation in clinical preference and local reimbursement policies [81, 82].

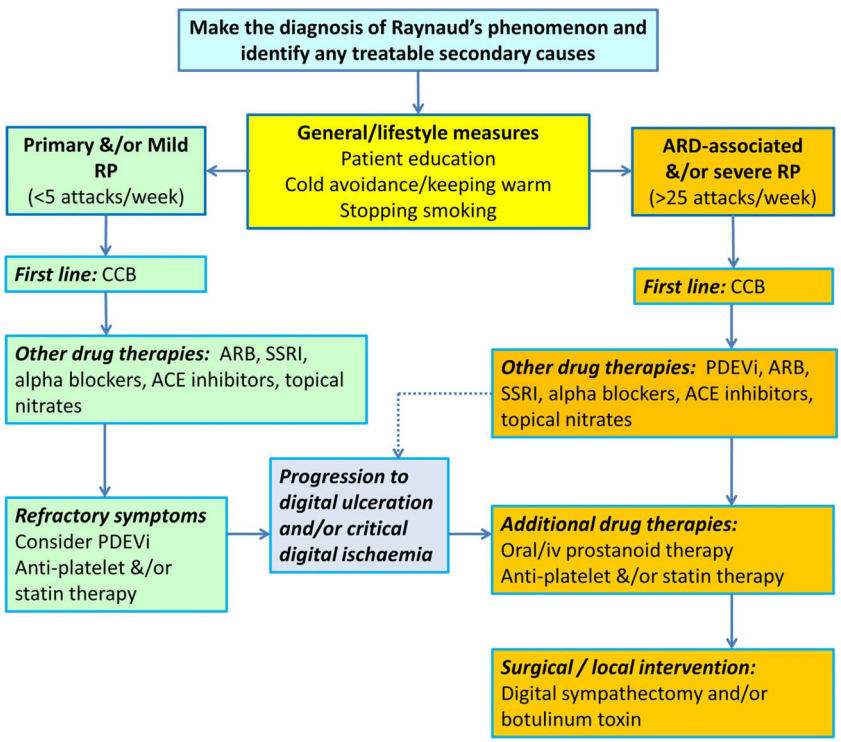


**Fig. 4** A practical approach to the management of Raynaud's phenomenon. Adapted from the consensus best practice pathways for the management of Raynaud's phenomenon devised by the UK Scleroderma Study Group and Scleroderma Clinical Trials Consortium/Canadian Scleroderma Research Group [63, 81]. These recommendations were devised with a focus on systemic sclerosis but can be used to inform the management of *all* patients with RP. Many clinicians will add new drug therapies in combination with existing agents after treatment failure. ACE angiotensin-converting enzyme, ARB angiotensin receptor blocker, CCB calcium channel blocker, IV intravenous, PDE-5 phosphodiesterase type 5, SSRI selective serotonin receptor inhibitor

The perceived benefit of vasodilator therapies amongst RP patients is limited with one survey reporting benefits from current vasodilator RP therapies in only ⅙ of respondents [45]. Clinicians may not be fully exploiting the range of pharmacological treatments available for the management of SSc-RP [85]. The perceived need for vasodilator therapy amongst physicians treating SSc appears to be at odds with the high burden and impact of RP symptoms reported by patients [51]. Drug intolerance can be a barrier to vasodilator medication usage with adverse effects ranging from vasoactive symptoms (such as headaches [often a transient symptom resolving with repeated dosing] and pre-syncope) to aggravation of gastro-oesophageal reflux symptoms in SSc.

### Surgery

Surgical intervention is only considered in refractory RP, usually in the context of digital ulceration or necrosis in SSc. Cervical sympathectomy is no longer performed due to lack of long-term efficacy and an unacceptable burden of side effects. There are favourable reports for digital (but not cervical) sympathectomy and botulinum toxin injection for RP [86–88].

## Conclusions

RP is a common symptom complex and, for the majority of people, it remains benign but intrusive vasospastic disorder. The existing definition and classification of RP may conceal a broader range of patient experiences and aetiopathogenic drivers than is currently appreciated. The evaluation of RP requires careful clinical and laboratory assessment. Lifestyle modification to maintain core temperature and promote peripheral vasodilation forms the cornerstone of self-management, irrespective of cause. Primary RP can often be managed without the need for vasodilator therapy. Secondary RP management should, where possible, target the cause of digital vasculopathy and vasodilator therapies are useful adjuncts to self-management approaches for important causes of RP such as SSc.

**Author contributions** JDP, MH and JEP conceived the idea for the manuscript, developed the search strategy and selection criteria. All authors contributed to the iterative drafting of the final manuscript.

### Compliance with ethical standards

**Conflict of interest** Dr Pauling has undertaken consultancy work and received speaker honoraria from Actelion pharmaceuticals. Dr Hughes has received speaker honoraria from Actelion pharmaceuticals. Dr Pope has undertaken consultancy work for AbbVie, Actelion, Baxter, Bayer, BMS, Lilly, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi and UCB.

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