Raynaud's phenomenon

Time to take it seriously

AMEE SONIGRA MB BS, MD(Med)
EMMA MITCHELL MB BS
JANE ZOCHLING MB BS, FRACP, MMed(ClinEpi), PhD

The prognosis for people with Raynaud's phenomenon depends on its severity and whether there is associated underlying medical illness, most commonly an autoimmune disease.

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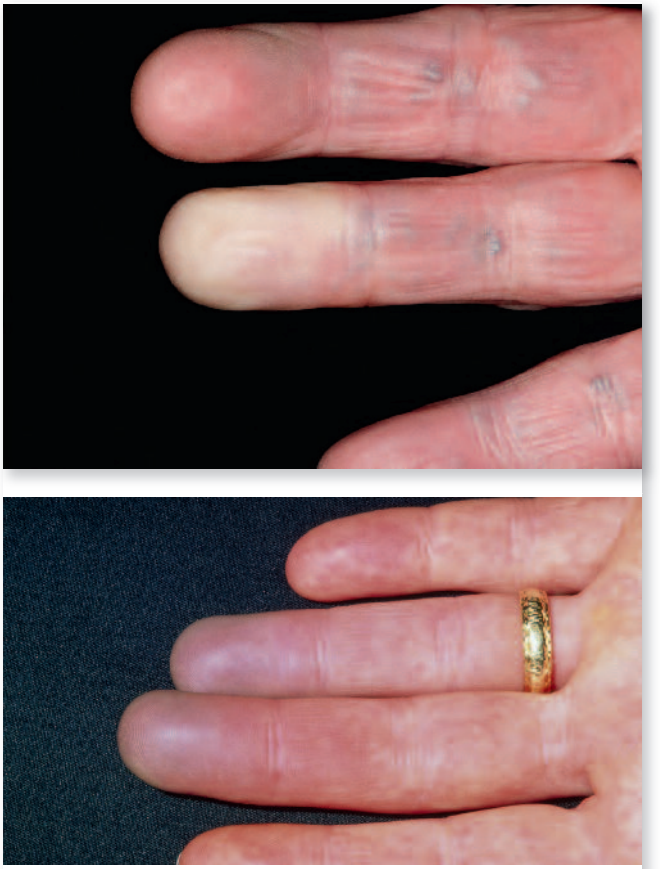
Poor circulation is often encountered in daily practice as an incidental complaint, particularly in colder months. However, cold hands and feet can sometimes herald something more sinister, and it is important to recognise the key features that might suggest an increased risk of circulatory compromise or tissue damage, or the presence of a significant underlying disease.

Dr Sonigra is a Rheumatology/General Medicine Advanced Trainee, and Dr Mitchell is a Rheumatology Resident, both at the Royal Hobart Hospital, Hobart. Dr Jane Zochling is Consultant Rheumatologist and Senior Research Fellow at the Menzies Research Institute, University of Tasmania, Hobart, Tas.

Australian Rheumatology Association

SERIES EDITORS: Dr Jane Zochling, MB BS, FRACP, MMed(ClinEpi), PhD, is a Research Fellow, Menzies Research Institute, University of Tasmania, Hobart, Tas. Professor Lyn March, MB BS, MSc, PhD, FRACP, FAFPHM, is Professor of Medicine at The University of Sydney, Department of Rheumatology at Royal North Shore Hospital, Sydney, NSW.



Figures 1a and b. Raynaud's phenomenon showing the triphasic colour response and clear line of demarcation between the affected and unaffected areas. a (top). Pallor. b (above). Cyanosis and erythema.

Raynaud's phenomenon refers to a progression of colour changes occurring in the fingers and toes, usually triggered by cold exposure. It is caused by episodic vasospasm of the peripheral vessels, resulting in typical white, blue and red colour changes that are often accompanied by pain, numbness, throbbing and tingling. Rarely, there may be ulceration of the fingers and toes. Raynaud's phenomenon is usually seen in the distal digits but may also involve the nose, ears and tongue. The duration of an attack may be less than a minute to hours. It was first described by the French medical student Maurice Raynaud in 1862, as 'episodic, symmetric, acral vasospasm characterized by pallor, cyanosis, suffusion, and a sense of fullness or tautness, which may be painful.'[1]

The phenomenon is characterised by a triphasic colour response with a clear line of demarcation between the affected

and unaffected areas. The three phases are as follows:

- phase 1 – pallor (white), due to vasoconstriction of the small muscular arterioles (Figure 1a)
- phase 2 – cyanosis (blue), due to venous pooling because of slow blood flow and deoxygenation of venous blood (Figure 1b)
- phase 3 – erythema (red), due to rapid arteriole reperfusion and dilation, and often associated with throbbing pain (Figure 1b).

Raynaud's phenomenon can occur as an isolated, benign phenomenon (primary Raynaud's phenomenon, or Raynaud's disease) or in the context of an underlying disease, most commonly an autoimmune disease (secondary Raynaud's phenomenon). Because of the underlying associated disease, secondary Raynaud's phenomenon has greater morbidity and more concerning complications than primary Raynaud's phenomenon. Its sequelae can include ulceration progressing to critical digital ischaemia (Figure 2).

EPIDEMIOLOGY

The age of onset for primary Raynaud's phenomenon is usually in the second or third decade of life. In comparison, secondary Raynaud's phenomenon usually begins alongside the underlying disease.

The prevalence of primary Raynaud's phenomenon varies among different populations, but the condition is typically more common in women, occurring in about 5 to 20% of women and about 4 to 13% of men.[2] Raynaud's phenomenon is more common in people with a first-degree relative with the condition, and more concordant in monozygotic than dizygotic twins, indicating a genetic component. It is also more common in people living in cooler climates.

PATHOPHYSIOLOGY

The full pathophysiology of Raynaud's phenomenon is not yet clearly understood but can be broadly described by three distinct mechanisms: vascular, neural and intravascular abnormalities (see the box on this page). Overactivity of α2C-adrenoreceptors causing cold-induced vasoconstriction of the blood vessels is thought to be the major causative mechanism (these receptors are involved in the regulation of neurotransmitter release from sympathetic nerves).

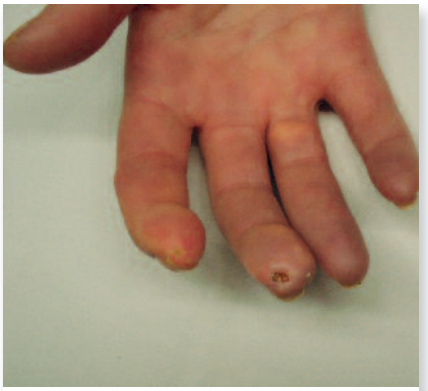


Figure 2. Digital ulcer in a patient with secondary Raynaud's phenomenon.

CLINICAL PRESENTATION

Patients with Raynaud's phenomenon of either type present with pathognomonic colour changes in one or more extremities,

PATHOPHYSIOLOGY OF RAYNAUD'S PHENOMENON

Vascular abnormalities	Neural abnormalities	Intravascular abnormalities
Endothelial dysfunction • Increased vasoconstrictive mediators (endothelin-1, angiotensin II) • Decreased vasodilatory mediators (nitric oxide) • Vasoactive stimuli (angiotensin, vasopressin, transforming growth factor-beta [TGF-beta]) triggering endothelin-1 release • Angiotensin II mediates fibrosis **Structural abnormalities** • Fibrotic proliferation of blood vessels	**Central mechanisms** • Patients with primary Raynaud's phenomenon do not habituate to stressful stimuli in the same way as healthy subjects hence there is cutaneous vasoconstriction in response to stressful stimuli **Impaired vasoconstriction** • Overactivity of α2C-adrenoreceptors, which causes cold-induced vasoconstriction of the blood vessels **Impaired vasodilation** • Reduced levels of calcitonin gene-related peptide, a potent vasodilator • Increased levels of neuropeptide Y, a potent vasoconstrictor	• Increased levels of thromboxane A2, a potent vasoconstrictor • Increased platelet activation and aggregation • Increased oxidative stress by reactive oxygen species • Decreased fibrinolysis has been implicated in patients with systemic sclerosis (scleroderma)

CONDITIONS AND DRUGS ASSOCIATED WITH RAYNAUD'S PHENOMENON (SECONDARY CAUSES)

Autoimmune syndromes
- Scleroderma (Raynaud's phenomenon [RD] present in 95 to 99% of cases)
- Mixed connective tissue disease (RD present in 95% of cases)
- Systemic lupus erythematosus (RD present in 20 to 40% of cases)
- Polymyositis/dermatomyositis (RD present in 10% of cases)
- Sjögren's syndrome (RD present in 33% of cases)
- Undifferentiated connective tissue disease (RD present in 50% of cases)
- Rheumatoid arthritis (RD present in 17% of cases)

Infections
- Hepatitis B and C infections (especially associated with mixed or type 3 cryoglobulinaemia)
- Mycoplasma infections (with cold agglutinins)

Neoplastic syndromes
- Lymphoma
- Leukaemia
- Myeloma
- Waldenström's macroglobulinaemia
- Polycythaemia
- Monoclonal (type 1) cryoglobulinaemia
- Lung adenocarcinoma

Haematological conditions
- Paroxysmal nocturnal haemoglobinuria
- Polycythaemia
- Cryofibrinogenaemia

Drugs
- Oral contraceptives
- Ergot alkaloids
- Bromocriptine
- Beta-adrenergic blocking drugs
- Antineoplastics (e.g. vinca alkaloids, bleomycin, cisplatin)
- Cyclosporin
- Alfa-interferon

which may be accompanied by numbness and pain in affected areas. Pain can be severe, and is considered to be a red flag for possible digital ischaemia.

History

Important aspects of the history in a patient with suspected Raynaud's phenomenon include hypersensitivity to cold or emotional stimuli and an occupational history. The phenomenon has been associated with trauma or frostbite, frequent use of vibrating tools such as jackhammers and sanders (the repetitive action may cause damage to digital arteries or nerves that control the arteries) and exposure to polyvinyl chloride, lead, arsenic or laboratory solvents (including xylene, toluene, acetone and chlorinated solvents). A history of migraine may also be relevant, as migraine and Raynaud's phenomenon both have vasospasm as the causative mechanism.

Medical conditions and drugs associated with secondary Raynaud's phenomenon are listed in the box on this page. It is important to distinguish Raynaud's phenomenon from syndromes that may present with similar symptoms, such as carpal tunnel syndrome or thromboembolic disease (see the box on this page).

Physical examination

A thorough physical examination helps not only in determining the severity of Raynaud's phenomenon but also in identifying features suggestive of secondary Raynaud's phenomenon and underlying associated conditions.

Digital ulcers, sclerodactyly and calcinosis are all important features suggesting underlying systemic sclerosis (scleroderma).

It is important to look for sharp demarcation between affected and unaffected areas to get an idea of circulatory compromise. Hyperaemia behind the ischaemic line is a particular danger sign for a threatened digit. Delayed capillary refill should be looked for. Refill time can be measured by holding a hand higher than heart-level (prevents venous reflux), pressing the soft pad of a finger until it turns white, and taking note of the time needed for the colour to return once pressure is released; normal refill time is less than two seconds.

Nailfold capillaroscopy can help differentiate between primary and secondary Raynaud's phenomenon. In the latter, a normal regular pattern of capillary refill loops is replaced with abnormally large loops. In early scleroderma, these large loops alternate with areas without any capillaries.

Signs suggestive of autoimmune diseases include rash, synovitis, arthritis and livedo reticularis (also present in coagulation disorders). Persistent bone pain may suggest a paraneoplastic syndrome associated with a hyperviscosity syndrome.

ANATOMICAL AND OTHER SYNDROMES MIMICKING RAYNAUD'S PHENOMENON

Anatomical syndromes
- Carpal tunnel syndrome
- Reflex sympathetic dystrophy syndromes
- Thoracic outlet syndrome

Miscellaneous circulatory syndromes
- Atherosclerosis
- Thromboangiitis obliterans (Buerger's disease)
- Vasculitis
- Thromboembolic disease (including cardiac microemboli)
- Subclavian aneurysm

Vasospastic syndromes
- Livedo reticularis
- Acrocyanosis
- Chilblains

DIAGNOSIS

Diagnosing Raynaud's phenomenon can be difficult because signs are not always

CRITERIA FOR DIAGNOSIS OF PRIMARY RAYNAUD'S PHENOMENON[3]

- Symmetrical attacks
- Absence of tissue necrosis, ulceration, or gangrene
- Absence of a secondary cause on the basis of a patient's history and general physical examination
- Normal nail fold capillaries on direct visualisation
- Negative antinuclear antibody testing
- Normal erythrocyte sedimentation rate

Adapted from: LeRoy EC, Medsger TA Jr. Raynaud's phenomenon: a proposal for classification. Clin Exp Rheumatol 1992; 10: 485-488.[3]

present during examination. Although there are several diagnostic criteria, there is no reliable gold standard for the diagnosis of the condition.

Certain clinical criteria can be used to distinguish patients with uncomplicated, or primary, Raynaud's phenomenon from those with secondary Raynaud's phenomenon (see the box on this page).[3] According to most investigators, a history of at least two colour changes (pallor and cyanosis) after cold exposure is necessary for a definite diagnosis.

A patient who meets the criteria for primary Raynaud's phenomenon and has been followed for a two-year period without the development of clinical or laboratory signs, is unlikely to develop secondary disease. However, about one in 10 patients with Raynaud's phenomenon can develop a secondary disorder on follow up, hence the importance of physical examination and clinical review.[4] (Symptoms of Raynaud's phenomenon may be evident years before the symptoms of an associated condition become apparent.)

The historical cold provocation test is not now required in diagnosing Raynaud's phenomenon.

TABLE 2. BASELINE AND SPECIFIC INVESTIGATIONS FOR SUSPECTED SECONDARY CAUSES OF RAYNAUD'S PHENOMENON

Suspected secondary cause	Investigations*
Baseline	Full blood count, urea creatinine and electrolytes, urinalysis, C-reactive protein, erythrocyte sedimentation rate
Autoimmune disorder	Antinuclear antibody
Scleroderma	Anti-centromere, anti-topoisomerase I and anti-RNA polymerase I/III antibodies
Antiphospholipid syndrome; systemic lupus erythematosus	Lupus anticoagulant, cardiolipin antibodies, beta-2 glycoprotein 1 antibodies; anti-double stranded DNA, complement C3 and C4 levels
Polymyositis, dermatomyositis	Creatine kinase
Rheumatoid arthritis	CCP antibody, rheumatoid factor
Cryoglobulinaemia	Hepatitis B and C serology
Mycoplasma infections	Cold agglutinins
Paraproteinaemia	Serum and urine protein electrophoresis

ABBREVIATION: CCP = cyclic citrullinated peptide.
* Investigations should be targeted to the individual case.

INVESTIGATIONS

Investigations in a patient with Raynaud's phenomenon are aimed at ruling out any underlying disease being responsible for the episodic vasospasm. Baseline tests should be performed, and then specific tests for suspected conditions (Table 2). If an underlying condition is suspected, it is important to refer the patient for further work up. This enables the con frmation or exclusion of an associated condition and, if confirmation, its treatment.

Nailfold capillaroscopy, usually performed by rheumatologists, is useful in differentiating primary from secondary Raynaud's phenomenon (Figures 3a and b). This procedure has a 47% positive predictive value and a 93% negative predictive value for eventual development of a secondary disease.[4,5] Enlarged or distorted capillary loops and a relative paucity of loops suggest an underlying connective tissue disease or an increased likelihood of developing one. If the enlargement is associated with loss of capillaries then the patient is more likely to have or develop systemic sclerosis.

Nailfold power Doppler ultrasonography can also detect capillary changes indicative of secondary Raynaud's phenomenon, and has been shown to be more accurate than capillaroscopy.[6] However, this technique is not available outside specialised centres.

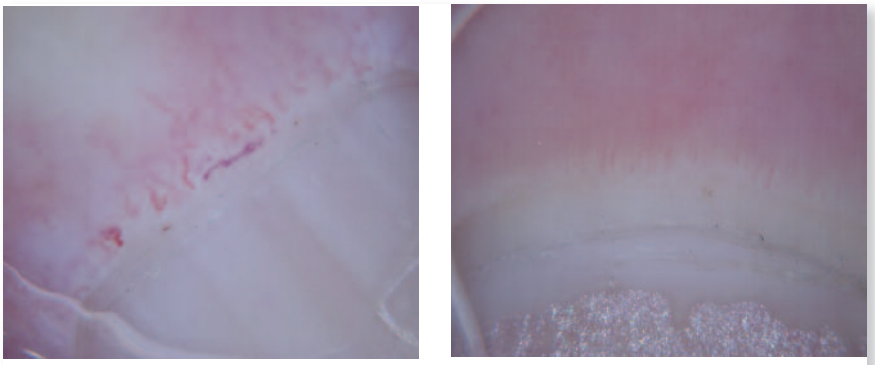
If a thromboembolic disease or vasculitis is suspected as a cause of Raynaud's phenomenon, CT angiography may be performed.

TREATMENT

Options for the management of Raynaud's phenomenon are summarised in Table 3.

Nonpharmacological management

Nonpharmacological management is the mainstay of current treatment of Raynaud's phenomenon. It is important to advise patients to avoid precipitants



Figures 3a and b. Nailfold capillaroscopy. a (left). In a patient with secondary Raynaud's phenomenon, showing capillary dropout. b (right). In a patient without Raynaud's phenomenon, for comparison (normal nailfold capillaroscopy).

such as sudden cold exposure and to minimise general heat loss by wearing thermal underwear and heat-conserving hats, gloves and socks in cold weather. Patients should also be advised to try and terminate an attack by warming the affected body area (e.g. placing their hands in warm water) as soon as they are aware of symptoms.

As mentioned earlier, the main causative mechanism of Raynaud's is thought to be local abnormal activation of the sympathetic nervous system causing vasoconstriction of digital arteries and cutaneous arterioles. Emotional stress and nicotine trigger vasospasm, therefore avoidance of cigarette smoking and stress is of paramount importance. Sympathomimetic drugs such as decongestants and diet pills should be avoided for the same reasons.

Pharmacological treatment

Pharmacological treatment of primary Raynaud's phenomenon is considered when a patient is symptomatic despite adequate nonpharmacological measures. There are several options available, listed below, each to be balanced against potential side effects.[2] In Australia, no drugs are indicated specifically for Raynaud's phenomenon.

- **Calcium channel blockers.** Calcium channel blockers are the drugs of first choice. These vasodilators block calcium channels in vascular smooth muscle, thereby preventing contraction of blood vessels. Nifedipine is the most commonly used medication, starting at a dose of 5 mg three times daily and increasing to 20 mg three times daily. Extended release forms enable easier administration, and include nifedipine starting at 30 mg once daily, amlodipine 5 mg once daily and felodipine 2.5 mg once daily. It is suggested that calcium channel blockers be used over the winter months; in Australia, from mid to late April until September is suggested. Patients should be warned of the common side effects of these medications, including tachycardia/palpitations, dizziness, headache, nausea, flushing and lower limb oedema. Care must be taken in patients who are already borderline hypotensive as any antihypertensive can cause significant postural hypotension. If a calcium channel blocker is ineffective or only partially effective, then other vasoactive drugs can be trialled (added or substituted) but they are generally less effective (see next point).
- **Losartan.** The angiotensin receptor blocker losartan is effective in both primary and scleroderma-associated Raynaud's phenomenon.
- **Fluoxetine.** The selective serotonin reuptake inhibitor fluoxetine has been shown to be effective in one study, and may be better tolerated in patients experiencing side effects of other vasodilators.
- **Topical nitrates.** Topical nitrates have

TABLE 3. MANAGEMENT STRATEGIES FOR RAYNAUD'S PHENOMENON

Strategy	Action/medication*
Nonpharmacological (all patients)	Avoidance of cold temperatures and other triggers Stop smoking Minimise vasoconstrictive medications
Pharmacological (if there is significant disability or a risk of circulatory compromise)	Vasodilators: calcium channel blockers (nifedipine, amlodipine, felodipine); angiotensin receptor blockers (losartan) Selective serotonin reuptake inhibitors (fluoxetine)
For digital ischaemia	Topical glyceryl trinitrate Potent vasodilators (sildenafil, tadalafil, intravenous iloprost, alprostadil) for threatened digits
Surgical (rare)	Sympathectomy Botox (experimental)

* Off-label uses of all drugs mentioned.

been shown to be effective in limited control studies, and are gaining popularity. Suggested doses are 1 cm of glyceryl trinitrate 2% ointment for 12 hours, and half of a low-dose glyceryl trinitrate patch. Topical nitrates can be particularly helpful in the short term, and are best applied to the wrists, where most of the vasospastic dysregulation occurs.

- **Phosphodiesterase type 5 inhibitors.** Phosphodiesterase type 5 inhibitors, including sildenafil and tadalafil, can be considered, especially in patients with severe Raynaud's phenomenon who have not responded to other therapies. However, the cost can be prohibitive.
- **Prostacyclin analogues.** Intravenous prostacyclin analogues (most commonly iloprost but also alprostadil) are used in particularly severe cases where digital integrity is compromised in an emergency situation. However, their use requires hospitalisation and specialist review.

At present there is no evidence favouring the use of antiplatelet agents (dipyridamole or aspirin) or anticoagulants in Raynaud's phenomenon.

Treatment for secondary Raynaud's is directed mainly towards addressing the underlying disorder but includes also all the options for primary Raynaud's phenomenon.

Surgery

Digital sympathectomy may be considered for patients unresponsive to the above measures. Cervical sympathectomy may offer temporary relief but is rarely recommended now due to recurrence of symptoms. Laser therapy and the use of botulinum toxin type A need further evaluation.

COMPLICATIONS

Primary Raynaud's phenomenon rarely causes any complications. In secondary Raynaud's phenomenon, complications are usually associated with the underlying disease and include digital ulcers, loss of tissue pulp, gangrene, superimposed infection and autoamputation.

Management of complications involves pain relief, treating infection if present and the use of oral vasodilators to improve blood flow. Iloprost, an intravenous prostacyclin analogue, is often used as a rescue therapy for threatened digits. Other treatments that may be useful include botulinum toxin type A injections around the affected digital vessel. These are still experimental and not carried out routinely in Australia. Failure of more conservative therapies may warrant surgical intervention with distal digital sympathectomy and arterial reconstruction.

PROGNOSIS

The prognosis of primary Raynaud's disease is very good. The prognosis of secondary Raynaud's, however, is related to the underlying disease and depends on the severity of digital ischaemia and the response to treatment.

SUMMARY

Raynaud's phenomenon is common and variably symptomatic, and is an exaggerated vasoconstrictive response to various stimuli, including cold temperature and emotional stress. The phenomenon is manifested clinically by sharply demarcated colour changes of the skin of the digits. Abnormal vasoconstriction of the digital arteries and cutaneous arterioles due to a local defect in normal vascular responses is thought to underlie the disorder.

The diagnosis of Raynaud's phenomenon is based on history and examination. Patients presenting with symptomatic Raynaud's phenomenon should be assessed for signs and symptoms suggestive of a secondary cause. Those with abnormal investigations or significant ischaemia need timely referral for further work up and treatment. Initial management should include the avoidance of precipitants (cold temperatures, emotional stress and vasoconstrictor drug preparations), the use of warm clothing and the cessation of smoking. Drug treatment needs to be considered if the attacks are poorly controlled and disabling, commencing with calcium channel blockers.

Most patients with Raynaud's phenomenon cope well with simple lifestyle measures to control the symptoms. A high index of suspicion will help to identify those who need more definitive treatment. MT

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FURTHER READING

A list of further reading is included in the pdf version of this article available at www.medicinetoday.com.au.

COMPETING INTERESTS: None.

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