Raynaud's phenomenon

ABSTRACT

Raynaud's phenomenon is a common vasospastic condition which carries a significant burden of pain and hand-related disability (Hughes and Herrick, 2016). The prevalence of Raynaud's phenomenon in the general population has been reported to be approximately 5% (Garner et al, 2015). Raynaud's phenomenon can occur either as a primary ('idiopathic') phenomenon or secondary to a wide range of underlying medical conditions and drug causes. Therefore, hospital-based specialists are frequently involved in the care of patients with Raynaud's phenomenon and need to be aware of associated conditions and prescribed medications for Raynaud's phenomenon. In particular, Raynaud's phenomenon is often the earliest manifestation of an underlying autoimmune connective tissue disease (e.g. systemic sclerosis). A comprehensive clinical assessment is required including performing targeted investigations (e.g. nailfold capillaroscopy and systemic sclerosis-associated autoantibodies). Patient education and lifestyle adaptations is first-line treatment for Raynaud's phenomenon. There is a wide range of pharmacological options including oral and intravenous drug therapies available to treat Raynaud's phenomenon. Surgical intervention is sometimes required for refractory Raynaud's phenomenon and tissue ischaemia. This review describes the clinical manifestations of Raynaud's phenomenon including potential secondary causes and presents an approach to assessment and management.

The vast majority of individuals (80–90%) affected by this condition have primary Raynaud's phenomenon and this usually tends to occur by 30 years of age. There is a wide range of secondary causes of Raynaud's phenomenon (*Table 1*) including underlying autoimmune rheumatic diseases (e.g. connective tissue diseases and systemic vasculitis) and conditions associated with increased plasma viscosity and reduced digital perfusion (e.g. cryoglobulinaemia and as a paraneoplastic phenomenon). Another important cause is vascular compression (e.g. from a cervical rib or as a result of thoracic outlet syndrome), which often presents with unilateral symptoms. There are also a number of 'other' secondary causes including (but not limited to) hypothyroidism and carpal tunnel syndrome. Progression from isolated Raynaud's phenomenon to secondary

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Table 1. Secondary causes of Raynaud's phenomenon

Cause	Example
Vascular (usually proximal large vessel disease, often unilateral symptoms)	Compressive, e.g. cervical rib
	Obstructive: non-inflammatory, e.g. atherosclerosis
	Inflammatory vascular disease, e.g. thromboangiitis obliterans (Buerger's disease)
Occupational	Hand–arm–vibration syndrome (vibration white finger)
Autoimmune conditions	Systemic sclerosis
	Systemic lupus erythematosus
	Sjögren's syndrome
	Mixed connective tissue disease or overlap syndromes
	Undifferentiated connective tissue disease
	Idiopathic inflammatory myopathies
Drug- or chemical-related	Amphetamines
	Beta-blockers
	Bleomycin
	Cisplatin
	Clonidine
	Ciclosporin
	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

Adapted from Hughes and Herrick (2017b)

Raynaud's phenomenon has been reported to occur in 14–37% of individuals with Raynaud's phenomenon (Maundrell and Proudman, 2015). Most patients with Raynaud's phenomenon only require annual review to ensure their condition has not changed, with expediated clinical review if the situation changes in the interim.

Pathogenesis

The pathogenesis of Raynaud's phenomenon is highly complex and incompletely understood. In primary Raynaud's phenomenon, the underlying mechanism is believed to result from an isolated functional vasospastic disorder. Genetic factors likely play an important role in primary Raynaud's phenomenon. Around half of patients with primary Raynaud's have a family history of Raynaud's phenomenon in first-degree relatives, in particular in women and those individuals with early-onset Raynaud's phenomenon (Maundrell and Proudman, 2015).

In secondary Raynaud's phenomenon, in particular systemic sclerosis-Raynaud's phenomenon, the underlying pathogenesis differs significantly and is often multifactorial in origin. The pathogenesis of secondary Raynaud's phenomenon can be broadly considered under the headings of 'vascular', 'neural' and 'intravascular' abnormalities (Herrick, 2012). Understanding the different mechanisms implicated in the pathogenesis of Raynaud's phenomenon is very important because these are potentially amenable to targeted therapeutic intervention(s). For example, treatment of an underlying haematological disorder or another cause of increased plasma viscosity may result in the resolution of Raynaud's symptoms.

Systemic sclerosis-vasculopathy is characterized by progressive vascular remodelling including intimal and smooth muscle hypertrophy which reduces the luminal diameter (Katsumoto et al, 2011; Denton and Khanna, 2017). Control of vascular tone is highly complex and neural abnormalities have been described in Raynaud's phenomenon, in particular the alpha-2 adrenergic receptor which plays a major role in control of digital vascular tone (Herrick, 2012). In systemic sclerosis there is an imbalance between vasoconstrictor (e.g. endothelin-1) and vasodilator (e.g. nitric oxide) factors. However, these are potentially amenable to therapeutic intervention, for example with endothelin antagonists and phosphodiesterase type 5 inhibitors respectively. Furthermore, endothelial cell death and dysfunction is recognized in systemic sclerosis including from targeting antibodies and increased oxidative stress (Herrick, 2005). In addition, platelet abnormalities have been described in patients with primary Raynaud's phenomenon and those with systemic sclerosis-Raynaud's phenomenon, and impaired fibrinolysis has also been reported in patients with systemic sclerosis (Herrick, 2005).

Clinical features

Attacks of Raynaud's phenomenon commonly affect the digital extremities including the fingers and toes. Involvement of the thumb can suggest the presence of an underlying autoimmune connective tissue disease (Chikura et al, 2010). Other vascular beds can also be involved including the nose, ears and lips.

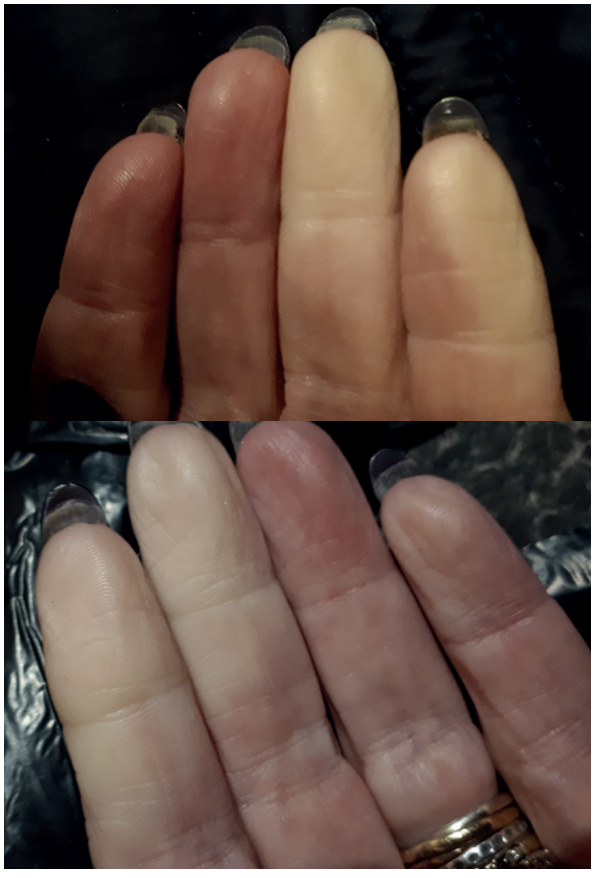

Figure 1. Mobile phone photographs from the same patient capturing an attack of Raynaud's phenomenon. There is marked pallor of the fingers during the attack.

The classical triphasic attacks of Raynaud's phenomenon consist of initial pallor/white, then blue/purple and finally red. These colour changes represent ischaemia, deoxygenation and tissue reperfusion or hyperaemia, the latter of which can be associated with significant discomfort and even overt pain. Patients may also report paraesthesia during attacks of Raynaud's phenomenon. Not all patients present with the classically described triphasic pattern and mono- and biphasic attacks of Raynaud's phenomenon are also recognized. An example of an attack of Raynaud's phenomenon affecting the hands is shown in *Figure 1*.

Usual triggers of an attack of Raynaud's phenomenon include exposure to cold and/or emotional stressors. Indeed, even subtle changes in temperature can trigger an attack. In addition, handling cold objects (such as a steering wheel in the morning) can trigger an attack of Raynaud's phenomenon. Irrespective of the underlying aetiology, Raynaud's phenomenon has a major impact on quality of life and function (Bassel et al, 2011; Hughes et al, 2015c). In a study which included responses from 443 subjects with self-reported Raynaud's phenomenon from 15 countries, most (78%) reported making at least one life adjustment as a result of Raynaud's phenomenon,

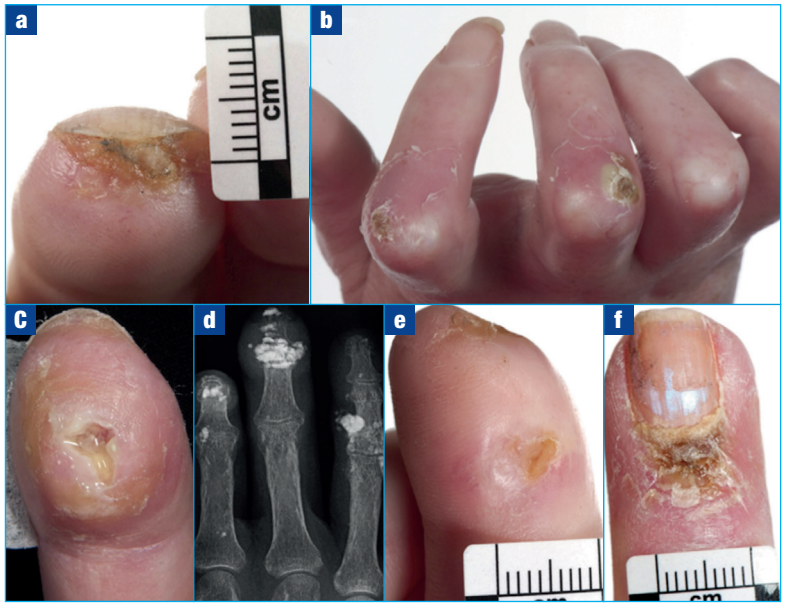

Figure 2. Digital ulcers in systemic sclerosis. Common sites for digital ulcers are **(a)** the fingertips and **(b)** over the extensor aspects of the hands. **c.** Digital ulcers can also occur overlying subcutaneous calcinosis which can be seen **(d)** on a plain radiograph. Other sites for digital ulcers include **(e)** the lateral aspect and **(f)** the nailbed of the fingers.

including patients with primary and secondary Raynaud's phenomenon (Hughes et al, 2015c).

Digital ischaemia

An absolutely key point is that tissue ischaemia in primary Raynaud's phenomenon is transient, whereas in secondary Raynaud's phenomenon patients can develop a spectrum of tissue ischaemia or damage (e.g. ulcers) which can be irreversible (e.g. digital gangrene). Digital ischaemia can occur as a result of a number of secondary conditions including those which are associated with hyperviscosity and structural microvascular and macrovascular disease (e.g. systemic sclerosis). Digital ischaemia can be the first presentation of an underlying secondary cause of Raynaud's phenomenon and should prompt the clinician to thoroughly investigate for underlying causative pathology.

Digital ulcers (*Figure 2*) are common in patients with systemic sclerosis and account for a significant burden of disease-related disability. Half of patients with systemic sclerosis report a history of digital ulcers and the reported point prevalence of ulcers is 5–10% (Hughes and Herrick, 2017a). Ulcers commonly occur on the tips of the fingers and also over the extensor or dorsal aspects of the hands, in particular overlying the small joints of the hands.

In general, fingertip ulcers are believed to be caused by ischaemia, whereas those which occur over the extensor or dorsal aspects of the hands are related to recurrent trauma at exposed sites of the hands and are also caused by increased skin tension from progressive skin sclerosis (Hughes et al, 2018). Digital ulcers can also occur at other sites of the hands including in relation to underlying subcutaneous calcinosis deposition, which itself may be driven by repetitive trauma in patients with systemic sclerosis (Hughes et al, 2019).

Digital ulcers are often slow to heal and are commonly infected (in particular with *Staphylococcus aureus*) which can progress to osteomyelitis. Critical digital ischaemia is a medical emergency and can result in loss of the digit either spontaneously or via the need for amputation. In a large (n=1169) cohort study of patients with systemic sclerosis during an 18-month period, 7.4% developed serious digital vasculopathy complications (defined as digital ulcerations, critical digital ischaemia or digital ischaemia) (Nihtyanova et al, 2008). Of these, 1.6% developed critical digital ischaemia and 1.4% developed digital gangrene.

Clinical assessment

The key is to perform a comprehensive clinical assessment (history and physical examination) in all patients with Raynaud's phenomenon, which is supplemented by supporting investigations. It is helpful for clinicians to be aware and mindful of proposed classification criteria for primary Raynaud's phenomenon during their clinical assessment of patients with Raynaud's (*Table 2*) (LeRoy and Medsger, 1992). These have been revised by Maverakis et al (2014), and of note do not include a normal erythrocyte sedimentation rate as part of their required criteria.

History and examination

The key task of the clinician is to differentiate between primary and secondary Raynaud's phenomenon. The clinician must therefore be aware of the wide range of potential secondary causes of Raynaud's phenomenon (*Table 1*) and should perform a comprehensive clinical assessment (history and physical examination). Key features in the history include eliciting features of a possible autoimmune connective tissue disease (e.g. aphthous mouth ulcers and ultraviolet photosensitivity), a detailed drug and occupational history (with reference to the potential causes in *Table 1*), any relevant family history (including Raynaud's phenomenon and connective tissue diseases), and impact on quality of life and on hand function. A full physical examination should be undertaken including (but not limited to) assessment of the peripheral pulses, close examination of the hands looking for evidence

Table 2. Proposed criteria for primary Raynaud's phenomenon

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 or low titre antinuclear antibody
Normal erythrocyte sedimentation rate
From LeRoy and Medsger (1992)

digital ischaemia and stigmata of an underlying connective tissue disease (e.g. sclerodactyly and telangiectases) and auscultation of the lungs (e.g. for inspiratory crackles suggesting possible interstitial lung disease).

Investigations

The minimal or basic set of investigations in patients with Raynaud's phenomenon is a full blood count, erythrocyte sedimentation rate or C-reactive protein, anti-nuclear antibody (ANA) and nailfold capillaroscopy (Hughes et al, 2015a). These should all be normal or of a low titre in patients with primary Raynaud's phenomenon (e.g. ANA). The ANA titre is reported as the lowest dilution at which immunofluorescence can still be seen. For example, a titre of 1:80 is much less significant than a titre of 1:2560. Therefore, a very low ANA titre is less significant for a connective tissue disease in the absence of other clinical symptoms compared to a high ANA titre.

Additional investigations which clinicians often request include biochemistry (e.g. renal and liver) profile, thyroid function tests, creatinine kinase, immunoglobulins with electrophoresis (where there is a suspicion of paraproteinaemia), complements C3 and C4 (e.g. where lupus is a differential diagnosis) and a chest (or thoracic) radiograph) to exclude a cervical rib (Hughes et al, 2015a). Testing can be used to determine the specific antigenic target of autoantibodies to extractable nuclear antigens and which can help to identify an underlying connective tissue disease including systemic sclerosis (anticentromere, anti-Scl-70 and anti-RNA-polymerase-III antibodies) and myositis-specific antibodies (e.g. anti-Jo-1). Where appropriate, testing for antiphospholipid syndrome (anticardiolipin and anti-b2-glycoprotein antibodies and lupus anticoagulant) and a fasting lipid profile (in patients at risk of atherosclerotic disease) should be performed.

The importance of both nailfold capillaroscopy and systemic sclerosis-associated antibodies is reflected through their inclusion in American College of Rheumatology/European League Against Rheumatism Criteria for systemic sclerosis (van Den Hoogen et al, 2013). Although most clinicians are able to request testing for ANA, nailfold capillaroscopy is not currently available in most hospitals. In a 20-year prospective study which included 586 patients with Raynaud's phenomenon and no definitive evidence of connective tissue disease who were followed up for 3197 person-years, 12.6% developed definitive systemic sclerosis (Koenig et al, 2008). Independent predictors of progression of Raynaud's phenomenon to definitive systemic sclerosis were autoantibodies (positive ANA hazard ratio = 5.67, systemic sclerosis autoantibodies hazard ratio = 4.7) and microvascular damage as assessed by nailfold capillaroscopy (hazard ratio = 4.5) (Koenig et al, 2008).

Vascular investigations

The key is to maintain a high index of clinician suspicion about the possibility of large vessel involvement including features elicited from the history (e.g. asymmetrical attacks of Raynaud's or unilateral digital ischaemia or ulceration) and physical examination (e.g. abnormalities of the pulses). Urgent vascular imaging, e.g. arterial (Doppler) ultrasound, is required to confirm abnormalities of the proximal vasculature early as these may be amenable to therapeutic intervention.

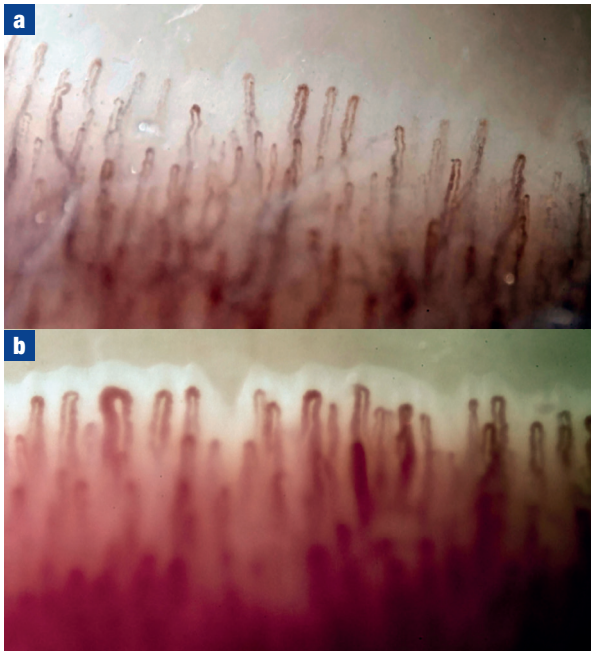

Figure 3. Nailfold capillaroscopy. **a.** Normal capillaroscopy in a healthy subject. The capillaries are homogenous in appearance and regularly distributed. **b.** Abnormal capillaroscopy in a patient with systemic sclerosis. There is evidence of nailfold vasculopathy including with enlarged capillaries.

Nailfold capillaroscopy

Nailfold capillaroscopy (*Figure 3*) provides the clinician with a non-invasive 'window' into the microcirculation. At the nailfold, the capillaries are oriented parallel instead of perpendicular to the surface of the skin which allows them to be observed in their entirety. Normal capillaries (*Figure 3a*) are reassuring in patients presenting with Raynaud's phenomenon, whereas in those with secondary Raynaud's phenomenon (*Figure 3b*), characteristic abnormalities (e.g. capillary enlargement and microhaemorrhages) are seen. A wide range of devices can be used to perform nailfold capillaroscopy. Low-magnification devices include the light microscope and dermatoscope (magnification approximately × 10). High-magnification video capillaroscopy (magnification × 200–600) is considered the gold standard but is not widely available outside of specialist Raynaud's phenomenon or systemic sclerosis centres at present (Baron et al, 2007; Hughes et al, 2015b). The wide availability of low-cost USB microscopy may widen access to capillaroscopy in future routine clinical practice.

Infrared thermography

Infrared thermography (*Figure 4*) measures skin surface temperature and different thermographic perimeters have been reported to successfully distinguish between primary

and secondary Raynaud's phenomenon. Unlike healthy controls, patients with primary Raynaud's phenomenon have a delayed response in rewarming after cold exposure. Furthermore, patients with underlying structural vascular disease (e.g. systemic sclerosis) do not rewarm even after a further rewarming challenge. Anderson et al (2007) reported that a 'distal dorsal difference' of ≥1°C (fingertips cooler than the dorsum of the hand) was very suggestive of an underlying autoimmune connective tissue disease. At present, thermography is not widely available outside of specialist centres because of the high cost of the equipment.

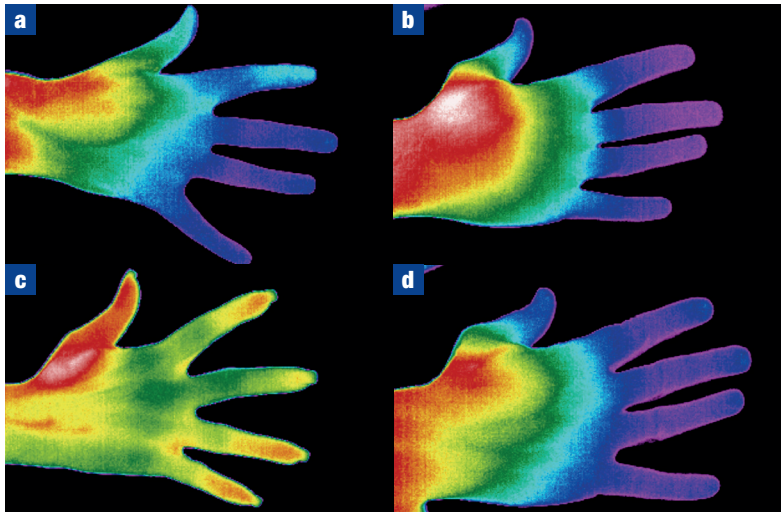

Figure 4. Thermography. **a.** and **(c)** infrared thermograms depicting the hands both before and after dynamic temperature challenge in a patient with primary Raynaud's phenomenon) and **(b)** and **(d)** systemic sclerosis. **a.** and **(b)** At 23°C the fingertips are cooler than the dorsum of the hand in both patients. At 30°C, unlike **(c)** in the patient with primary Raynaud's phenomenon, **(d)** there are persisting temperature gradients (the fingertips cooler) along all of the fingers in the patient with systemic sclerosis.

Management

Raynaud's phenomenon has a significant impact on quality of life irrespective of the underlying cause, including in patients with primary Raynaud's phenomenon. Both non-pharmacological and pharmacological interventions are indicated in the management of Raynaud's phenomenon. *Figure 5* summarizes an approach to the management of Raynaud's phenomenon.

Non-pharmacological

Patient education and behaviour adaptations (e.g. cold avoidance and wearing multiple layers of clothing to keep warm) are first-line treatment in all patients with Raynaud's phenomenon. Patients should be counselled about the importance of smoking cessation, as smoking promotes vasoconstriction.

Pharmacological

Pharmacological treatment is indicated if general and lifestyle measures are ineffective. Pharmacological therapies for Raynaud's phenomenon are mainly vasodilators, although other mechanisms (e.g. via acting on platelets)

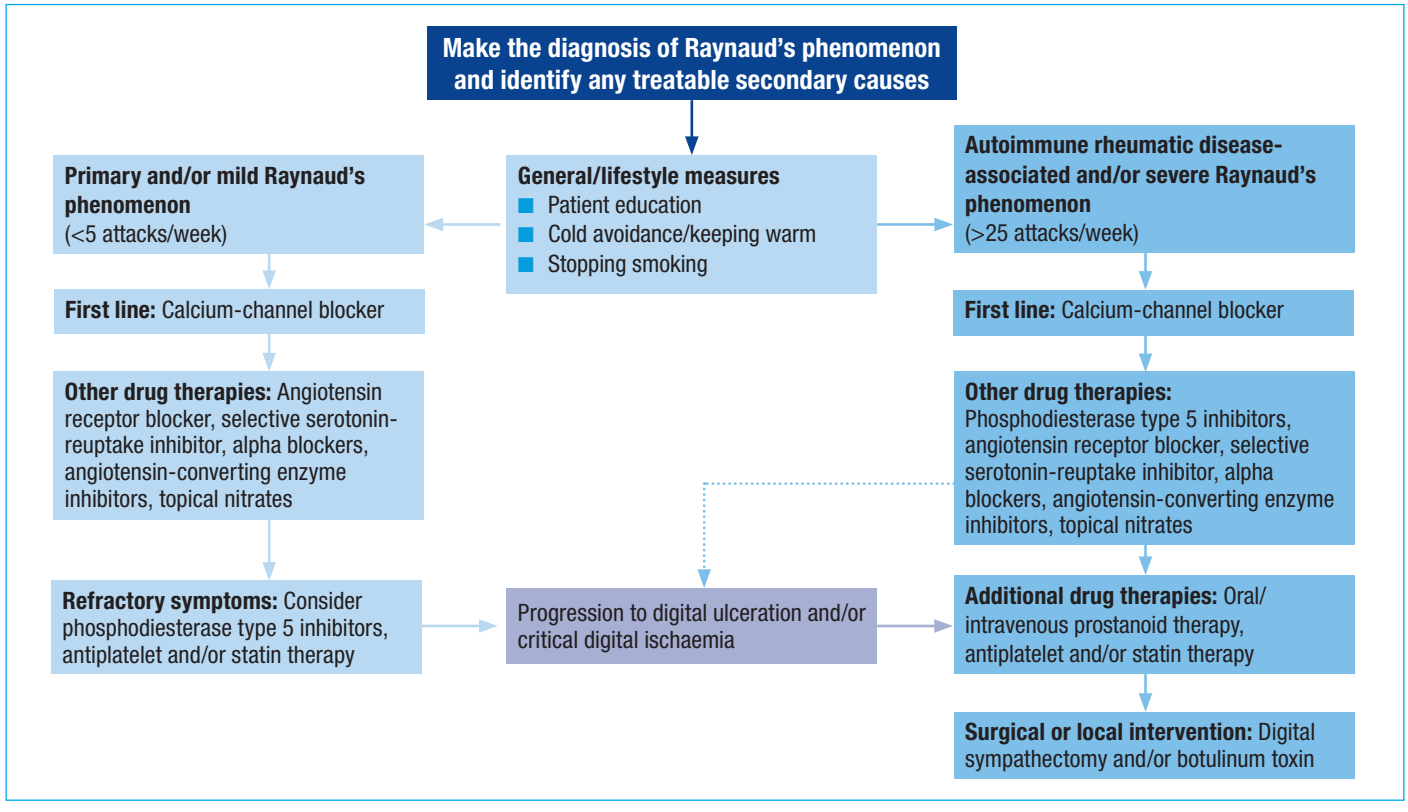

Figure 5. An overview of the management of Raynaud's phenomenon, showing the range of pharmacological and other treatment approaches used by specialists who treat Raynaud's phenomenon (Pauling et al, 2019).

are also implicated. In general, treatments are started at a low dose and gradually increased incrementally if not efficacious and/or associated with dose-limiting side effects. Modified or sustained-release treatments are often better tolerated.

A wide range of oral drug therapies is available, and these are presented in *Table 3* with examples of dosing in adults. First-line treatment is with calcium-channel blockers. Phosphodiesterase type 5 inhibitors are increasingly being used earlier in the pharmacological management of Raynaud's phenomenon, including after failure of calcium-channel blockers for systemic sclerosis-Raynaud's phenomenon. It is important to highlight that sildenafil is contraindicated in those patients who are receiving treatment with nitrates (e.g. glyceryl trinitrate) because the risk of potentially fatal hypotension is significantly elevated. Other drug classes used in Raynaud's phenomenon include therapies which target the renin–angiotensin system (e.g. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), selective serotonin-reuptake inhibitors (useful in patients who are prone to vasodilatory side effects) and alpha blockers. Oral drug therapies for Raynaud's phenomenon are often used in combination but require careful monitoring (e.g. of blood pressure to prevent significant hypotension). Intravenous prostanoid therapy (e.g. iloprost) is reserved for severe, refractory Raynaud's phenomenon and systemic sclerosis-digital ischaemia (e.g. digital ulcers and ischaemia).

Many patients elect to try different complementary therapies for Raynaud's phenomenon including vitamin supplementation (e.g. vitamins C and E); although there is a lack of evidence to support these interventions, the overall risk of potential harm is low (Hughes et al, 2015a).

Surgical management

Surgical intervention is indicated in patients with refractory Raynaud's phenomenon and/or digital ischaemia where medical management has failed (Hughes et al, 2015a). Digital debridement (e.g. for digital ulcers) and even amputation may be required for progressive ischaemia (e.g. digital gangrene). Other indications for surgery include deeper bony infection (e.g. osteomyelitis) and severe (including nocturnal pain) which suggests the development of tissue necrosis and/or an abscess. In the case of secondary Raynaud's phenomenon and digital ulcers requiring debridement, this should be discussed with a specialist centre, as conservative management is often favoured as a result of poor healing. Iloprost is also often required for any debridement or ischaemia to aid healing. Digital (periarterial) sympathectomy and/or botulinum toxin injection can be considered in severe Raynaud's phenomenon and/or digital ischaemia (Muir and Herrick, 2019). Cervical sympathectomy is no longer performed because there is a high rate of unacceptable associated side effects.

Role of hospital-based specialists

The key is to identify and consider the underlying aetiology in patients with Raynaud's phenomenon, in particular if there are features to suggest an underlying autoimmune connective tissue disease (e.g. systemic sclerosis). It is important to be aware when prescribing that certain medications (*Table 1*) have been reported to either provoke and/or exacerbate Raynaud's phenomenon. Close dialogue with rheumatology is essential for both the diagnosis and management of Raynaud's phenomenon, in particular after failure of first-line drug treatment for primary and/or 'mild' Raynaud's phenomenon and in patients with autoimmune rheumatic disease-associated and/or 'severe' Raynaud's phenomenon. Colleagues in hospital-based specialities may be actively involved in managing associated organ-based complications of associated conditions (e.g. respiratory medicine and interstitial lung disease) and surgical complications (e.g. digital ischaemia).

Conclusions

Raynaud's phenomenon is common in the general population, impacts significantly on the patient's quality of life and function and will be encountered routinely by hospital-based specialists. Careful clinical assessment is essential to identify the wide range of potential underlying medical conditions and drug therapies associated with Raynaud's phenomenon. Hospital-based specialists play an important role in both the early identification and management of patients with Raynaud's phenomenon, including those in the earliest forms of autoimmune connective tissue diseases. In addition, hospital-based

Table 3. Examples of oral drug therapies used for the treatment of Raynaud's phenomenon

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

From Hughes et al (2015a)

KEY POINTS

- Raynaud's phenomenon is a common episodic vasospastic disorder and is associated with significant burden of pain and hand-related disability.
- Raynaud's phenomenon can occur as a primary phenomenon or secondary to a wide range of underlying medical conditions and drug causes.
- Great care must be taken to differentiate between primary and secondary Raynaud's phenomenon as the prognosis and management can vary significantly.
- Persistent tissue ischaemia (e.g. digital ulcers) is only seen in secondary Raynaud's phenomenon.
- Raynaud's phenomenon is often the earliest symptom in systemic sclerosis.
- Patient education and lifestyle adaptations are first-line treatment in all patients with Raynaud's phenomenon.
- A wide range of pharmacological treatments is available for Raynaud's phenomenon including oral and intravenous drug therapies.
- Surgical intervention is sometimes required including for refractory Raynaud's phenomenon and/or persistent tissue ischaemia.

specialists are heavily involved in the management of associated organ-based and surgical complications.

Raynaud's phenomenon should not be regarded as a 'benign' inconvenience because associated symptoms can be significantly intrusive. Non-pharmacological treatment is indicated in all patients with Raynaud's phenomenon. Where possible, any secondary cause of Raynaud's phenomenon should be treated. There is a wide range of oral and intravenous-based drug therapies available for the treatment of Raynaud's phenomenon. Surgical intervention is indicated for severe or refractory Raynaud's phenomenon and for digital ischaemia (e.g. ulcers and ischaemia). Early case identification of Raynaud's phenomenon and input from colleagues in rheumatology, including performing specialist investigations (e.g. nailfold capillaroscopy) is essential for the optimal management of Raynaud's phenomenon including the early diagnosis of autoimmune connective tissue diseases such as systemic sclerosis. **BJHM**

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