Raynaud's Phenomenon and Ulcers

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Introduction

Raynaud's phenomenon (RP) is a common vasospastic condition which manifests as an episodic colour change of the extremities (fingers and toes) in response to cold exposure and/or emotional stress. Other vascular beds can also be affected by attacks of RP including the lips, nose, ears and nipples. The skin colour (physiological rationale in parentheses) progresses from pallor (deoxygenation) to blue (cyanosis) and finally red (reactive hyperaemia). An example of an attack of RP is presented in Fig. 6.1. The hyperaemic phase can be associated with significant pain and discomfort. Patients may report mono- or biphasic colour change during attacks of RP. Symptoms usually resolve promptly (often within minutes) after rewarming. Although many individuals report sensitivity to the cold, in RP there must be an associated colour change.

The majority of patients with RP will have primary (idiopathic) Raynaud's phenomenon (PRP) in which vasospastic episodes are completely reversible and therefore are not associated with irreversible ischaemic tissue damage (e.g. digital pitting and ulcers). However RP can also occur due to an underlying aetiology (secondary RP; SRP) as presented in Table 6.1. RP is common in patients with autoimmune connective tissue diseases (CTD) and is often the presenting feature in systemic sclerosis (SSc) and therefore provides a window of opportunity (not to be missed) for early diagnosis [1–3].

Irrespective of the underlying aetiology, RP can be associated with significant morbidity. In an international online survey which included 443 responses from subjects with self-reported RP (originating from 15 countries), the majority of subjects with both PRP and SRP reported making at least one life adjustment due to RP (87% and 71%, respectively) [4]. Furthermore, the current perceived quality of life (where 10 was the best imaginable) with RP was impaired in both PRP and SRP (6.5 and 5.2, respectively). In patients with SSc, RP is responsible for much of the pain and disability associated with the disease. In a Canadian national survey which included 464 individuals with SSc, RP was the second highest-ranked symptom (out of 59) in terms of frequency and moderate to severe impact on the activities of daily living [5].

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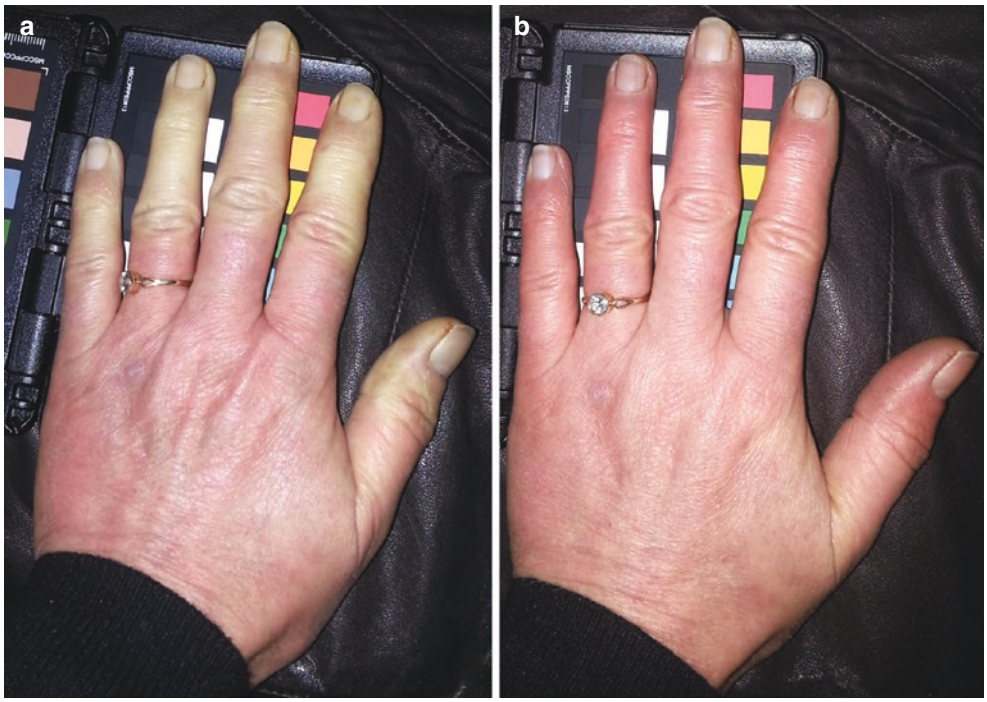

Fig. 6.1 Photographs of an attack of Raynaud's phenomenon taken by a patient with systemic sclerosis. (**a**) There is whiteness (pallor of the fingertips). (**b**) Normal colour has been restored to the fingers. The time between the two photographs was approximately 16 min. (Photographs provided courtesy of Dr. Graham Dinsdale, The University of Manchester)

Table 6.1 The classification of Raynaud's phenomenon [105]

Primary (idiopathic) RP	Secondary RP
Vascular (usually proximal large vessel disease, often unilateral symptoms)	Compressive (e.g. cervical rib) Obstructive: noninflammatory (i.e. atherosclerosis) Inflammatory vascular disease (e.g. thromboangiitis obliterans [Buerger's disease])
Hand-arm vibration syndrome (vibration white finger)	
Autoimmune conditions	Systemic sclerosis Systemic lupus erythematosus Sjogren's syndrome Mixed connective tissue disease/overlap syndromes Undifferentiated connective tissue disease Idiopathic inflammatory myopathies
Drug-/chemical-related	Amphetamines Beta-blockers Bleomycin Cisplatin Clonidine Cyclosporine Interferons Methysergide Polyvinyl chloride
Conditions associated with increased plasma viscosity and reduced digital perfusion	Cryoglobulinaemia Cryofibrinogenaemia Paraproteinaemia Malignancy (including as a paraneoplastic phenomenon)
Other causes and associations	Carpal tunnel syndrome Frostbite Hypothyroidism

Epidemiology

The reported prevalence of RP has varied in previous studies, and this likely reflects differences in study design and geographical variations. In general, most studies have reported the prevalence of RP to be 3–5% [6]. RP is three to four times more common in females compared to males [7]. Patients with PRP (in particular females) often have an early onset and a family history (up to 50%) of RP in a first-degree relative [8, 9]. Conversely, late-onset RP (over the age of 40 years) is more likely to be SRP, and therefore the clinician must maintain a high index of suspicion.

As previously highlighted, RP often occurs in patients with autoimmune CTDs compared to the general population. For example, RP occurs in the majority (approximately 80–90%) of patients with mixed CTD [10, 11] and almost half of patients with systemic lupus erythematous [12]. In particular, RP almost invariably occurs in patients with SSc during the course of their disease. In an analysis (which included 7655 patients with SSc) from the European Scleroderma Trials and Research (EUSTAR) group, almost all (96.5%) patients had RP, with no difference in patients with limited or diffuse cutaneous subsets of the disease [13]. In patients with limited cutaneous SSc (lcSSc), there is often a long history of preceding RP (often decades) [14], whereas in diffuse cutaneous SSc (dcSSc), RP usually develops in close temporal relation (within a year before or after) of the onset of skin sclerosis [14].

Differential Diagnosis

The differential diagnosis is wide, and therefore the clinician must maintain a high index of diagnostic suspicion and perform a comprehensive clinical assessment with a key role for targeted investigations as discussed later. The conditions which can mimic RP are presented in Table 6.2 including a description of those clinical features which can help to differentiate from RP.

Table 6.2 The differential diagnosis of Raynaud's phenomenon

Condition	Description
Acrocyanosis	Presents as persistent, painless, symmetrical cyanotic colour of the hands, feet and knees. Like RP, acrocyanosis can be aggravated by cold exposure; however, unlike RP there is no pallor. Similar to RP, acrocyanosis typically occurs in young (aged 20–30 years) females. The condition can occur in isolation or secondary to a number of causes (e.g. haematological and malignant diseases)
Chilblains (primary pernio)	These present as palpable (often painful) inflammatory red/purple lesions after exposure to cold. Like RP the hands and feet (as well as the ears and nose) are typically affected and typically occurs in young females
Chilblain lupus	Characterised by painful erythematosus/purple colour change of the extremities (and often nose and ears) after cold exposure. Sporadic and familial forms are recognised. Can be associated with other cutaneous or systemic lupus features
Complex regional pain syndrome	This can mimic RP when patients present with blue/purple change of the extremities and pain
Erythromelalgia	Characterised by erythematous colour change and pain upon exposure to warmth. Can occur secondary to a wide range of secondary causes including myeloproliferative diseases
Frostbite	Cold-induced injury causing marked vasospasm resulting in tissue ischaemia, which can progress to necrosis and gangrene
Livedo reticularis and racemosa	Livedo reticularis presents as an erythematous/violaceous netlike network after cold exposure and resolves completely with warming. Livedo racemosa is characterised by an asymmetrical pattern of violaceous broken circles and does not reverse with rewarming. Whereas livedo reticularis is a normal physiological finding, livedo racemosa occurs secondary to an underlying inflammatory (e.g. SLE) or vascular disease (e.g. haematological malignancies and, in particular, antiphospholipid syndrome)
Thoracic outlet syndrome	Can present with pain, paraesthesia and discolouration of the fingers but not the feet (unlike RP)

Adapted from McMahan and Paik [106]

Pathogenesis

An understanding of the pathogenesis of RP is helpful for the clinician to understand the therapeutic rationale for the management (in particular drug therapies) of RP. Although the pathogenesis of RP will be considered under four discrete headings, it is important to be aware that these distinctions are somewhat arbitrary and that there is a complex interplay between the underlying pathogenic mechanisms. A schematic representation of the mechanisms implicated in the pathogenesis of RP is provided in Fig. 6.2.

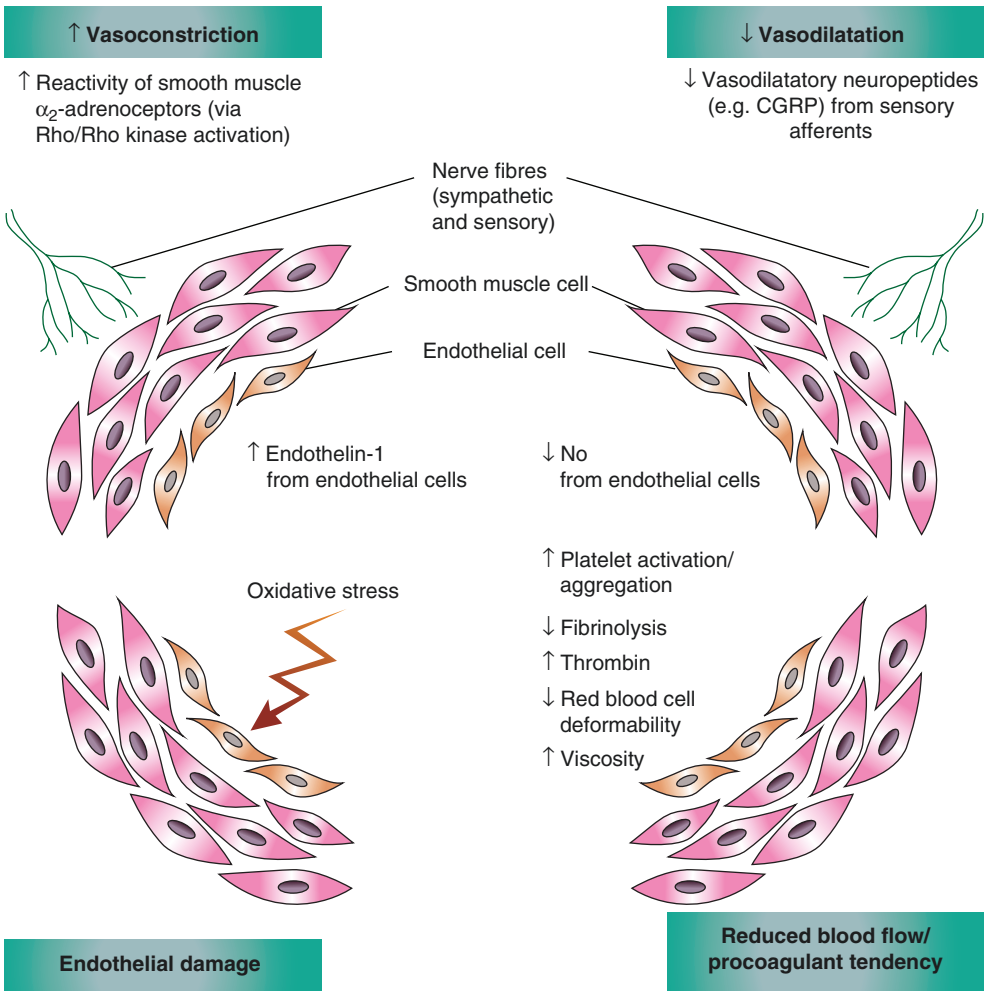

Fig. 6.2 The pathogenesis of Raynaud's phenomenon. CGRP calcitonin gene-related peptide, NO nitric oxide. (Reproduced from Herrick [24], with permission from Oxford University Press)

Vascular Abnormalities

Functional Vascular Abnormalities

In SSc, impaired endothelial-dependent and to a lesser extent endothelial-independent vasodilation have been reported in SSc [15–17]. Similar abnormalities have also been observed in patients with PRP [18]. Baseline finger blood flow in both PRP and SRP has been reported to be lower compared to healthy controls [19], with a greater sensitivity to cold exposure, in particular in SRP [20]. In patients with RP (unlike healthy controls), blood flow is reduced through both arteriovenous anastomoses and nutritional capillaries after cold exposure [19]. Furthermore, in patients with both PRP and SRP, there is marked constriction (vasospasm) of the digital arteries compared to healthy controls [21]. Vascular tone is the result of a complex interplay of vasoconstrictory and vasodilatory factors. For example, increased endothelin-1 and angiotensin II (both vasoconstrictors) have both been implicated in the pathogenesis of RP [22, 23], whereas, although the role of nitric oxide (a potent vasodilator) is complex and likely variable throughout the disease course in SSc, reduced nitric oxide from endothelial cells is likely to be a contributory mechanism in RP [24].

Structural Abnormalities

Abnormalities in both the microcirculation and the digital arteries have been well described in patients with RP. In SSc, the progressive microangiopathy that characterises the disease results in typical changes that include enlargement of capillaries with areas of avascularity that can easily be appreciated by capillaroscopy (Fig. 6.3). The nailfold capillaries are normal in patients with PRP, although slightly increased capillary dimensions compared to healthy controls have been reported [25]. Arterial disease is also well recognised in SSc, including abnormalities of the digital and ulnar arteries [26–29], the latter of which has been associated with digital ulcer (DU) disease [30, 31]. Furthermore, an increased risk of cardiovascular disease has been reported in patients with SSc [32, 33], although this remains a controversial topic requiring further research. Endothelial cell dysfunction and death [34, 35], including the presence of anti-endothelial antibodies [36, 37], have been postulated to be an early (and perhaps even initiating) mechanism in the aetiopathogenesis of SSc. In SSc, it is likely that episodes of ischaemia-reperfusion (with reduced nutritional blood flow during attacks of RP as previously described) result in local hypoxia which results in activation of inflammatory and fibrotic mechanisms.

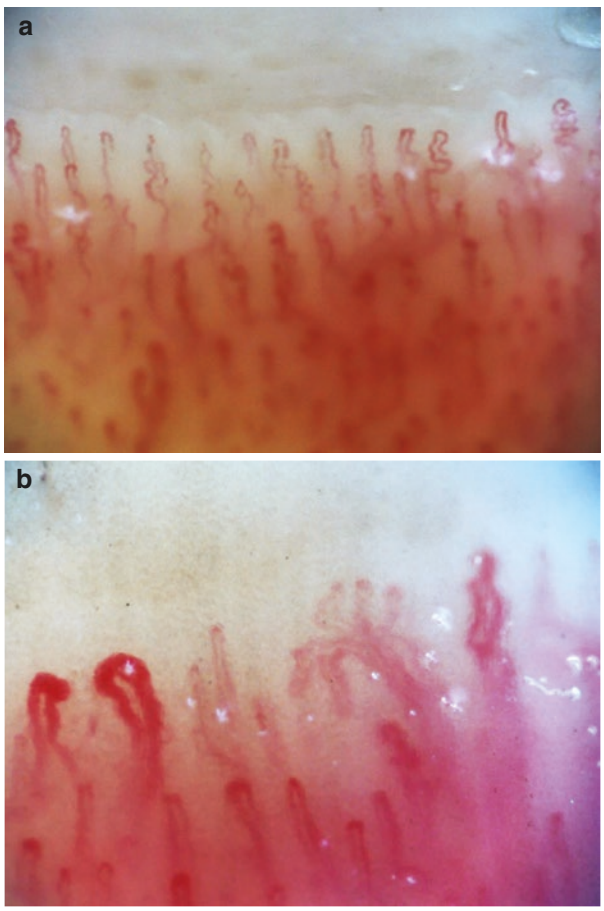

Fig. 6.3 Nailfold capillaroscopy. (**a**) Normal capillaroscopy images acquired by videocapillaroscopy. The capillaries are homogenous ('hairpin' like) in appearance, and this is reassuring in patients presenting with RP. (**b**) Abnormal nailfold capillaroscopy in a patient with SSc with capillary enlargement and areas of avascularity

Neural Abnormalities

Neural abnormalities may result in both increased vasoconstriction and reduced vasodilation in RP. In patients with PRP, and in particular SSc, reduced calcitonin gene-related peptide (which is vasodilatory) has been reported [38]. In RP, increased cold sensitivity is mediated through increased activity of smooth muscle alpha-2 adrenergic receptors [39, 40]. In particular, the alpha-2c receptor has been highly implicated in the mechanism of cold sensitivity, resulting in movement to the cell surface from the Golgi compartment [39, 40]. Vasoconstriction has been reported with increased activity of protein tyrosine kinase and tyrosine phosphorylation in both PRP- and SSc-related RP [41, 42]. Although many patients report attacks of RP resulting from stress, the role of the central nervous system in the pathogenesis of RP is little studied, and this is an area which requires future research.

Intravascular Abnormalities

Intravascular abnormalities can be both directly causative and contributory (e.g. in SSc) in the pathogenesis of RP. For example, in some conditions (Table 6.1), RP is likely directly driven by hyperviscosity and/or reduced digital microvascular perfusion (e.g. malignancy including through the presence of an associated cryoglobulin and/or paraprotein). In particular in SSc, increased platelet activation has been implicated in the pathogenesis of RP [43, 44]. Activated platelets produce a number of important molecules (e.g. vascular endothelial growth factor and transforming growth factor-β) [24], which can have a diverse range of effects on the vasculature as well as inflammatory and fibrotic pathways. The other intravascular abnormalities that have been described in the pathogenesis of RP are depicted in Fig. 6.2.

Other Factors

The importance of both genetic and hormonal factors has already been described in the epidemiology of RP. These likely have a range of important roles in the aetiopathogenesis of RP, including possibly through increased responsiveness of the alpha-2C adrenergic receptor [45].

Raynaud's Phenomenon and Digital Ulcers

Although there is a theoretical rationale to suspect that the severity of RP is associated with worse DU disease in SSc, at present there is little evidence to support such an association. Nonetheless it seems likely that increased severity of RP attacks, including marked vasospastic disease of the digital artery, results in poor flow within the microcirculation, promoting digital ischaemia that can progress to tissue ulceration. In a multicentre study, patients with SSc living in the subtropical compared to tropical (warmer) climate were (5.4 times) more likely to develop DUs and had worse RP [46]. A key difference is that irreversible ischaemic tissue damage (e.g. DUs) is only observed in SRP and never PRP.

History and Examination

When assessing patients with RP, it is useful for the clinician to be aware of the classification criteria proposed by LeRoy and Medsger [47], which incorporate both clinical features and investigations and which have recently been revisited by Maverakis et al. [48].

It is useful for the clinician to consider the following two questions when assessing the patient presenting with RP:

Proposed Criteria for Primary Raynaud's Phenomenon [47]
Episodic attacks of acral pallor or cyanosis.
Peripheral pulses should be strong and symmetrical.
No evidence of digital pitting, ulceration or gangrene.
Normal nailfold capillaries.
Negative antinuclear antibody.
Normal erythrocyte sedimentation rate.

1. What is the aetiology of RP? In particular, could she/he have an autoimmune CTD?
2. What is the severity of RP? As this will dictate the need (and intensity) of treatment. For example, in patients with mild RP, symptoms may be sufficiently controlled with conservative measures alone, whereas in patients with more severe RP, drug therapies are often indicated, in particular, in the presence of digital ischaemic complications.

A full medical history should be elicited including those clinical features that could suggest the presence of an autoimmune CTD (e.g. aphthous mouth ulcers and UV photosensitivity). The impact of RP on the activities of daily living should be elicited including a history of DUs. A full systems enquiry and a drug history should be elicited with an awareness of the secondary causes of RP (Table 6.1). The patients occupational history should be explored as this may be contributory (e.g. vibratory tool use) and various occupational

exposures (e.g. exposure to epoxy resins and vinyl chloride) have been associated with the development of SSc-like disorders. In addition, any potentially relevant family history should be documented, specifically of autoimmune CTDs.

A full physical examination must be completed in all patients with RP, in particular, focussing on the fingers and toes looking for signs of digital ischaemia (pitting scars and ulcers), skin sclerosis (sclerodactyly) and any visible nailfold changes. The peripheral pulses must be palpated, abnormalities of which indicate proximal (large) vessel disease. The clinician should carefully examine for associated signs which could indicate the presence of an autoimmune CTD (e.g. bibasal inspiratory crepitations that could indicate the presence of interstitial lung disease).

Investigations

The main purpose of investigating the patient presenting with Raynaud's phenomenon (RP) is to establish whether or not there is an underlying cause, i.e. to differentiate between primary (idiopathic) RP and RP secondary to an underlying disease/disorder, because this has major implications for management. Most patients with PRP may be reassured and discharged from follow-up, whereas if a diagnosis is made of, for example, a SSc-spectrum disorder, then the patient will require further investigation and long-term follow-up.

Investigations generally performed in the patient with RP are summarised below. In the patient with PRP, the full blood count, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) and nailfold capillaroscopy will all be normal/negative (see Chap. 7). In the context of a patient in whom PRP is strongly suspected (onset of RP in the late teens or in the twenties in a patient who is otherwise well and with no abnormalities on examination), then no other investigations are required. Many clinicians, however, will in addition request a biochemical profile with thyroid function and a thoracic inlet radiograph to look for a bony cervical rib. Other investigations will depend on the clinical context. For example, if a diagnosis of a connective tissue disease is suspected, then other immunological investigations will be indicated, for example, SSc-specific autoantibodies.

Investigations Commonly Performed in the Patient Presenting with Raynaud's Phenomenon

Basic set (for all patients)
- Full blood count
- Erythrocyte sedimentation rate (ESR)
- Antinuclear antibody (ANA)
- Nailfold capillaroscopy

Other commonly requested investigations
- Biochemical profile
- Thyroid function tests
- Thoracic outlet radiograph (to look for a bony cervical rib)
- (Thermography – available in certain specialist centres)

Other investigations will depend on the clinical context and may include:
- SSc-specific autoantibodies
- Complement levels
- Cryoglobulin and cryofibrinogen
- Immunoglobulins with protein electrophoresis
- Lupus anticoagulant, anticardiolipin antibodies and anti-β2 glycoprotein 1 antibodies
- Arterial Dopplers (if any suggestion that there may be a large [proximal] vessel component)

Nailfold capillaroscopy is discussed in Chap. 7. Normal nailfold capillaries (Fig. 6.3) are reassuring in patients with RP. Many rheumatologists will not have access to high-magnification videocapillaroscopy (the 'gold standard') or to a stereomicroscope: in this instance, an ophthalmoscope [49], dermatoscope [50–54] or USB microscope may be used (the dermatoscope or USB microscope is preferable to the ophthalmoscope because of their wider field of view). The dermatoscope is very portable being a hand-held device. A recent study suggested that dermoscopy compared favourably to videocapillaroscopy [54], although videocapillaroscopy images were more likely to be classifiable (and were graded more severely) than dermoscopy images.

Thermography (Fig. 6.4), which measures surface temperature, can help to differentiate between PRP- and SSc-related RP. Most thermography protocols incorporate a temperature challenge, usually a cold challenge [55–57]. We have found that the persistence of a temperature gradient of ≥1 °C along one or more fingers at a room temperature of 30 °C (Fig. 6.4) is a useful discriminator between PRP- and SSc-related RP [58, 59]. Thermography, however, requires specialist equipment and therefore at present is only available in certain specialist centres.

Although there are a number of other techniques that help to differentiate between PRP and SRP, at present these are primarily research tools [60]. These include laser Doppler imaging (using a laser-based system to measure blood flow over a defined area) and finger systolic pressure measurement [60].

Investigation for large (proximal) vessel disease If there is any question of large (proximal) vessel disease, for example, asymmetry of RP symptoms, or difficulty in detecting the peripheral pulses, then arterial Doppler ultrasound should be performed [61]. If large vessel disease is suspected, then large vessel imaging (discussed in Chap. 16) will be required.

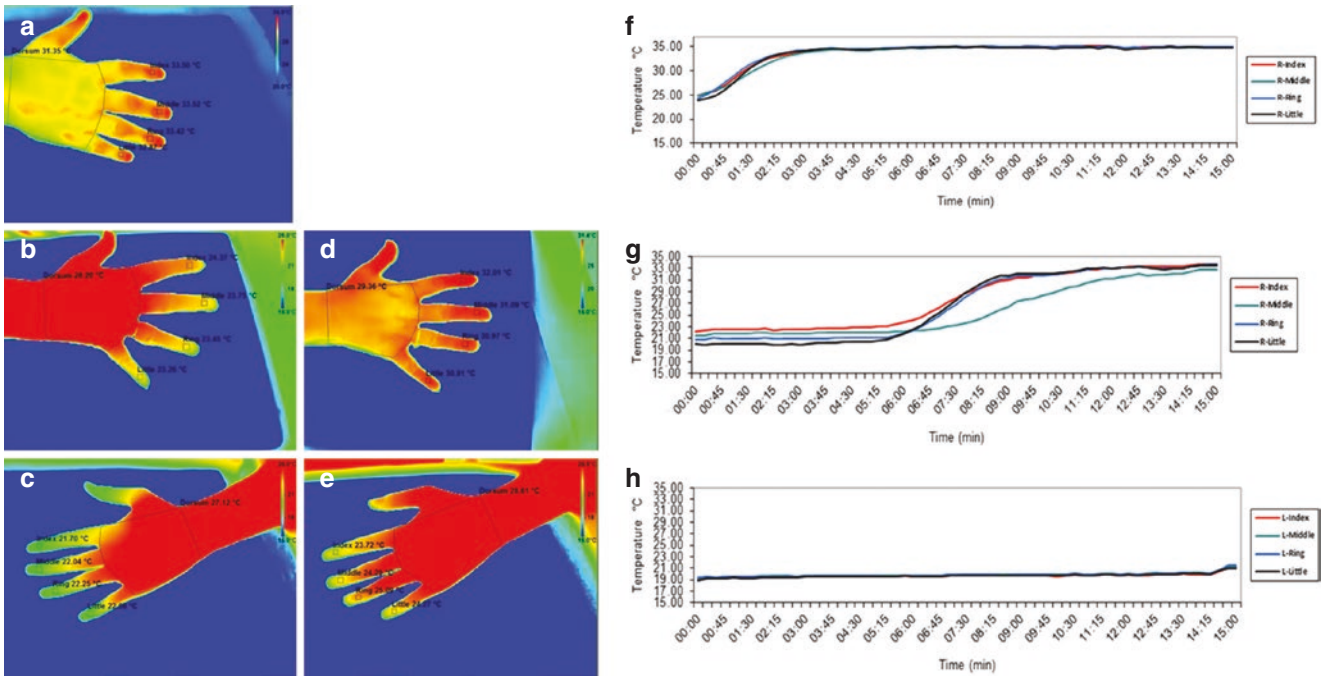

Fig. 6.4 Thermographic imaging of the hands during a dynamic temperature challenge. Left column, thermal images at 23 °C; middle column, thermal images at 30 °C; right column, rewarming curves after cold challenge. At 23 °C, the fingertips are cooler than the dorsum of the hand in patients with both primary RP (PRP) and secondary RP (SRP) (**b** and **c**), whereas, in healthy controls, the fingertips are warm (**a**). At 30 °C, unlike in PRP (**d**), there are persistent temperature gradients (fingers cooler than the dorsum of the hand) in SRP (**e**). Rewarming curves demonstrate prompt rewarming in a healthy control subject (top, **f**), whereas there is complete but delayed rewarming in a patient with PRP (middle, **g**) and no rewarming at all in a patient with SSc (bottom, **h**)

Management

The management of RP depends on its severity and on whether or not there is an underlying cause amenable to specific intervention. For example, the treatment of mild PRP, which does not progress to digital ulceration or to critical ischaemia, is very different from that of a patient with severe SSc-related RP and digital ulceration. The UK Systemic Sclerosis Study group has recently produced a 'consensus best practice pathway' for management of SSc-related digital vasculopathy [62]. This pathway includes three algorithms for management of (1) RP (relevant to RP not only due to SSc but also to other causes), (2) digital ulceration in patients with SSc and (3) critical digital ischaemia in patients with SSc. Although these algorithms are all reproduced here (Figs. 6.5, 6.6, and 6.7) because they put the management of 'mild' and 'severe' RP into context, only treatment of 'uncomplicated' RP will be considered here. By 'uncomplicated' we mean RP which has not progressed to digital ulceration and/or critical ischaemia.

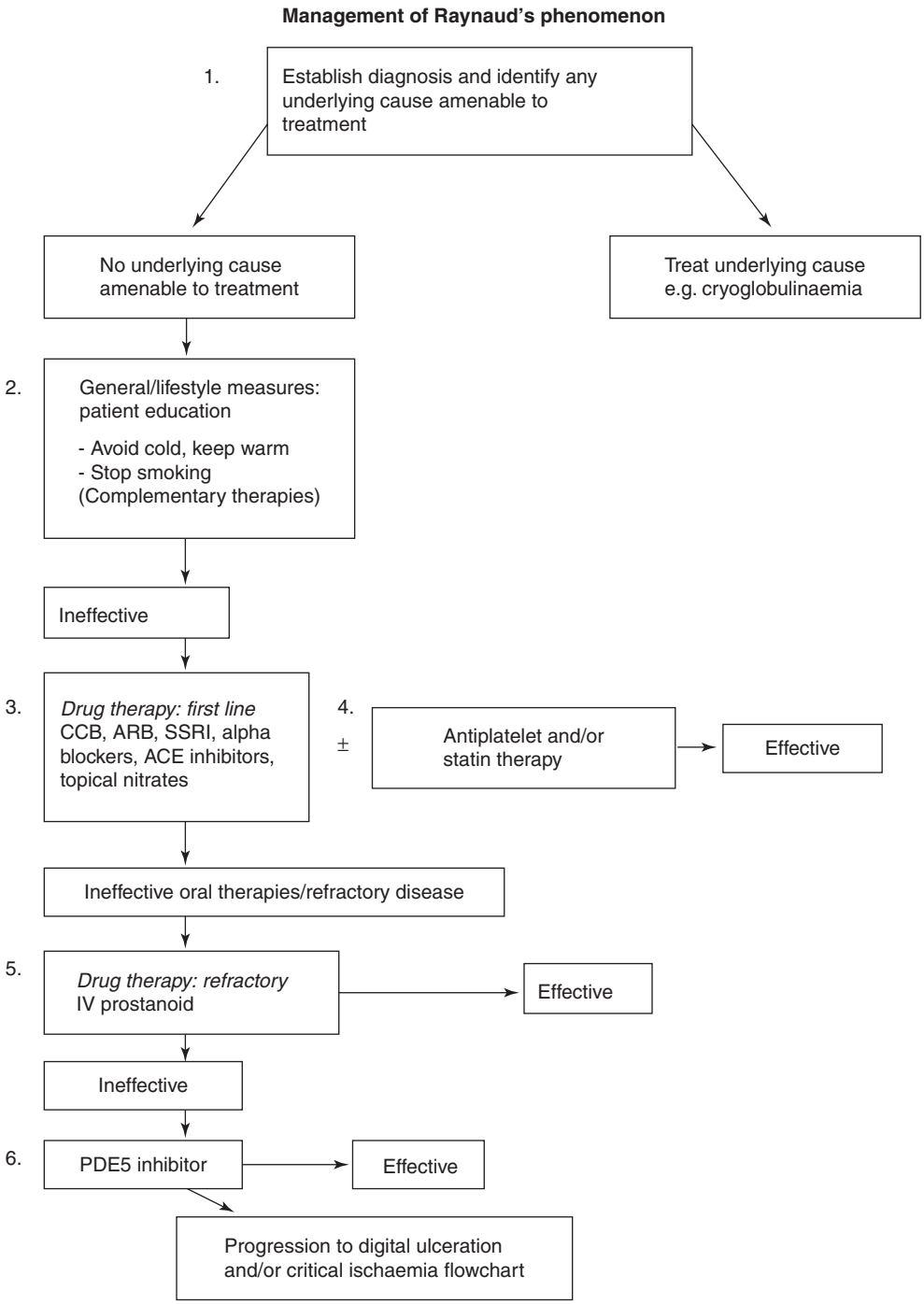

Fig. 6.5 The management of SSc-related Raynaud's phenomenon. If treatment of underlying or contributory causes is ineffective, further treatment should be commenced. Note that all patients with RP irrespective of aetiology (including patients with PRP) and who are symptomatic should be offered treatment. Clinicians who practise outside the United Kingdom might modify their approach depending on their access to drug therapies. ACE angiotensin-converting enzyme, ARB angiotensin receptor blocker, CCB calcium channel blocker, IV intravenous, PDE5 phosphodiesterase type 5, SSRI selective serotonin receptor inhibitor. (Reproduced with permission [62])

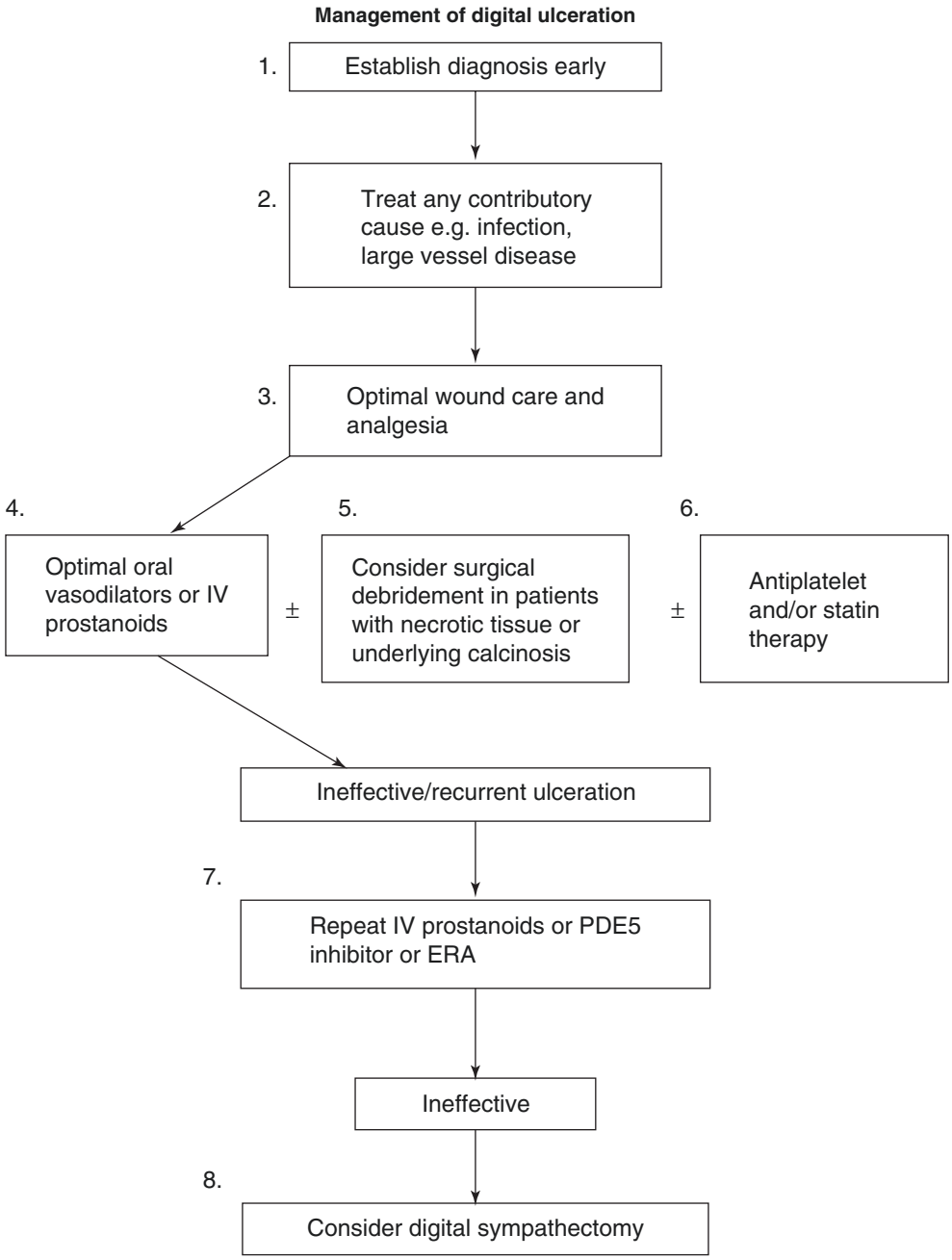

Fig. 6.6 The management of SSc-related digital ulceration. ERA endothelin-1 receptor antagonist, IV intravenous, PDE5 phosphodiesterase type 5. (Reproduced with permission [62])

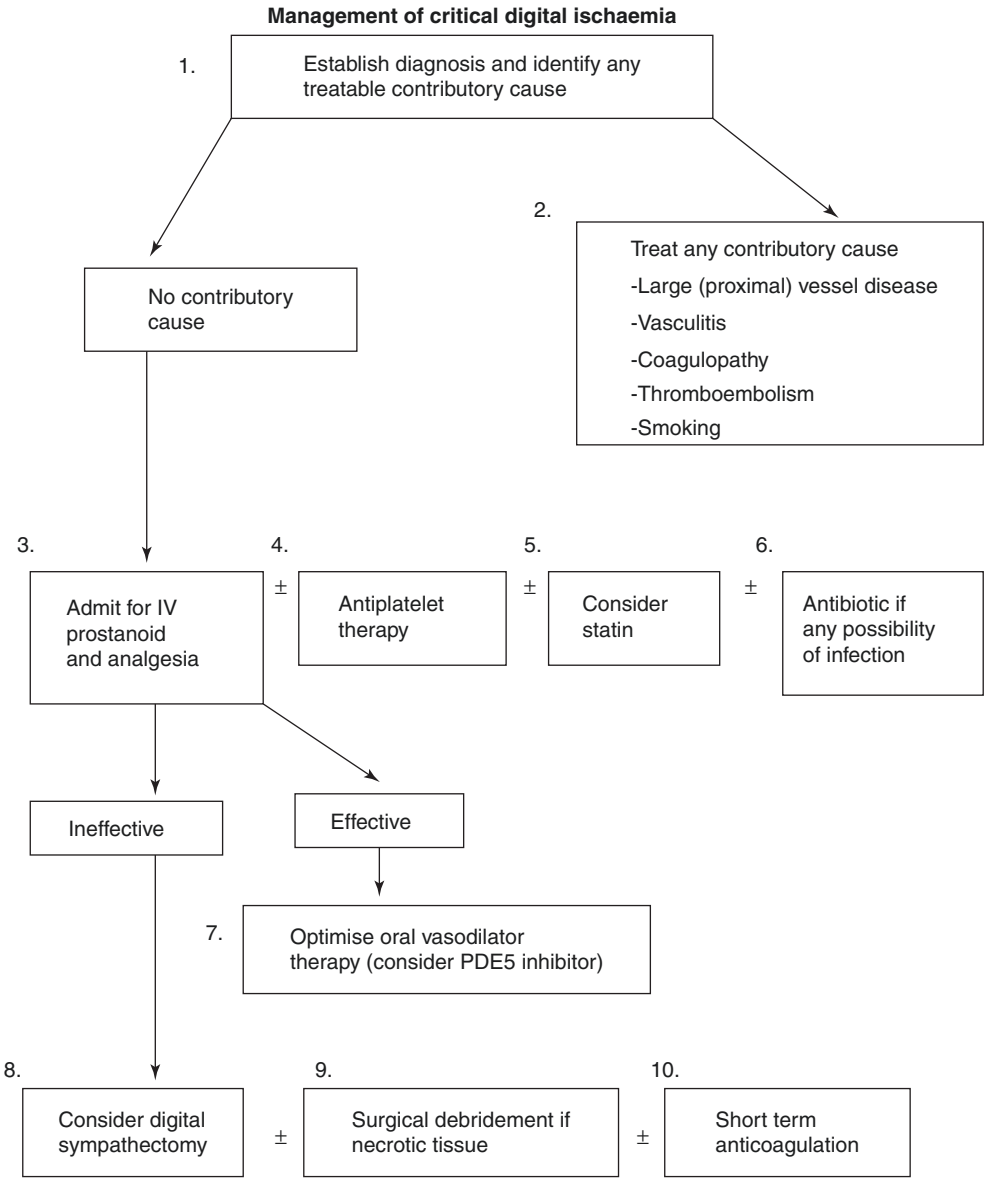

Fig. 6.7 The management of SSc-related critical digital ischaemia. IV intravenous, PDE5 phosphodiesterase type 5. (Reproduced with permission [62])

Treatment of Any Underlying Cause

To identify and treat (if possible) any underlying cause is the first principle of management in all patients with RP. Examples include (but are not limited to) treatment of paraproteinaemia or of a subclavian stenosis.

Patient Education/General Measures

This is a key aspect of management of all patients with RP that is often overlooked. Patients should try to avoid the impact of (even slight) temperature changes and dress warmly (including multiple layers), including wearing hat, socks and gloves. Hand warmers may be helpful or electrically heated gloves. Patient support groups provide excellent information leaflets. Patients should be strongly encouraged to stop smoking [63–65].

Drug Treatment

Drug theraphy, RP should be offered to those patients who remain symptomatic despite the 'general' measures outlined above. Most patients with SSc-related RP will require drug treatment, as their RP is generally more severe than in those patients with PRP. The general approach to drug treatment for SSc-related RP is presented in Fig. 6.5 (although as previously highlighted, this is also relevant to RP due to other causes). Examples of drug doses are provided in Table 6.3.

It is worth highlighting that as a generalisation, the evidence base for drug treatment of RP is weak, because the number of randomised controlled trials is relatively small. This is in part due to the difficulty in conducting trials of RP that tend to be of short duration and run over the winter months [66]. However, on a positive note, there are now increasing numbers of clinical trials in patients with RP, including in patients with SSc-related digital vasculopathy.

Calcium Channel Blockers

These are generally considered first-line drug treatment for both PRP and SRP [67, 68], as reflected by both the recent British Society of Rheumatology and European League Against Rheumatism treatment recommendations for SSc [69, 70]. Calcium channel blockers act on smooth muscle cells to produce vasodilation. Adverse effects are common, including vasodilatory effects such as headache, dizziness and flushing. It is best to commence in low dose and gradually increase. Many clinicians through experience of treating patients with RP consider that sustained release preparations (e.g. sustained release nifedipine or amlodipine) are better tolerated than short-acting preparations. A recent Cochrane review of calcium channel blockers in PRP [71] that included

Table 6.3 Examples of drugs used in the treatment of Raynaud's phenomenon [62]

Drug class	Drug	Usual dose range in adults
Calcium channel blockers	Nifedipine (sustained release)	10 mg bd → 40 mg bd
	Amlodipine	5 mg od →10 mg od
	Diltiazem	60 mg bd →120 mg bd
Angiotensin receptor blockers	Losartan	25 mg od → 100 mg od
Selective serotonin reuptake inhibitors	Fluoxetine	20 mg od
Alpha-blockers	Prazosin	500 micrograms bd → 2 mg bd
Angiotensin-converting enzyme inhibitors	Lisinopril	5 mg od → 20 mg od
Phosphodiesterase type 5 inhibitors	Sildenafil	20 mg/25 mg tds → 50 mg tds
	Tadalafil	10 mg alternate days → 20 mg od

7 randomised trials and 296 patients reported that calcium channel blockers were only minimally effective. Despite the relatively small number of patients included in this and other meta-analyses [67, 68], calcium channel blockers are nonetheless the group of drugs that has been most studied in RP: two fairly recent reviews have both highlighted the lack of evidence base for other classes of drugs [72, 73].

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers

There is a strong rationale for inhibition of the renin-angiotensin system in RP, especially secondary to SSc. In particular, angiotensin-converting enzyme (ACE) inhibitors prevent deleterious fibrous remodelling in myocardial infarction, and angiotensin II is a potent vasoconstrictor. The evidence base for ACE inhibitors and angiotensin II receptor blockers in SSc-related RP is however weak. Earlier studies of ACE inhibitors (captopril and enalapril) were limited and conflicting [74]. In a multicentre, double-blind, placebo-controlled trial of quinapril, which included 210 patients with either limited cutaneous SSc or antibody-positive RP, there was no reported benefit in peripheral vascular manifestations after 2–3 years' treatment [75]. The angiotensin II receptor blocker losartan has been reported to be more effective than nifedipine, but this was in a small open study, and the dose of nifedipine was relatively low (20 mg) [76].

Supplementation of the L-Arginine/Nitric Oxide Pathway, Including Phosphodiesterase Type 5 Inhibitors

For the practising clinician, the important recent change in the management of 'uncomplicated' RP is the increasing use of phosphodiesterase type 5 (PDE5) inhibitors for RP [69, 70, 77, 78]. NO is a potent vasodilator, and PDE5 inhibitors enhance the effect of NO by inhibiting degradation of cyclic guanosine monophosphate. Although earlier clinical trials of PDE5 inhibitors in RP including patients with SSc gave somewhat conflicting results, more recent studies have suggested that PDE5 inhibitors confer benefit in patients with SRP. In a recent meta-analysis which included 244 patients (almost all of whom had CTD and, in particular, SSc-related RP) from 6 randomised clinical trials (1 with sildenafil, 1 with modified-release sildenafil, 3 with tadalafil and 1 with vardenafil), treatment was associated with a 'significant but moderate efficacy in SRP' [79].

Topical (transdermal) NO donation is another approach to treatment of RP. Topically applied glyceryl trinitrate (GTN), an NO donor, produces both local [80] and systemic [81] vasodilation. When given by transdermal patch for its systemic effects [81], it is often poorly tolerated and is therefore seldom used, although a retrospective report from the United Kingdom suggested that this approach was beneficial in children [82]. What is required is a preparation that maximises local efficacy but minimises adverse systemic effects. Although there is currently no commercially available preparation for application to the fingers, it is encouraging that topical nitrate therapy is being revisited. In a multicentre, placebo-controlled trial of MCQ-503, a novel preparation of GTN, 4 weeks of treatment (applied to the fingers immediately before or up to 5 min after the onset of an attack of RP) was associated with a reduction in the Raynaud's condition score, but not the frequency or duration of attacks [83]. Subsequently, in a laboratory-based, multicentre, double-blind, randomised, placebo-controlled, crossover study [84] examining two different doses of gel (0.5% and 1.25%), the proportion of subjects achieving baseline blood flow after a cold challenge was higher with MCQ-503 (66.2% and 69%, respectively) compared to placebo (45.8%).

Serotonin Reuptake Inhibitors

Serotonin is a vasoconstrictor, and therefore drugs antagonising its effects or limiting its availability may prevent vasoconstriction and improve symptoms of RP. Fluoxetine, a selective serotonin reuptake inhibitor, was beneficial in an open-label study [85] including patients with both primary and secondary RP. Serotonin reuptake inhibitors are less likely to cause vasodilatory side effects than some of the other drugs discussed above and so may be helpful in patients intolerant of other medications. However, further research is warranted to establish their place in the treatment of RP.

α-Adrenergic Blockers

These block vasoconstriction and so are sometimes prescribed for RP. However, the evidence base for non-selective α-receptor blockade in RP is very weak [86], mirroring the situation for many other classes of drug.

Prostanoids

These are seldom used in 'uncomplicated' RP, although they may have a role in patients with severe attacks impacting on quality of life, especially in patients in whom RP is secondary to SSc. Prostanoids are thought to have multiple modes of action, including vasodilation, inhibition of platelet aggregation and vascular remodelling [87]. In patients with SSc, they are effective in reducing frequency and severity of Raynaud's attacks as well as in healing DUs [88, 89], and many clinicians prescribe intravenous prostanoids to patients with SSc and severe RP at the onset of winter, with the aim of reducing severity of Raynaud's attacks and preventing digital ulceration. However, patients require hospitalisation to receive intravenous drug therapies, including the associated expense and inconvenience for the patient. Experience with oral prostanoids has been disappointing [90, 91]; however, oral prostanoids are being revisited. In an open-label laboratory study that included 19 patients, treatment with oral treprostinil diethanolamine increased finger perfusion

and temperature [92]. In a recent multicentre, randomised, double-blind, placebo-controlled trial, 20-week treatment with oral treprostinil was associated with a small but not statistically significant reduction in DU burden [93].

Antiplatelet Agents and Statins

There is a strong therapeutic rationale for antiplatelet agents for patients in whom RP is secondary to SSc, because, as previously described, platelet activation is well recognised. Many clinicians therefore give low-dose aspirin (or an alternative antiplatelet agent when there are concerns about upper gastrointestinal side effects) to patients with SSc and severe digital ischaemia: however at present, there is no good evidence base to support this approach.

Regarding statin therapy, Abou-Raya et al. reported improvements in both clinical and laboratory measurements in patients with SSc-related RP treated with atorvastatin for 4 months (including an improvement in RP severity compared to placebo treatment), indicating that statins deserve further research in RP [94]: at present there is insufficient evidence to recommend these routinely.

Antioxidants

The evidence base for antioxidant therapy is limited and conflicting, with only some studies reporting an improvement in SSc-associated RP. In a controlled trial, treatment with probucol (a synthetic antioxidant) was associated with a significant reduction in RP symptoms (frequency and severity) compared to nifedipine [95]. Intravenous [96, 97] but not oral [98] N-acetylcysteine has been reported to improve RP symptoms (frequency and severity of RP attacks), as well as to reduce DU burden [97]. In a placebo-controlled, double-blind, crossover study that included 33 patients, treatment with a combination of micronutrient antioxidants was not associated with any clinical benefit in RP compared to placebo [99].

Surgery

Surgery has no role to play in 'uncomplicated' RP. There is increasing international experience using botulinum toxin injection and/or digital sympathectomy in the content of severe RP (refractory to treatment strategies previously described) and DU disease [100–103]. However, at present there is only a limited evidence base to support these interventions. Trials of botulinum toxin are ongoing. Fat grafting is a novel surgical approach which is being used in some centres for the management of SSc-related digital vascular disease [104].

Summary and Conclusions

In conclusion, RP is a common condition that can be associated with significant pain and disability, irrespective of the underlying aetiology. In patients with SSc, RP exists within a spectrum of digital vascular disease and can progress to ischaemic tissue loss. The clinician must perform a comprehensive clinical assessment and request key investigations (in particular, nailfold capillaroscopy and SSc-associated autoantibodies) in patients with RP. The management of RP must be tailored to the individual, although patient education is mandatory in all patients with RP. Future research is required to inform the management of RP, including the role for drug therapies (e.g. statins and antiplatelet agents) used in other conditions, and to better understand the complex pathogenesis underlying RP, which could drive therapeutic advances.

References

1. LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumatol [Internet]. 2001 [cited 2016 Jun 20];28(7):1573–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11469464.
2. Matucci-Cerinic M, Allanore Y, Czirjak L, Tyndall A, Muller-Ladner U, Denton C, et al. The challenge of early systemic sclerosis for the EULAR Scleroderma Trial and Research group (EUSTAR) community. It is time to cut the Gordian knot and develop a prevention or rescue strategy. Ann Rheum Dis [Internet]. 2009 [cited 2017 Mar 24];68(9):1377–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19674983.
3. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis [Internet]. 2011 [cited 2016 Jun 18];70(3):476–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21081523.
4. Hughes M, Snapir A, Wilkinson J, Snapir D, Wigley FM, Herrick AL. Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. Rheumatology (Oxford). 2015;54(8):1443–7.
5. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. Rheumatology (Oxford) [Internet]. 2011 [cited 2016 Jun 21];50(4):762–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21149249.
6. Maundrell A, Proudman SM. Epidemiology of Raynaud's phenomenon. In: Wigley FM, Herrick AL, Flavahan NA, editors. Raynaud's phenomenon. New York: Springer Science+Buisness Media; 2015. p. 21–35.
7. Silman A, Holligan S, Brennan P, Maddison P. Prevalence of symptoms of Raynaud's phenomenon in general practice. BMJ [Internet]. 1990 [cited 2017 Mar 9];301(6752):590–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2242457.

8. Planchon B, Pistorius M-A, Beurrier P, De Faucal P. Primary Raynaud's phenomenon. Angiology [Internet]. 1994 [cited 2017 Mar 9];45(8):677–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8048777.
9. Freedman RR, Mayes MD. Familial aggregation of primary Raynaud's disease. Arthritis Rheum [Internet]. 1996 [cited 2017 Mar 9];39(7):1189–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8670329.
10. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease--an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med [Internet]. 1972 [cited 2017 Mar 9];52(2):148–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4621694.
11. Burdt MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. Arthritis Rheum [Internet]. 1999 [cited 2017 Mar 9];42(5):899–909. Available from: http://doi.wiley.com/10.1002/1529-0131%28199905%2942%3A5%3C899%3A%3AAID-ANR8%3E3.0.CO%3B2-L.
12. Hoffman IEA, Peene I, Meheus L, Huizinga TWJ, Cebecauer L, Isenberg D, et al. Specific antinuclear antibodies are associated with clinical features in systemic lupus erythematosus. Ann Rheum Dis [Internet]. 2004 [cited 2017 Mar 9];63(9):1155–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15308527.
13. Meier FMP, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis [Internet]. 2012 [cited 2016 Jun 18];71(8):1355–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22615460.
14. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol [Internet]. 1988 [cited 2016 Jun 18];15(2):202–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3361530.
15. Anderson ME, Moore TL, Hollis S, Clark S, Jayson MI, Herrick AL. Endothelial-dependent vasodilation is impaired in patients with systemic sclerosis, as assessed by low dose iontophoresis. Clin Exp Rheumatol [Internet]. [cited 2016 Jun 28];21(3):403. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12846066.
16. Gunawardena H, Harris ND, Carmichael C, McHugh NJ. Maximum blood flow and microvascular regulatory responses in systemic sclerosis. Rheumatology (Oxford) [Internet]. 2007 [cited 2016 Jun 28];46(7):1079–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17494087.
17. Rossi M, Bazzichi L, Di Maria C, Franzoni F, Raimo K, Della Rossa A, et al. Blunted increase of digital skin vasomotion following acetylcholine and sodium nitroprusside iontophoresis in systemic sclerosis patients. Rheumatology [Internet]. 2008 [cited 2017 Mar 24];47(7):1012–7. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/ken117.
18. Khan F, Litchfield SJ, McLaren M, Veale DJ, Littleford RC, Belch JJ. Oral L-arginine supplementation and cutaneous vascular responses in patients with primary Raynaud's phenomenon. Arthritis Rheum [Internet]. 1997 [cited 2017 Mar 24];40(2):352–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9041947.
19. Coffman JD, Cohen AS. Total and capillary fingertip blood flow in Raynaud's phenomenon. N Engl J Med [Internet]. 1971 [cited 2017 Mar 24];285(5):259–63. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM197107292850505.
20. Engelhart M, Kristensen JK. Raynaud's phenomenon: blood supply to fingers during indirect cooling, evaluated by laser Doppler flowmetry. Clin Physiol [Internet]. 1986 [cited 2017 Mar 24];6(6):481–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2947773.
21. Singh S, de Trafford JC, Baskerville PA, Roberts VC. Digital artery calibre measurement–a new technique of assessing Raynaud's phenomenon. Eur J Vasc Surg [Internet]. 1991 [cited 2017 Mar 24];5(2):199–203. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2037091.
22. Pignone A, Rosso A Del, Brosnihan KB, Perfetto F, Livi R, Fiori G, et al. Reduced circulating levels of angiotensin-(1–7) in systemic sclerosis: a new pathway in the dysregulation of endothelial-dependent vascular tone control. Ann Rheum Dis [Internet]. 2007 [cited 2017 Mar 24];66(10):1305–10. Available from: http://ard.bmj.com/cgi/doi/10.1136/ard.2006.064493.
23. Vancheeswaran R, Azam A, Black C, Dashwood MR. Localization of endothelin-1 and its binding sites in scleroderma skin. J Rheumatol [Internet]. 1994 [cited 2017 Mar 24];21(7):1268–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7525957.
24. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol [Internet]. 2012 [cited 2017 Mar 24];8(8):469–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22782008.
25. Bukhari M, Hollis S, Moore T, Jayson MI, Herrick AL. Quantitation of microcirculatory abnormalities in patients with primary Raynaud's phenomenon and systemic sclerosis by video capillaroscopy. Rheumatology (Oxford) [Internet]. 2000 [cited 2017 Mar 24];39(5):506–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10852981.
26. Rodnan GP, Myerowitz RL, Justh GO. Morphologic changes in the digital arteries of patients with progressive systemic sclerosis (scleroderma) and Raynaud phenomenon. Medicine (Baltimore) [Internet]. 1980 [cited 2015 Oct 2];59(6):393–408. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7442530.
27. Hasegawa M, Nagai Y, Tamura A, Ishikawa O. Arteriographic evaluation of vascular changes of the extremities in patients with systemic sclerosis. Br J Dermatol [Internet]. 2006 [cited 2015 Sep 11];155(6):1159–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17107383.
28. Allanore Y, Seror R, Chevrot A, Kahan A, Drapé JL. Hand vascular involvement assessed by magnetic resonance angiography in systemic sclerosis. Arthritis Rheum [Internet]. 2007 [cited 2016 Jun 20];56(8):2747–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17665441.
29. Wang J, Yarnykh VL, Molitor JA, Nash RA, Chu B, Wilson GJ, et al. Micro magnetic resonance angiography of the finger in systemic sclerosis. Rheumatology (Oxford) [Internet]. 2008 [cited 2016 Jun 20];47(8):1239–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18559373.
30. Taylor MH, McFadden JA, Bolster MB, Silver RM. Ulnar artery involvement in systemic sclerosis (scleroderma). J Rheumatol [Internet]. 2002 [cited 2016 Jun 20];29(1):102–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11824945.
31. Park JH, Sung Y-K, Bae S-C, Song S-Y, Seo HS, Jun J-B. Ulnar artery vasculopathy in systemic sclerosis. Rheumatol Int [Internet]. 2009 [cited 2016 Jun 20];29(9):1081–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19363679.
32. Au K, Singh MK, Bodukam V, Bae S, Maranian P, Ogawa R, et al. Atherosclerosis in systemic sclerosis: a systematic review and meta-analysis. Arthritis Rheum [Internet]. 2011 [cited 2016 Jun 19];63(7):2078–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21480189.
33. Man A, Zhu Y, Zhang Y, Dubreuil M, Rho YH, Peloquin C, et al. The risk of cardiovascular disease in systemic sclerosis: a population-based cohort study. Ann Rheum Dis [Internet]. 2013 [cited 2015 Sep 11];72(7):1188–93. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4386728&tool=pmcentrez&rendertype=abstract.

34. Katsumoto TR, Whitfield ML. The pathogenesis of systemic sclerosis. Annu Rev Pathol. 2011;6:509–37.
35. Altorok N, Wang Y, Kahaleh B. Endothelial dysfunction in systemic sclerosis. Curr Opin Rheumatol [Internet]. 2014 [cited 2016 Jun 21];26(6):615–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25191994.
36. Renaudineau Y, Revelen R, Levy Y, Salojin K, Gilburg B, Shoenfeld Y, et al. Anti-endothelial cell antibodies in systemic sclerosis. Clin Diagn Lab Immunol [Internet]. 1999 [cited 2016 Jun 21];6(2):156–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10066646.
37. Mihai C, Tervaert JWC. Anti-endothelial cell antibodies in systemic sclerosis. Ann Rheum Dis [Internet]. 2010 Feb [cited 2016 Jun 21];69(2):319–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20107031.
38. Bunker CB, Terenghi G, Springall DR, Polak JM, Dowd PM. Deficiency of calcitonin gene-related peptide in Raynaud's phenomenon. Lancet (London, England) [Internet]. [cited 2017 Mar 24];336(8730):1530–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1979366.
39. Flavahan NA. Pathophysiological regulation of the cutaneous vascular system in Raynaud's phenomenon. In: Wigley FM, Herrick A, Flavahan NA, editors. Raynaud's phenomenon. New York: Springer Science+Buisness Media; 2015. p. 57–79.
40. Flavahan NA. A vascular mechanistic approach to understanding Raynaud phenomenon. Nat Rev Rheumatol [Internet]. 2015 [cited 2016 May 28];11(3):146–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25536485.
41. Furspan PB, Chatterjee S, Freedman RR. Increased tyrosine phosphorylation mediates the cooling-induced contraction and increased vascular reactivity of Raynaud's disease. Arthritis Rheum [Internet]. 2004 [cited 2017 Mar 24];50(5):1578–85. Available from: http://doi.wiley.com/10.1002/art.20214.
42. Furspan PB, Chatterjee S, Mayes MD, Freedman RR. Cooling-induced contraction and protein tyrosine kinase activity of isolated arterioles in secondary Raynaud's phenomenon. Rheumatology (Oxford) [Internet]. 2005 [cited 2017 Mar 24];44(4):488–94. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/keh517.
43. Kallenberg CG, Vellenga E, Wouda AA, The TH. Platelet activation, fibrinolytic activity and circulating immune complexes in Raynaud's phenomenon. J Rheumatol [Internet]. [cited 2017 Mar 24];9(6):878–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7161779.
44. Pamuk GE, Turgut B, Pamuk ON, Vural O, Demir M, Cakir N. Increased circulating platelet-leucocyte complexes in patients with primary Raynaud's phenomenon and Raynaud's phenomenon secondary to systemic sclerosis: a comparative study. Blood Coagul Fibrinolysis [Internet]. 2007 [cited 2017 Mar 24];18(4):297–302. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001721-200706000-00001.
45. Eid AH, Maiti K, Mitra S, Chotani MA, Flavahan S, Bailey SR, et al. Estrogen increases smooth muscle expression of alpha2C-adrenoceptors and cold-induced constriction of cutaneous arteries. Am J Physiol Heart Circ Physiol [Internet]. 2007 [cited 2017 Mar 24];293(3):H1955–61. Available from: http://ajpheart.physiology.org/cgi/doi/10.1152/ajpheart.00306.2007.
46. Souza E, Muller C, Horimoto A, Rezende R, Guimarães I, Mariz H, et al. Geographic variation as a risk factor for digital ulcers in systemic sclerosis patients: a multicentre registry. Scand J Rheumatol [Internet]. 2016 [cited 2017 Mar 25];1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27996340.
47. LeRoy EC, Medsger TA. Raynaud's phenomenon: a proposal for classification. Clin Exp Rheumatol [Internet]. 1992 [cited 2016 Jun 18];10(5):485–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1458701.
48. Maverakis E, Patel F, Kronenberg DG, Chung L, Fiorentino D, Allanore Y, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. J Autoimmun [Internet]. 2014 [cited 2017 Mar 24];48–49:60–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24491823.
49. Anders HJ, Sigl T, Schattenkirchner M. Differentiation between primary and secondary Raynaud's phenomenon: a prospective study comparing nailfold capillaroscopy using an ophthalmoscope or stereomicroscope. Ann Rheum Dis [Internet]. 2001 [cited 2016 May 30];60(4):407–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1753600&tool=pmcentrez&rendertype=abstract.
50. Bergman R, Sharony L, Schapira D, Nahir MA, Balbir-Gurman A. The handheld dermatoscope as a nail-fold capillaroscopic instrument. Arch Dermatol [Internet]. 2003 [cited 2017 Mar 9];139(8):1027–30. Available from: http://archderm.jamanetwork.com/article.aspx?doi=10.1001/archderm.139.8.1027.
51. Baron M, Bell M, Bookman A, Buchignani M, Dunne J, Hudson M, et al. Office capillaroscopy in systemic sclerosis. Clin Rheumatol [Internet]. 2007 [cited 2016 May 30];26(8):1268–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17160528.
52. Hudson M, Taillefer S, Steele R, Dunne J, Johnson SR, Jones N, et al. Improving the sensitivity of the American College of Rheumatology classification criteria for systemic sclerosis. Clin Exp Rheumatol [Internet]. 2007 [cited 2017 Mar 9];25(5):754–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18078627.
53. Moore TL, Roberts C, Murray AK, Helbling I, Herrick AL. Reliability of dermoscopy in the assessment of patients with Raynaud's phenomenon. Rheumatology (Oxford) [Internet]. 2010 [cited 2016 May 30];49(3):542–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20028729.
54. Hughes M, Moore T, O'Leary N, Tracey A, Ennis H, Dinsdale G, et al. A study comparing videocapillaroscopy and dermoscopy in the assessment of nailfold capillaries in patients with systemic sclerosis-spectrum disorders. Rheumatology (Oxford) [Internet]. 2015 [cited 2016 May 29];54(8):1435–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25749623.
55. Darton K, Black CM. Pyroelectric vidicon thermography and cold challenge quantify the severity of Raynaud's phenomenon. Br J Rheumatol [Internet]. 1991 [cited 2017 Mar 9];30(3):190–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2049579.
56. O'Reilly D, Taylor L, el-Hadidy K, Jayson MI. Measurement of cold challenge responses in primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis. Ann Rheum Dis [Internet]. 1992 [cited 2016 May 30];51(11):1193–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1012453&tool=pmcentrez&rendertype=abstract
57. Pauling JD, Flower V, Shipley JA, Harris ND, McHugh NJ. Influence of the cold challenge on the discriminatory capacity of the digital distal-dorsal difference in the thermographic assessment of Raynaud's phenomenon. Microvasc Res [Internet]. 2011 [cited 2016 May 30];82(3):364–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21420982.
58. Clark S, Hollis S, Campbell F, Moore T, Jayson M, Herrick A. The "distal-dorsal difference" as a possible predictor of secondary Raynaud's phenomenon. J Rheumatol [Internet]. 1999 [cited 2016 May 30];26(5):1125–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10332978.
59. Anderson ME, Moore TL, Lunt M, Herrick AL. The "distal-dorsal difference": a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. Rheumatology (Oxford) [Internet]. 2007 [cited 2016 May 30];46(3):533–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17018538.
60. Murray A, Pauling J. Non-invasive methods of assessing Raynaud's phenomenon. In: Wigley FM, Herrick AL, Flavahan NA, editors.

Raynaud's phenomenon. New York: Springer Science+Buisness Media; 2015. p. 199–242.
61. White C. Clinical practice. Intermittent claudication. N Engl J Med [Internet]. 2007 [cited 2017 Mar 9];356(12):1241–50. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMcp064483.
62. Hughes M, Ong VH, Anderson ME, Hall F, Moinzadeh P, Griffiths B, et al. Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. Rheumatology [Internet]. 2015 [cited 2015 Jun 29];54(11):2015–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26116156.
63. Harrison BJ, Silman AJ, Hider SL, Herrick AL. Cigarette smoking as a significant risk factor for digital vascular disease in patients with systemic sclerosis. Arthritis Rheum [Internet]. 2002 [cited 2015 Sep 3];46(12):3312–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12483737.
64. Suter LG, Murabito JM, Felson DT, Fraenkel L. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. Am J Med [Internet]. 2007 [cited 2017 Mar 9];120(3):264–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17349450.
65. Hudson M, Lo E, Lu Y, Hercz D, Baron M, Steele R, et al. Cigarette smoking in patients with systemic sclerosis. Arthritis Rheum [Internet]. 2011 [cited 2017 Mar 9];63(1):230–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20936633.
66. Wilkinson J. Design and reporting of randomized controlled trials for Raynaud's phenomenon. In: Wigley FM, Herrick AL, Flavahan NA, editors. Raynaud's phenomenon. New York: Springer Science+Buisness Media; 2015.
67. Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. Arthritis Rheum [Internet]. 2001 [cited 2017 Mar 24];44(8):1841–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11508437.
68. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. Rheumatology [Internet]. 2005 [cited 2017 Mar 24];44(2):145–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15546967.
69. Denton CP, Hughes M, Gak N, Vila J, Buch MH, Chakravarty K, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford) [Internet]. 2016.; [cited 2016 Jun 17]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/27284161.
70. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis [Internet]. 2016 [cited 2017 Mar 24];annrheumdis-2016-209909editorsnote. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27941129.
71. Ennis H, Hughes M, Anderson ME, Wilkinson J, Herrick AL. Calcium channel blockers for primary Raynaud's phenomenon. In: Herrick AL, editor. Cochrane database systematic reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2016 [cited 2017 Mar 24]. p. CD002069. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26914257.
72. Stewart M, Morling JR. Oral vasodilators for primary Raynaud's phenomenon. In: Stewart M, editor. Cochrane database systematic reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2012 [cited 2017 Mar 24]. p. CD006687. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22786498.
73. Pope J. Overview – Raynaud's phenomenon (primary) [Internet]. [cited 2017 Mar 24]. Available from: http://clinicalevidence.bmj.com/x/systematic-review/1119/overview.html.
74. Hughes M, Herrick AL. Prophylactic ACE inhibitor therapy in Raynaud's phenomenon: helpful or harmful? In: Cutolo M, Smith V, editors. Novel insights into systemic sclerosis management. Future Medicine Ltd; 2011. p. 232–241.
75. Gliddon AE, Doré CJ, Black CM, McHugh N, Moots R, Denton CP, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. Arthritis Rheum [Internet]. 2007 [cited 2015 Aug 7];56(11):3837–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17968938.
76. Dziadzio M, Denton CP, Smith R, Howell K, Blann A, Bowers E, 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 [Internet]. 1999 [cited 2017 Mar 24];42(12):2646–55. Available from: http://doi.wiley.com/10.1002/1529-0131%28199912%2942%3A12%3C2646%3A%3AAID-ANR21%3E3.0.CO%3B2-T.
77. Pope J, Harding S, Khidmas S, Bonner A, Hudson M, Markland J, et al. Agreement with guidelines from a large database for management of systemic sclerosis: results from the Canadian Scleroderma Research Group. J Rheumatol [Internet]. 2012 [cited 2017 Mar 24];39(3):524–31. Available from: http://www.jrheum.org/cgi/doi/10.3899/jrheum.110121.
78. Walker KM, Pope J. Treatment of systemic sclerosis complications: what to use when first-line treatment fails—a consensus of systemic sclerosis experts. Semin Arthritis Rheum [Internet]. 2012 [cited 2017 Mar 24];42(1):42–55. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0049017212000170.
79. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski J-L. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Ann Rheum Dis [Internet]. 2013 [cited 2017 Mar 24];72(10):1696–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23426043.
80. Anderson ME, Moore TL, Hollis S, Jayson MI V, King TA, Herrick AL. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. Rheumatology (Oxford) [Internet]. 2002 [cited 2015 Sep 9];41(3):324–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11934971.
81. 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 [Internet]. 1995 [cited 2017 Mar 24];34(7):636–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7670782.
82. Gargh K, Baildam EM, Cleary GA, Beresford MW, McCann LJ. A retrospective clinical analysis of pharmacological modalities used for symptomatic relief of Raynaud's phenomenon in children treated in a UK paediatric rheumatology centre. Rheumatology [Internet]. 2010 [cited 2017 Mar 24];49(1):193–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19797310.
83. Chung L, Shapiro L, Fiorentino D, Baron M, Shanahan J, Sule S, et al. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. Arthritis Rheum [Internet]. 2009 [cited 2016 May 30];60(3):870–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19248104.
84. Hummers LK, Dugowson CE, Dechow FJ, Wise RA, Gregory J, Michalek J, et al. A multi-centre, blinded, randomised, placebo-controlled, laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine, in patients with Raynaud phenomenon. Ann Rheum Dis [Internet]. 2013 [cited 2016 May 30];72(12):1962–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23268365.
85. Coleiro B, Marshall SE, Denton CP, Howell K, Blann A, Welsh KI, et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Rheumatology (Oxford) [Internet]. 2001 [cited 2017 Mar 24];40(9):1038–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11561116.

86. Harding SE, Tingey PC, Pope J, Fenlon D, Furst D, Shea B, et al. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. In: Pope J, editor. Cochrane database of systematic reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 1998 [cited 2017 Mar 24]. p. CD000956. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10796398.
87. Fishman AP. Pulmonary Hypertension — Beyond Vasodilator Therapy. N Engl J Med [Internet]. 1998 [cited 2017 Mar 24];338(5):321–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9445414.
88. Wigley FM, Seibold JR, Wise RA, McCloskey DA, Dole WP. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol [Internet]. 1992 [cited 2015 Sep 3];19(9):1407–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1279170.
89. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. In: Pope J, editor. Cochrane Database Syst Rev [Internet]. 2000 [cited 2017 Mar 24];(2):CD000953. Available from: http://doi.wiley.com/10.1002/14651858.CD000953.
90. Wigley FM, Korn JH, Csuka ME, Medsger TA, Rothfield NF, Ellman M, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. Arthritis Rheum [Internet]. 1998 [cited 2016 Jul 24];41(4):670–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9550476.
91. Vayssairat M. Preventive effect of an oral prostacyclin analog, beraprost sodium, on digital necrosis in systemic sclerosis. French Microcirculation Society Multicenter Group for the Study of Vascular Acrosyndromes. J Rheumatol [Internet]. 1999 [cited 2017 Mar 24];26(10):2173–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10529135.
92. Shah AA, Schiopu E, Hummers LK, Wade M, Phillips K, Anderson C, et al. Open label study of escalating doses of oral treprostinil diethanolamine in patients with systemic sclerosis and digital ischemia: pharmacokinetics and correlation with digital perfusion. Arthritis Res Ther [Internet]. 2013 [cited 2017 Mar 24];15(2):R54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23597147.
93. Seibold J, Wigley F, Schiopu E, Denton C, Silver RM, Steen VD, et al. Digital ulcers in SSc treated with oral treprostinil: a randomized, double-blind, placebo-controlled study with open-label follow-up. J Scleroderma Relat Disord. 2017;2(1):1–68.
94. Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. J Rheumatol [Internet]. 2008 [cited 2015 Sep 9];35(9):1801–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18709692.
95. Denton CP, Bunce TD, Dorado MB, Roberts Z, Wilson H, Howell K, et al. Probucol improves symptoms and reduces lipoprotein oxidation susceptibility in patients with Raynaud's phenomenon. Rheumatology (Oxford) [Internet]. 1999 [cited 2017 Mar 24];38(4):309–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10378706.
96. Sambo P, Amico D, Giacomelli R, Matucci-Cerinic M, Salsano F, Valentini G, et al. Intravenous N-acetylcysteine for treatment of Raynaud's phenomenon secondary to systemic sclerosis: a pilot study. J Rheumatol [Internet]. 2001 [cited 2015 Sep 3];28(10):2257–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11669166.
97. Rosato E, Borghese F, Pisarri S, Salsano F. The treatment with N-acetylcysteine of Raynaud's phenomenon and ischemic ulcers therapy in sclerodermic patients: a prospective observational study of 50 patients. Clin Rheumatol [Internet]. 2009 [cited 2015 Sep 3];28(12):1379–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19690939.
98. Correa MJU, Mariz HA, Andrade LEC, Kayser C. [Oral N-acetylcysteine in the treatment of Raynaud's phenomenon secondary to systemic sclerosis: a randomized, double-blind, placebo-controlled clinical trial]. Rev Bras Reumatol [Internet]. 2014 [cited 2017 Mar 24];54(6):452–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S048250041400151X.
99. Herrick AL, Hollis S, Schofield D, Rieley F, Blann A, Griffin K, et al. A double-blind placebo-controlled trial of antioxidant therapy in limited cutaneous systemic sclerosis. Clin Exp Rheumatol [Internet]. [cited 2017 Mar 24];18(3):349–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10895372.
100. Iorio ML, Masden DL, Higgins JP. Botulinum toxin A treatment of Raynaud's phenomenon: a review. Semin Arthritis Rheum [Internet]. 2012 [cited 2015 Sep 10];41(4):599–603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21868066.
101. Neumeister MW. Botulinum toxin type A in the treatment of Raynaud's phenomenon. J Hand Surg Am [Internet]. 2010 [cited 2015 Sep 10];35(12):2085–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21134617.
102. Motegi S-I, Yamada K, Toki S, Uchiyama A, Kubota Y, Nakamura T, et al. Beneficial effect of botulinum toxin A on Raynaud's phenomenon in Japanese patients with systemic sclerosis: a prospective, case series study. J Dermatol [Internet]. 2016 [cited 2015 Sep 9];43(1):56–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26173902.
103. Momeni A, Sorice SC, Valenzuela A, Fiorentino DF, Chung L, Chang J. Surgical treatment of systemic sclerosis-is it justified to offer peripheral sympathectomy earlier in the disease process? Microsurgery [Internet]. 2015 [cited 2015 Sep 9];35(6):441–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25585522.
104. Bank J, Fuller SM, Henry GI, Zachary LS. Fat grafting to the hand in patients with Raynaud phenomenon: a novel therapeutic modality. Plast Reconstr Surg [Internet]. 2014 [cited 2015 Oct 6];133(5):1109–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24445877.
105. Hughes M, Herrick AL. Raynaud's phenomenon. Best Pract Res Clin Rheumatol. 2016;30(1):112–32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27421220.
106. McMahan Z, Paik J. Raynaud's mimics. In: Wigley F, Herrick AL, Flavahan NA, editors. Raynaud's phenomenon. New York: Springer Science+Buisness Media; 2015. p. 163–85.