

The Diagnosis and Treatment of Raynaud's Phenomenon

A Practical Approach

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Abstract

Raynaud's phenomenon is a common disorder with vasospasm of the digital arteries causing pallor with cyanosis and/or rubor. It can be primary (idiopathic), where it is not associated with other diseases, or secondary to several diseases or conditions, including connective tissue diseases, such as scleroderma and systemic lupus erythematosus. Raynaud's is often mild enough to not require treatment; however, with secondary Raynaud's there is not only vasospasm but also fixed blood vessel defects so the ischaemia can be more severe. Complications can include digital ulcers and could, rarely, lead to amputation. Treatment is often non-pharmacological including avoiding cold and smoking cessation. Calcium channel antagonists, such as nifedipine, are often considered when treatment is needed; however, adverse effects of these drugs can include hypotension, vasodilatation, peripheral oedema and headaches. Other treatments have been studied in randomised, controlled trials including classes of drugs, such as angiotensin II inhibitors, selective serotonin reuptake inhibitors, phosphodiesterase-5 inhibitors (e.g. sildenafil), nitrates (topical or oral; the latter can be limited by adverse effects, such as flushing, headache and hypotension), and for more serious Raynaud's or its complications prostacyclin agonists may be used. There are two large studies that demonstrate that endothelin receptor blockade with bosentan can reduce the number of new digital ulcers in scleroderma patients. However, it does not affect the healing period.

Thus, Raynaud's is common and often requires non-pharmacological treatment. When secondary Raynaud's is suspected, such as Raynaud's with an older age at onset or other features of connective tissue disease, then an appropriate history, physical examination and laboratory tests may be indicated to reach an appropriate diagnosis. There have been advances in pharmacological treatment, but some of the treatments are limited by adverse effects.

1. Definition of Raynaud's Phenomenon

Raynaud's phenomenon is episodic vasospasm of the peripheral arteries, causing pallor followed by cyanosis and/or erythema. It occurs in 3–5% of the population and can run in families.^[1] It can cause pain and sometimes paraesthesia, and can rarely cause ulceration of the fingers and toes (and in some cases of the ears or nose). Primary or idiopathic Raynaud's (Raynaud's disease) occurs without an underlying disease. Secondary Raynaud's (Raynaud's syndrome) occurs in association with an underlying disease – usually connective tissue disorders, such as scleroderma, systemic lupus erythematosus (SLE), Sjogren's syndrome, rheumatoid arthritis and polymyositis. Secondary Raynaud's may be associated with vasculitis, severe peripheral vascular disease, including Berger's disease, and rarely malignancy or chemotherapy. Vibration trauma, such as in jackhammer operators, may precipitate Raynaud's (there is debate in the literature as to whether this should be considered primary or secondary^[2,3]). This article aims to pro-

vide a practical guide to help physicians develop an approach to the diagnosis and treatment of Raynaud's and its complications in daily practice.

2. Pathophysiological Features

Vasospasm is a normal reaction to cold or temperature change. However, it is exaggerated in primary Raynaud's with increased vasospasm. Many factors are upregulated in patients with primary Raynaud's; and more so in patients with secondary Raynaud's, including calcitonin gene-related product (CGRP), serotonin receptors and endothelin. Genetics can be associated with Raynaud's, but it appears to be polygenic and differs across nationalities.^[4] For example, if someone has primary Raynaud's they may have a family history of primary or secondary Raynaud's. Similarly, someone with secondary Raynaud's may have a family history of connective tissue disease with or without Raynaud's or even a family history of primary Raynaud's (table I).

Table I. Features of primary and secondary Raynaud's phenomenon

Feature	Primary	Secondary
Prevalence	Common (3–5%)	Rare (0.2% approximately)
Associated with other diseases (e.g. CTD)	No	Yes
Associated with strongly positive ANA	No	Often
Associated with dilated capillaries at nailbed	No	Often
Can occur in family history of Raynaud's phenomenon	Yes	Yes
Can occur more frequently in family history of CTD	Yes	Yes
Needs pharmacological intervention	Occasionally	Frequently
Can be associated with complications	No (rarely)	Yes
May become less symptomatic over time	Yes (often)	Occasionally

ANA = antinuclear antibody; **CTD** = connective tissue disease.

Raynaud's can only be diagnosed with an appropriate history. It is normal to go mottled or cyanotic in the cold. Therefore, the history has to include fingertips or tips of the toes that go white (pallor) and are usually well demarcated and, then, upon rewarming can go blue or red or both. Pallor must be present to make the diagnosis. It is not necessary to place a patient's hands in cold water to demonstrate Raynaud's. The pathophysiological aspects of Raynaud's and current thinking in this area are more thoroughly described by Boin and Wigley.^[5]

3. Differences Between Primary and Secondary Raynaud's Phenomenon

As stated in section 1, primary or idiopathic Raynaud's is not associated with a concomitant disease. However, secondary Raynaud's may predate a connective tissue disease, such as limited systemic sclerosis, by several years or may occur around the same time as the onset of diffuse sclerosis or polymyositis. It can occur anytime in a patient with rheumatoid arthritis, SLE or Sjogren's syndrome, and is often an early feature of many connective tissue diseases. Secondary Raynaud's has abnormal vasospasm, but also has more pronounced abnormalities of the blood vessel endothelium, such as CGRP, endothelin and vascular endothelial growth factor.^[6] In connective tissue disease, the most severe Raynaud's is associated with sclerosis where the blood vessels are in spasm, but are also abnormal with significant intimal proliferation and sometimes extremely limited blood flow even without vasospasm being a permanent feature. In conditions with medium vessel vasculitis, such as polyarteritis nodosa and occasionally SLE, there may be significant gangrene of the fingertip or entire finger. The history and physical examination should give triggers for suspicion of secondary Raynaud's (later-age onset and/or association of connective tissue disease symptoms). Findings on physical examination include inflammatory arthritis, telangiectasia,

photosensitive rash and/or the presence of dilated capillaries seen at the nailbeds (just proximal to the base of the nails). It is important to determine if there is an underlying disease where the diagnosis might aid in appropriate medical care.

Treatment is often not necessary in primary Raynaud's and may or may not be necessary in secondary Raynaud's. For example, many patients with SLE, Sjogren's syndrome, rheumatoid arthritis or polymyositis might not require treatment for Raynaud's or may use only as-needed (occasional) calcium channel antagonist treatment. However, Raynaud's is more likely to require treatment in patients with sclerosis.

Complications in primary Raynaud's are extremely rare. In secondary Raynaud's, particularly sclerosis, complications can include digital ulcers, digital pits (fibrotic plugs from ischaemia), digital tuft resorption, threatened ischaemic digit, infection including osteomyelitis and the requirement of surgical amputation, or, indeed, autoamputation may occur. The location of ischaemic digital ulcers is on the tips, whereas traumatic ulcers (particularly in sclerosis) are often on the extensor surfaces of the fingers at areas that bend with little subcutaneous tissue, such as the extensor surfaces of the proximal interphalangeal joints. Vasodilator therapy is not appropriate for treating traumatic ulcers. Instead, treatment should focus on protecting the digits from further trauma and treating superimposed infection, if and when it occurs, as well as analgesia as needed.

Raynaud's certainly may fluctuate in patients with both primary and secondary types. Many patients report it more at seasonal changes, such as spring and autumn (fall), as the absolute daily change in temperature, and cold, wet days may affect them more. In addition, patients who put their hands in freezers, who attend places with significant air conditioning or who go swimming may also precipitate attacks with these actions. In addition,

there are some drugs that increase vasospasm, such as ergotamine.

Raynaud's is more common in the hands than in the feet. It can occur in the fingertip; proximally including an entire finger or even, rarely, a hand, wrist or forearm. Raynaud's can also include digital artery spasm on one side of the finger and not the other, which results in Raynaud's just on one side of the finger. The toes may be less involved because environmentally they are more protected (warmer) as we tend to wear shoes most of the year. Complications are more common in the hands than the feet, probably again because of more cold, but also more local trauma.

4. Patient Assessment

When assessing a patient, it is important to determine if a patient has an associated disease with Raynaud's as one of its manifestations. It is more common to have primary Raynaud's (3–5% of the population) than to have Raynaud's associated with a connective tissue disease. The likelihood of an associated connective tissue disease increases with new-onset Raynaud's at age >40 years, the presence of a strongly positive antinuclear antibody (ANA) test and/or the presence of visible dilated capillaries at the nailbeds.^[7] The dilated capillaries occur from dropout of capillaries with secondary hyperplasia and hypertrophy of the remaining blood vessels. Therefore, they become visible and can look like palisades or red pen marks, and are most often seen at the cuticle.

The workup of the patient should include:

1. A history compatible with Raynaud's.
2. A history to determine the frequency and severity of the attacks.
3. Smoking history.
4. A history of present illness and review of systems to rule out secondary causes, such as connective tissue disease, which could include inflammatory arthritis, morning stiffness, rash, photosensitivity,

alopecia, significant dry eyes/dry mouth, puffiness of fingers or tightness of the skin, significant oesophageal dysmotility or gastroesophageal reflux disease, etc.

5. Family history of Raynaud's and connective tissue disease such as rheumatoid arthritis, SLE, scleroderma, Sjogren's syndrome, polymyositis and juvenile rheumatoid arthritis. For other causes of secondary Raynaud's it may be obvious such as a malignancy with weight loss or a chemotherapeutic exposure or severe peripheral vascular disease.

6. A physical examination should include an overview of general health and blood pressure, looking for signs of connective tissue disease or peripheral vascular disease (such as livedo reticularis, which could occur in either condition). Magnification such as using an otoscope or ophthalmoscope can be used to study the nailbeds of the fingers.

If a patient is in his or her teens or younger and has no other complaints, the author would probably not do a further workup beyond the history and physical examination. However, if the patient has new-onset Raynaud's at an older age, such as >40 years, or has some features on history or physical examination that create concern about secondary causes, then an ANA with its titre and pattern, complete blood count (CBC), erythrocyte sedimentation rate (ESR), creatinine and urinalysis can be performed. This would be a screen looking, in particular, for connective tissue disease. It may be appropriate for patients in their 20s and 30s (if they develop new-onset Raynaud's) to consider the possibility of connective tissue disease. One can magnify with a dermatoscope, otoscope or ophthalmoscope the nailfolds just beyond the nails and could consider an abbreviated workup of the patient such as CBC, ESR, ANA and possibly anti-extractable nuclear antigens (ENA).^[8]

The prevalence of Raynaud's varies in different connective tissue diseases (table II). The natural

Table II. Prevalence of Raynaud's phenomenon in the general population and those with connective tissue diseases

	Disease prevalence (%)	Percentage with Raynaud's
General population		3–5
Disease		
rheumatoid arthritis	0.8	20
systemic lupus erythematosus	0.1	30
Sjogren's syndrome	0.09	13
scleroderma	0.02	90

history of idiopathic Raynaud's is to wax and wane and improve in many patients over the next 5 years.

If someone has a strongly positive ANA, the presence of dilated capillaries at the nailbed, an uncommon ANA pattern, such as an anti-centromere pattern or, less predictive, an elevated ESR, then the patient should be followed as in some studies up to 30% will develop a connective tissue disease within the next 5 years and, in particular, scleroderma, especially if there is an anti-centromere antibody and/or dilated capillaries at the periungual region.^[7]

5. Treatment

Many patients do not require treatment but they all require education about staying warm and avoiding smoking. There are no randomised controlled trials (RCTs) of smoking cessation in Raynaud's, but there are vasoconstrictive substances in cigarettes and their smoke that are likely to worsen Raynaud's. In addition, there can be confounding with atherosclerosis in smokers (in the older population) and cigarette smoke is likely to adversely affect the upregulation of factors already occurring in Raynaud's. One sub-analysis within an RCT has suggested that those with digital ulcers from Raynaud's are less likely to heal if they are smokers.^[9] This also has been consistent with clinical observations.

Medications that worsen vasospasm should be avoided if possible. It has been thought that β -

adrenoceptor antagonists (β -blockers) may worsen Raynaud's;^[10] however, an RCT of calcium channel antagonists given in conjunction with β -blockers shows that when combined they may decrease vasospasm.^[11] This effect may possibly have a similar mechanism as to what is seen in β -blocker use for migraine prevention.

The majority of patients with primary Raynaud's will not need pharmacological treatment, but if they do, calcium channel antagonists are usually used. The dihydropyridine calcium channel antagonists are the most studied, particularly long or short acting nifedipine or nicardipine. The usual benefit is approximately a 30% reduction in frequency of attacks. Most RCTs showed no improvement in severity of attacks, but the doses used were quite low.^[12] If calcium channel antagonists are used, they can certainly be prescribed on an as-needed basis, such as in cold weather or when someone is participating in outdoor winter activities. Adverse effects of calcium channel antagonists include hypotension, flushing, dizziness and peripheral oedema due to peripheral vasodilatation (see figure 1 for drug doses). Note that the doses suggested are starting doses, but if patients tolerate the dose (lack of symptoms of hypotension) the dose can be increased. It is the author's opinion that a higher dose of many of the calcium channel antagonists may be more effective than lower doses in many patients, but this is based on clinical experience and no RCTs using large doses have been systematically studied by meta-analysis.

If calcium channel antagonists are not tolerated or ineffective, even with increasing the dose or switching to another calcium channel antagonist, then other medications can be tried. There are positive trials in the literature including angiotensin II inhibitors (losartan),^[13] selective serotonin reuptake inhibitors (fluoxetine),^[14] ACE inhibitors in primary Raynaud's (captopril)^[15] and α -blockers.^[10] The problem with many older treatments (α -blockers

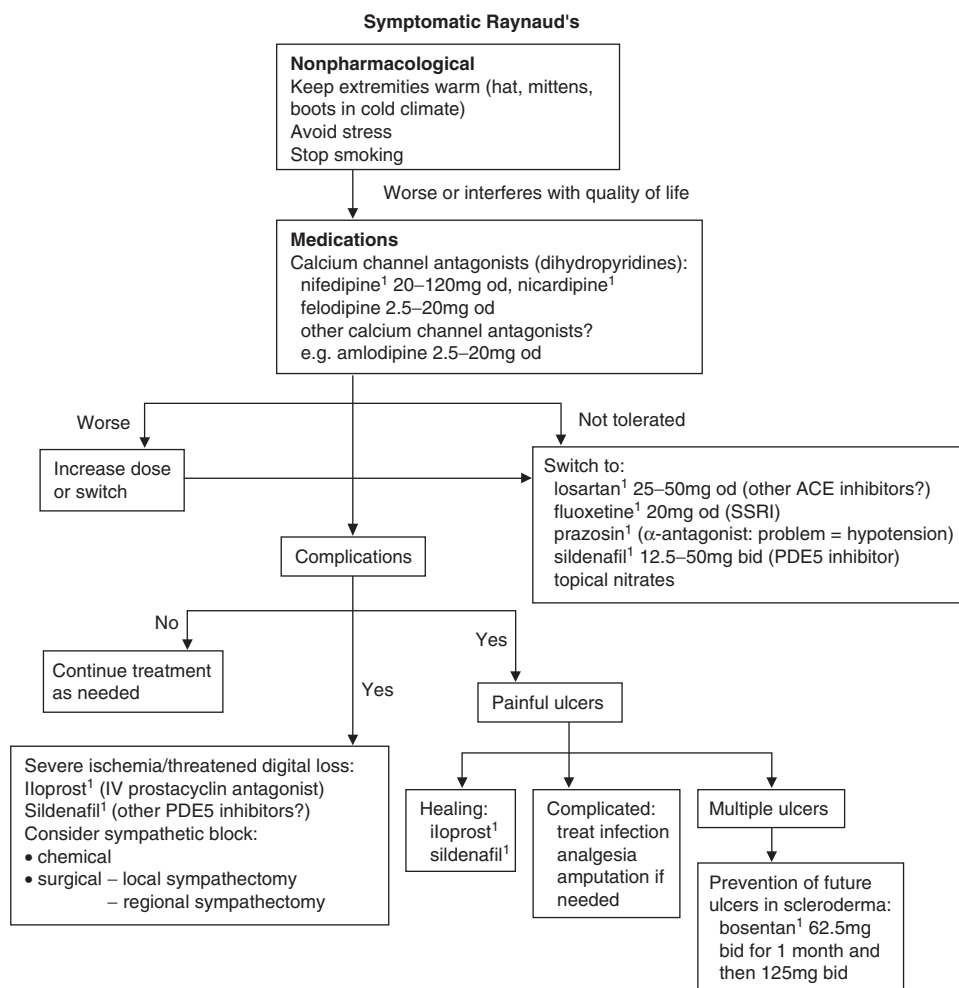


Fig. 1. Treatment algorithm for Raynaud's phenomenon. **bid** = twice daily; **IV** = intravenous; **od** = once daily; **PDE5** = phosphodiesterase 5; **SSRI** = selective serotonin reuptake inhibitor. **1** = randomised, controlled trial evidence exists.

such as prazosin, ganglion blockers such as guanethidine or reserpine) is that they are indeed effective in Raynaud's, but often cause significant hypotension including postural hypotension. Many patients with Raynaud's already have baseline low blood pressures (as those with idiopathic Raynaud's are often young and otherwise healthy) so their use is infrequent.

There are RCTs of topical nitrates that vasodilate blood vessels and can be effective in the treatment of Raynaud's. They have been found to decrease the

frequency and severity of attacks in primary and secondary Raynaud's and may improve digital ulcers.^[16,17] Oral, transdermal or topical nitrates may cause adverse effects, such as headaches, which can limit their use.

There is one published trial of sildenafil used in severe Raynaud's, particularly associated with scleroderma.^[18] The trial was positive in decreasing the frequency and severity of Raynaud's attacks. In addition, it was noted that sildenafil had a higher

chance of healing digital ulcers than placebo, but that was not a primary outcome of the study.

Complementary and alternative medicines are frequently used in the treatment of chronic conditions; Raynaud's is no exception. Certain herbal products, as well as devices, have been studied for Raynaud's specifically. Fish oil and evening primrose have been investigated in double-blinded, placebo-controlled studies because they are precursors to prostaglandins. Fish oil has shown an increase in digital systolic pressure and an increase in the time to onset of symptoms after exposure to cold in patients with primary and secondary Raynaud's ($n = 32$).^[19] In a small study (21 patients), evening primrose showed a decrease in the frequency of Raynaud's attacks.^[20] A reduction in the number of events per week was seen in a trial of *Ginkgo biloba* in a population with primary Raynaud's.^[21] Other non-pharmacological therapies were also assessed and showed positive effects. Acupuncture ($n = 33$, primary Raynaud's),^[22] low-level laser therapy ($n = 47$, primary and secondary Raynaud's)^[23] and ceramic impregnated gloves ($n = 93$, secondary Raynaud's)^[24] were studied in blinded, placebo-controlled trials and found to be beneficial. The mechanism of action is not always fully understood and occasionally some outcomes associated with the effects are inconclusive; however, there was a positive effect on symptoms in all of the aforementioned trials. The use of tested complementary and alternative medicines may be an alternative to traditional treatment in patients who experience adverse effects of pharmaceuticals or those reticent to using conventional treatment. However, in general, only one trial has been done and not replicated. Thus, bias could be introduced and reproducibility has not been proven. Caution is needed to interpret these results as they have not been replicated in other RCTs.

Complications, even in secondary Raynaud's, fortunately are rare. Digital ulcers can occur in 30–50% of patients with scleroderma and fingertip

ulcers occur at any one point in time in scleroderma with a prevalence of 17%.^[25] They increase with disease duration, probably due to worsening obliterative vasculopathy. There are two RCTs in the literature suggesting digital ulcer healing in scleroderma (one using iloprost, an intravenous epoprostenol [prostacyclin] and one using sildenafil),^[18,26] Digital ulcers can rarely be complicated by local infection or even osteomyelitis. They are painful and often require significant analgesia and occasionally require amputation. If someone has a digital ulcer with scleroderma, there is only a 60% chance of healing by 6 months. There is a 1–2% chance of requiring amputation with digital ulcers in scleroderma.^[27,28]

Inhaled prostacyclin agonists are not commonly used for Raynaud's; however, in the UK they are being used at times for pulmonary arterial hypertension in connective tissue diseases, such as scleroderma, and can indeed improve Raynaud's symptoms. However, the main trials have been conducted with: (i) oral prostacyclin agonists, which are usually not stable and/or well absorbed and, therefore, not very effective; and (ii) intravenous prostacyclin agonists, such as iloprost, for which there is a lot of clinical trial data in Raynaud's that is severe and secondary to scleroderma, including the aforementioned study.^[26]

One drug has been studied in two RCTs for the prevention of digital ulcers.^[29,30] Bosentan is an endothelin receptor blocker and yields the highest prevention of new ulcers in patients with multiple (e.g. ≥ 3) digital ulcers at presentation; however, it does not increase healing of current ulcers. Patients with ulcers can have loss of digital pulp, which causes pain, especially when performing fingertip activities, such as typing on a keyboard and doing up buttons. Endothelin is upregulated in the digital arteries and finger pulp in scleroderma.

Some patients with connective tissue disease or vasculitis can present at some point in time with severe ischaemia with threatened digital loss. Treat-

ment of these patients could include intravenous iloprost, phosphodiesterase-5 inhibition (which has not been specifically studied in RCTs for this indication, but there are case reports that sildenafil is helpful) or other intravenous prostacyclin agonists such as epoprostenol or the subcutaneous prostacyclin agonist treprostinil. In patients with significant Raynaud's or risk of threatened ischaemic digit, sympathetic blocks can be done, such as stellate ganglion blocks or lumbar sympathetic blocks with guanethidine or surgical blocks such as a local or regional sympathectomy (see figure 1).

6. Conclusion

Primary or idiopathic Raynaud's is common and is more of a nuisance than something that would be predicted to require pharmacological therapy or develop complications. Secondary Raynaud's is often more severe and the treatment response in these patients may be blunted. It still can have a spectrum of disease from being uncomfortable to having a major impact on quality of life and, rarely, complications. It is important to complete a history and physical examination to rule out secondary Raynaud's when a patient presents with Raynaud's and to perform bloodwork where appropriate looking for connective tissue disease. The most predictive abnormalities in someone with current Raynaud's who may go on to have secondary Raynaud's include strongly positive ANA, presence of superficial dilated capillaries in the periungual area and, although they may be associated with an elevated risk, there are less predictive risks such as an elevated ESR (which is nonspecific) or even a slightly positive ANA. Whether Raynaud's is primary or secondary it is important to counsel about smoking cessation.

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