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Raynaud's Phenomenon

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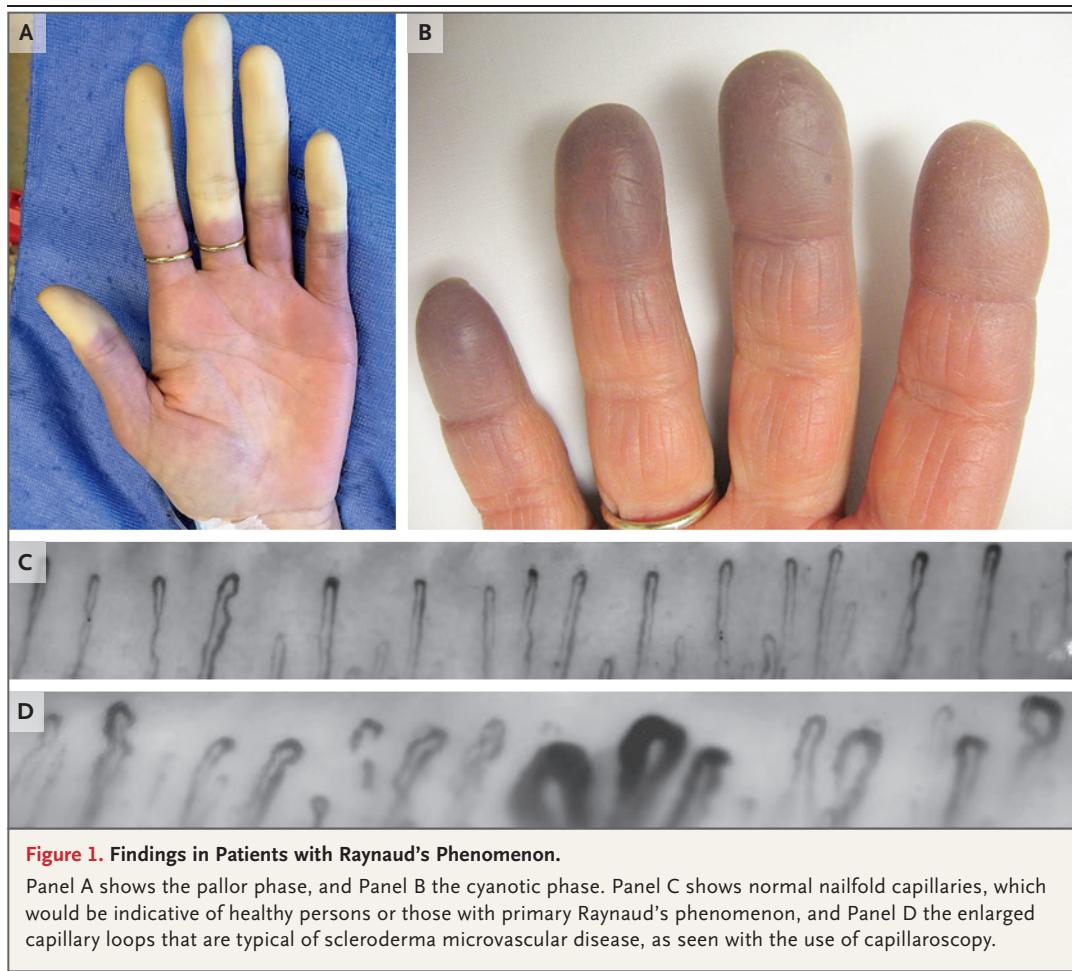
IN HIS 1862 THESIS, MAURICE RAYNAUD DESCRIBES THE CONDITION AFflicting a 26-year-old female patient: "Under the influence of a very moderate cold . . . she sees her fingers become ex-sanguine, completely insensible, and of a whitish yellow color. This phenomenon happens often without reason, lasts a variable time, and terminates by a period of very painful reaction, during which the circulation is re-established little by little and recurs to the normal state."[1] The term "Raynaud's disease" was used to describe these vascular events until Hutchinson, who argued that multiple etiologic factors could be responsible, introduced the concept of "Raynaud's phenomenon."[2] Although results vary according to sex, local environmental climate,[3] and work exposures,[4] most population-based surveys estimate the prevalence of the disorder in the general population at 3 to 5%.[5] We currently classify patients into two groups: those with primary Raynaud's phenomenon, which is diagnosed when no underlying disease is found; and those with secondary Raynaud's phenomenon, which is diagnosed when there is associated disease. This review provides an update on new insights into the mechanism and pathogenesis of Raynaud's phenomenon and on current approaches to the management of this disorder.[6]

DIAGNOSIS AND CLINICAL FEATURES

Although laboratory testing provides important information about the hemodynamic and physiological features of Raynaud's phenomenon, clinical assessment by means of history or direct observation remains the best approach for diagnosis. Most experts agree that at least biphasic (white [pallor] and blue [cyanosis]) change in the skin color of the digits is needed (Fig. 1).[7,8] A major challenge in managing this disorder is determining the cause (Fig. 2) as well as the potential for serious complications and deterioration in quality of life.
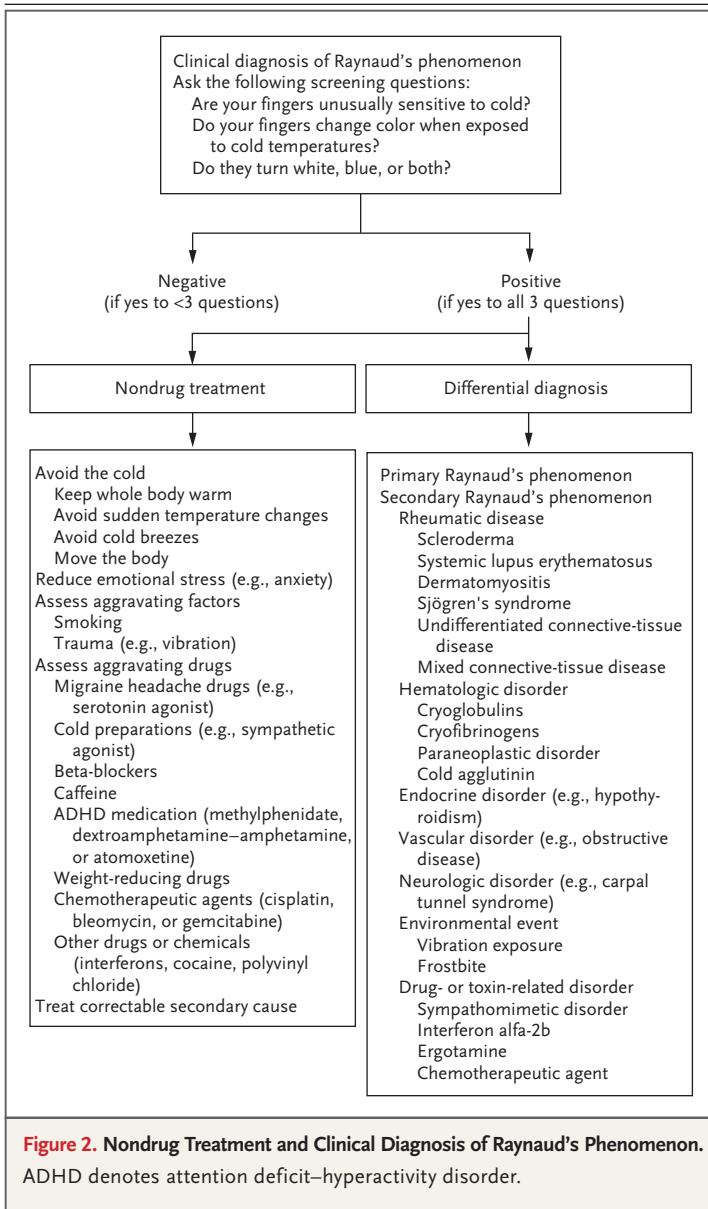
In primary Raynaud's phenomenon, patients have a younger age at onset (usually between 15 and 30 years) than do those with secondary Raynaud's phenomenon, the thumb is generally spared,[9] and there is no evidence of a secondary cause, peripheral vascular disease, digital ischemic injury, or abnormal nailfold capillaries (Fig. 1). In the past, proposed criteria required a normal erythrocyte sedimentation rate in order to confirm a diagnosis of primary Raynaud's phenomenon. An international panel has now recommended that a normal erythrocyte sedimentation rate is no longer required in order to distinguish primary from secondary forms of Raynaud's phenomenon and noted that a negative or low-titer antinuclear antibody may also be present (≤1:40 by indirect immunofluorescence).[8] Surveys show that approximately 30 to 50% of patients with primary Raynaud's phenomenon have a first-degree relative with the condition, which suggests a yet-to-be-defined genetic susceptibility.[10]

Figure 1. Findings in Patients with Raynaud's Phenomenon.

Panel A shows the pallor phase, and Panel B the cyanotic phase. Panel C shows normal nailfold capillaries, which would be indicative of healthy persons or those with primary Raynaud's phenomenon, and Panel D the enlarged capillary loops that are typical of scleroderma microvascular disease, as seen with the use of capillaroscopy.

Patients who initially present with Raynaud's phenomenon and then have progression to an underlying secondary disease generally have a connective-tissue disease, commonly systemic sclerosis (scleroderma). One study showed that 37.2% of 3029 persons who were thought to have primary Raynaud's phenomenon subsequently had a connective-tissue disease.[11]

Raynaud's phenomenon is included in the 2013 American College of Rheumatology–European League against Rheumatism classification criteria for scleroderma, which helps to identify patients with subtle expressions of the disease.[12] Recent studies have emphasized that factors such as the onset of Raynaud's phenomenon near the age of 40 years, severe frequent events, and the presence of abnormal nailfold capillaries (Fig. 1) can help predict whether a connective-tissue disease will develop[11] and are especially helpful in identifying early scleroderma.[13] A survey that followed 299 patients with primary Raynaud's phenomenon for a median of 4 years showed that if capillaroscopy reveals normal nailfold capillaries and if all tests for scleroderma-specific antibodies are negative, then the chance that scleroderma will develop is less than 2%.[14] Scleroderma-type or nonspecific abnormalities in nailfolds (i.e., nailfolds that are tortuous or enlarged or that include hemorrhages or capillary loss) can be seen in patients with other rheumatic diseases such as dermatomyositis, systemic lupus erythematous, Sjögren's syndrome, mixed connective-tissue disease, or undifferentiated connective-tissue disease. Capillaroscopy is a useful addition to the clinical examination for distinguishing patients with a connective-tissue disease from those with primary Raynaud's phenomenon.[15]

Clinical diagnosis of Raynaud's phenomenon
Ask the following screening questions:
  Are your fingers unusually sensitive to cold?
  Do your fingers change color when exposed
    to cold temperatures?
  Do they turn white, blue, or both?

Negative
(if yes to <3 questions)

Positive
(if yes to all 3 questions)

Nondrug treatment

Differential diagnosis

Avoid the cold
  Keep whole body warm
  Avoid sudden temperature changes
  Avoid cold breezes
  Move the body
Reduce emotional stress (e.g., anxiety)
Assess aggravating factors
  Smoking
  Trauma (e.g., vibration)
Assess aggravating drugs
  Migraine headache drugs (e.g.,
    serotonin agonist)
  Cold preparations (e.g., sympathetic
    agonist)
  Beta-blockers
  Caffeine
  ADHD medication (methylphenidate,
    dextroamphetamine–amphetamine,
    or atomoxetine)
  Weight-reducing drugs
  Chemotherapeutic agents (cisplatin,
    bleomycin, or gemcitabine)
  Other drugs or chemicals
    (interferons, cocaine, polyvinyl
    chloride)
Treat correctable secondary cause

Primary Raynaud's phenomenon
Secondary Raynaud's phenomenon
  Rheumatic disease
    Scleroderma
    Systemic lupus erythematosus
    Dermatomyositis
    Sjögren's syndrome
    Undifferentiated connective-tissue
      disease
    Mixed connective-tissue disease
  Hematologic disorder
    Cryoglobulins
    Cryofibrinogens
    Paraneoplastic disorder
    Cold agglutinin
  Endocrine disorder (e.g., hypothy-
    roidism)
  Vascular disorder (e.g., obstructive
    disease)
  Neurologic disorder (e.g., carpal
    tunnel syndrome)
  Environmental event
    Vibration exposure
    Frostbite
  Drug- or toxin-related disorder
    Sympathomimetic disorder
    Interferon alfa-2b
    Ergotamine
    Chemotherapeutic agent

Figure 2. Nondrug Treatment and Clinical Diagnosis of Raynaud's Phenomenon.
ADHD denotes attention deficit–hyperactivity disorder.

PATHOGENESIS

Raynaud's phenomenon is highly localized and affects the arterial inflow of specific skin areas such as fingers, toes, and tips of the nose and ears. These sites are distinct from other skin areas in that they have specialized structural and functional features for thermoregulation.[16] They have a high density of arteriovenous anastomoses, which bypass capillaries and provide direct connections between arterioles and venules. Arteriovenous anastomoses therefore do not contribute to capillary blood flow, which provides essential nutritional support to the skin, but instead function as thermoregulatory structures.[16,17] During exposure to cold, arteriovenous anastomoses remain predominantly closed, whereas they are fully dilated during the elimination of heat. Cold-induced cutaneous vasoconstriction is mediated by a reflex increase in sympathetic constrictor nerve activity and local cold-induced amplification of the sympathetic response.[16]

Arteriovenous anastomoses are richly innervated by sympathetic nerves and are normally exposed to increased sympathetic vasoconstriction under resting thermoneutral conditions and when sympathetic activity is increased during stress or exposure to cold.[16,17] Although such vasoconstriction can cause large fluctuations in total blood flow, capillary blood flow in the skin is normally resistant to sympathetic vasoconstriction.[16] In persons with Raynaud's phenomenon, the already-heightened sympathetic vasoconstriction in these specialized areas is further amplified in intensity and scope: exposure to cold can evoke intense sympathetic-mediated vasoconstriction throughout this vascular network, including upstream arteries, which undergo vasospasm, arteriovenous anastomoses, and arterioles providing nutritional support to the skin.[16]

There are important differences between primary Raynaud's phenomenon and secondary forms of Raynaud's phenomenon, such as scleroderma. Although nutritional flow is normally protected from cold-induced sympathetic vasoconstriction, this protection is mildly impaired in patients with primary Raynaud's phenomenon and is severely interrupted in those with scleroderma, resulting in sympathetic-mediated disruption of nutritional capillary blood flow.[16] This difference in response probably reflects the presence of endothelial dysfunction in patients with scleroderma but not in those with primary Raynaud's phenomenon.[16]

Dysfunctional endothelial cells have reduced activity of vasodilators, nitric oxide, and prostacyclin and can express increased thrombotic and inflammatory activity, including the increased release of the vasoconstrictor endothelin-1.[16] The maintenance of nutritional capillary blood flow is normally ensured by the conduction of vasodilatation to upstream vessels that results from flow-mediated activation of the endothelium.[16] Impairment of this protective mechanism, combined with structural limitations of the vascular

supply in patients with scleroderma, probably contributes to compromised nutritional blood flow in patients with this disease, leading to tissue injury and ulcerations.[16]

The normal targeting of these specialized sites by the sympathetic system and the further amplification that occurs in patients with Raynaud's phenomenon are mediated by the activation of smooth-muscle α_2-adrenoceptors.[16,17] Vasoconstriction that is mediated by α_2-adrenoceptors is markedly increased at reduced temperatures, which enables local cold-induced potentiation (amplification) of sympathetic vasoconstriction.[16] The characteristic pallor that is observed in patients with attacks of Raynaud's phenomenon reflects the intense constriction of arterial inflow and arteriovenous anastomoses, combined with the mobilization of venous blood, whereas other color changes (bluing or reddening) can reflect distinct vasomotor changes occurring in arteries, veins, and arteriovenous anastomoses.[16]

GENERAL APPROACHES TO MANAGEMENT

Many persons with Raynaud's phenomenon do not seek medical advice because the events are not severe, have little effect on their quality of life, and can improve with time,[18] which may reflect lifestyle modifications such as the avoidance of cold[19] and stress management. A survey involving 443 persons with self-reported Raynaud's phenomenon showed that 64% had poor ability to control their attacks and only 16% believed that one current medication was effective.[20] As expected, the survey showed that quality of life was more affected in patients with secondary Raynaud's phenomenon than in those with primary Raynaud's phenomenon. There is little evidence to support the use of various complementary forms of therapy, including biofeedback, acupuncture, laser therapy, and herbal agents.[21]

The avoidance of cold remains the most effective therapy for any cause of Raynaud's phenomenon and is a key component in the successful management of the disorder in all patients. Cold avoidance should not be considered to be a passive approach. Systemic and local warming are highly effective at increasing blood flow in the skin.[16,17] Systemic warming is best accomplished by keeping the whole body warm with layered clothing, gloves, and head covering; avoiding rapidly shifting temperatures, such as rushing into an air-conditioned area; and avoiding cold and breezy conditions. Local hand warming with gloves and rubbing the hands in warm water or with chemical warmers can help prevent an attack or speed recovery. A typical attack lasts 15 to 20 minutes after rewarming.

Effective education and clear explanation of a planned approach reduce anxiety and provide reassurance, which can help alleviate the severity of the disorder. A variety of factors can potentially aggravate the disorder and should be avoided, including smoking and the use of sympathomimetic drugs, agents for the treatment of attention deficit–hyperactivity disorder, and agents for the treatment of migraine headaches.[6] Although estrogen, caffeine, and nonselective beta-blockers are often listed as aggravating factors, the evidence is not solid that they need to be avoided.[6]

CURRENT APPROACHES TO DRUG THERAPY

Evidence from clinical trials is still needed to provide solid guidelines. There is little doubt that effective cold avoidance and stress reduction constitute the foundation of any treatment program for Raynaud's phenomenon. This approach alone treats the majority of patients who present with primary Raynaud's phenomenon and is also a major factor in treating patients with secondary Raynaud's phenomenon.

Drug therapy is initiated when nonpharmacologic approaches are ineffective in reducing the severity of vasospastic attacks and improving quality of life. Reviews of agents that have been used to treat primary Raynaud's phenomenon[22,23] point out that few high-quality clinical trials have been conducted, in part owing to the variability of the events, a high placebo effect, and the lack of a standard outcome measure.[24] In patients with secondary Raynaud's phenomenon, current evidence supports the use of a calcium-channel blocker or synthetic prostacyclin analogue (iloprost), but solid evidence is lacking for other agents.[25,26] Despite the lack of robust evidence from clinical trials, several agents are used in practice. This practical approach to the management of the disorder is based on published information, expert opinion, and current practices (Fig. 3 and Table 1).

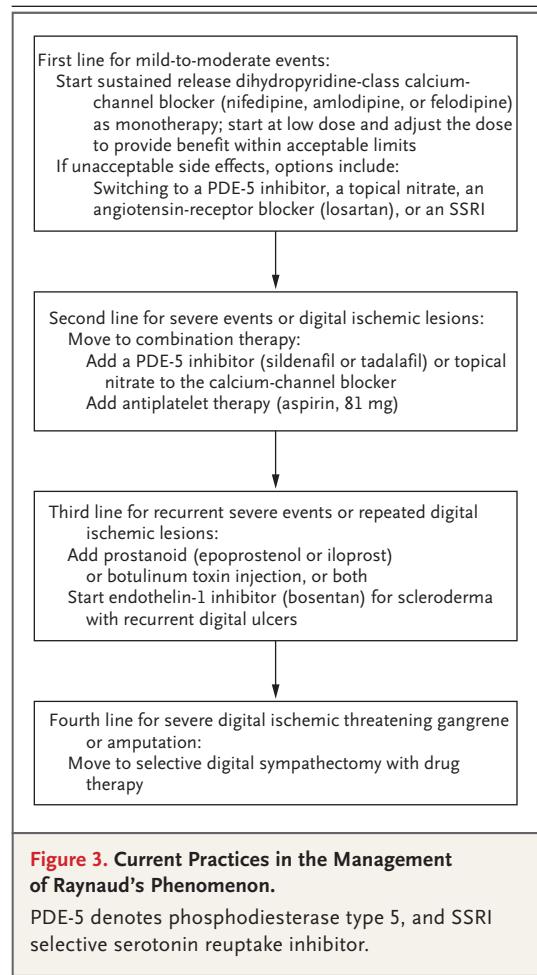**Table 1. Drug Treatment of Raynaud's Phenomenon.***

Agent	Dose
Calcium-channel blocker	
Nifedipine	10–30 mg 3 times daily orally
Sustained-release nifedipine	30–120 mg daily orally
Amlodipine	5–20 mg daily orally
Felodipine	2.5–10.0 mg twice daily orally
Isradipine	2.5–5.0 mg twice daily orally
Diltiazem†	30–120 mg 3 times daily orally
Sustained-release diltiazem†	120–300 mg daily orally
Phosphodiesterase-5 inhibitor	
Sildenafil	20 mg 3 times daily or 50 mg twice daily
Tadalafil	20 mg every other day
Vardenafil	10 mg twice daily
Sympatholytic agent: prazosin	1–5 mg twice daily
Angiotensin II–receptor type 1 antagonist: losartan	25–100 mg daily orally
Selective serotonin reuptake inhibitor: fluoxetine	20–40 mg daily orally
Vasodilator: nitroglycerin	$1/4$–$1/2$ in. of 2% ointment applied topically daily
Other vasoactive drug	
Pentoxifylline	400 mg 3 times daily orally
Botulinum toxin	50–100 units per hand
Prostaglandin	
Epoprostenol‡	0.5–6.0 ng per kilogram per min intravenously for 6 to 24 hr for 2 to 5 days
Iloprost§	0.5–2.0 ng per kilogram per min intravenously for 6 to 24 hr for 2 to 5 days

* Adapted from Wigley.[27]
† Diltiazem is not as effective as the dihydropyridine class of calcium-channel blockers.[22]
‡ The Food and Drug Administration has approved the use of epoprostenol for the treatment of pulmonary hypertension.
§ Iloprost is not available in the United States.

Figure 3. Current Practices in the Management of Raynaud's Phenomenon.

PDE-5 denotes phosphodiesterase type 5, and SSRI selective serotonin reuptake inhibitor.

Currently, a popular clinical practice is to use a long-acting dihydropyridine calcium-channel blocker as monotherapy, adjusted to the maximally effective dose with the fewest side effects (Figs. 3 and 4). A 2005 meta-analysis of randomized trials involving 361 patients with primary Raynaud's phenomenon showed benefit with the use of calcium-channel blockers, with a reduction in the frequency of attacks by an average of 2.8 to 5 attacks per week.[28] A recent Cochrane review[29] provided moderate-quality evidence that oral calcium-channel blockers are minimally effective in the treatment of primary Raynaud's phenomenon as measured by the frequency of attacks; there were 1.72 fewer attacks per week (95% confidence interval [CI], 0.60 to 2.84) with a calcium-channel blocker than with placebo. A 2001 meta-analysis of randomized trials involving patients with scleroderma and Raynaud's phenomenon supported the view that these drugs are moderately effective in patients with secondary Raynaud's phenomenon.[26] The frequency of attacks was lower with calcium-channel blockers than with placebo over a period of 2 weeks (weighted mean difference, −8.3 attacks; 95% CI, −15.7 to −0.9).

If calcium-channel blockers are ineffective as determined by self-reported responses by patients on an office-administered Raynaud's Condition Score (on a scale from 0 to 10, with
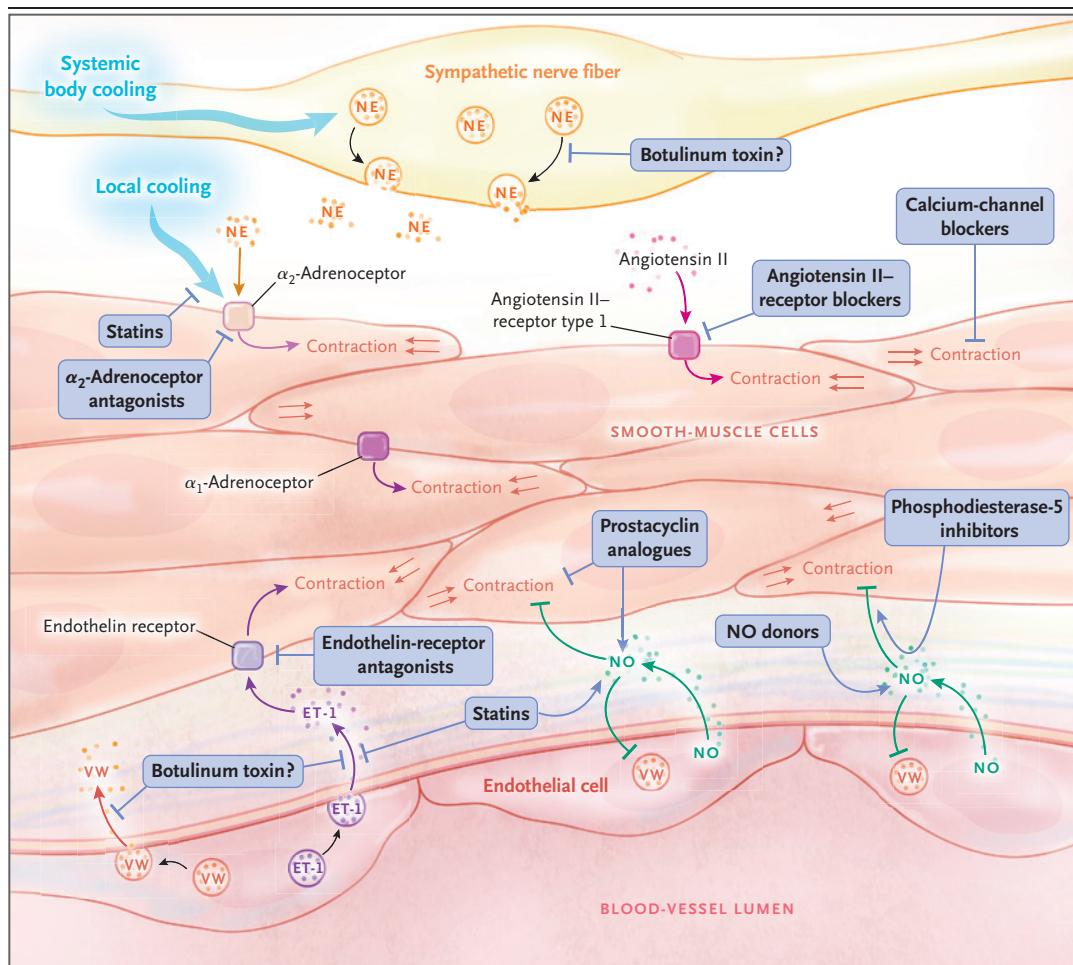
Figure 4. Cutaneous Blood-Vessel Wall and Site of Action of Current Treatment Approaches in Patients with Raynaud's Phenomenon.

Vasoconstriction is achieved by contraction of smooth-muscle cells, and the primary pathway for constriction is increased activity of the sympathetic nervous system. Systemic or body cooling increases the activity of sympathetic nerve fibers and the release of norepinephrine (NE), which causes constriction by predominantly stimulating α_2-adrenergic receptors located on smooth-muscle cells. Local cooling amplifies α_2-adrenergic–receptor constrictor activity. Endothelial cells, which form a single cell layer lining the vascular lumen, are a primary mediator of vasodilatation by means of increased production of nitric oxide (NO) and prostacyclin. NO also acts on endothelial cells to reduce the release of endothelial storage granules, which store von Willebrand factor (VW) and can store endothelin-1 (ET-1) peptides. Endothelial dysfunction, which is present in secondary forms of Raynaud's phenomenon (e.g., scleroderma) but not in primary Raynaud's phenomenon, is associated with diminished activity of NO and increased expression and release of ET-1, a powerful vasoconstrictor.

higher scores indicating greater difficulty with the disorder),[30] if they cannot be taken because of side effects, or if there is persistence of a secondary complication with digital ischemic lesions, popular options include the use of a phosphodiesterase type 5 (PDE-5) inhibitor or a topical nitrate, alone or in combination with the calcium-channel blocker. There is also some evidence to support the use of selective serotonin reuptake inhibitors (SSRIs) or angiotensin II–receptor blockers (ARBs).[6] In an open-label crossover study, the effects over a period of 6 weeks of treatment with the SSRI fluoxetine (at a dose of 20 mg daily) were compared with those of a calcium-channel blocker (nifedipine, at a dose of 40 mg per day); the findings suggested that fluoxetine was effective in both primary and secondary Raynaud's phenomenon.[31] In a

15-week study that compared the ARB losartan (at a dose of 50 mg per day) with nifedipine (at a dose of 40 mg per day), losartan was associated with less severity and a lower frequency of attacks among patients with primary Raynaud's phenomenon and scleroderma-related Raynaud's phenomenon.[32] Additional agents that have been used for the treatment of Raynaud's phenomenon are prazosin (an α_1-adrenoceptor antagonist), pentoxifylline (a xanthine derivative), cilostazol (a PDE-3 inhibitor), and *N*-acetylcysteine (an antioxidant). Evidence suggests that angiotensin-converting–enzyme inhibitors, which inhibit the generation of angiotensin II, are not helpful in the treatment of Raynaud's phenomenon or its complications in patients with scleroderma.[6]

Currently, the most popular approach to manage resistant cases of Raynaud's phenomenon is to amplify or mimic the vasodilator and protective activity of endothelium-derived nitric oxide (Figs. 3 and 4). Topical nitric-oxide donors (transdermal nitrates), which include patches, creams, gels, and ointments, are reported to reduce the frequency and severity of vasospastic attacks in patients with primary or secondary Raynaud's phenomenon. Unfortunately, no formal study has characterized their long-term use or potential benefit with regard to digital ischemic injury. Nitric oxide causes dilatation by stimulating guanylate cyclase and increasing cyclic guanosine monophosphate (GMP), which is then degraded by PDE enzymes. Preliminary results suggest that PDE-5 inhibitors may lessen the frequency and duration of vasospastic events in patients with Raynaud's phenomenon; a meta-analysis of six randomized, controlled trials that included 244 patients with secondary Raynaud's phenomenon showed a moderate but significant benefit, as measured by the Raynaud's Condition Score as well as by the frequency and duration of attacks. There are minimal data regarding digital ischemic injury in patients with secondary Raynaud's phenomenon.[33] Given these data, it is reasonable to add a PDE-5 inhibitor to a calcium-channel blocker or to switch from a calcium-channel blocker to a PDE-5 inhibitor in patients who do not have a response to a calcium-channel blocker alone.

Prostacyclin inhibits vasoconstriction, thrombosis, inflammation, and pathologic vascular remodeling and stimulates the release of endothelium-derived nitric oxide.[16] A systematic review supports the use of intravenous prostacyclin analogues in patients with severe secondary Raynaud's phenomenon, indicating that such drugs reduce the severity of vasospastic attacks and also heal and prevent digital ischemic ulcers.[34] The use of such agents therefore shows that the dual goal of inhibiting vasospastic attacks and preventing tissue injury is achievable. Although orally administered prostacyclin analogues are effective for the treatment of pulmonary hypertension, there is little current evidence of benefit in patients with Raynaud's phenomenon.[35,36]

When there is critical ischemia or resistant digital ulcers and vasodilatory therapy (oral, intravenous, or topical) does not quickly result in increased blood flow, surgical intervention should be considered. Sympathectomy in the digits, and not proximal thoracic procedures, is recommended when critical ischemia threatens a digit despite aggressive medical therapy.[37,38] Although digital sympathectomy may be helpful in treating primary Raynaud's phenomenon, patients rarely require a surgical approach. The reported degree and duration of abatement of severe secondary Raynaud's phenomenon are quite variable after sympathectomy without solid evidence from clinical trials to provide guidance. Repair of obstructive macrovascular disease is an uncommon option in selected cases of severe secondary Raynaud's phenomenon when there is macrovascular disease and critical digital ischemia.

NEW TREATMENT OPTIONS

Although the reduction of vasospastic attacks is an obvious goal in patients with Raynaud's phenomenon, we should not overlook the importance of restoring nutritional blood flow and preventing ischemic tissue injury in patients with secondary Raynaud's phenomenon. It is important to consider the site of vasodilator activity within the vascular network of the skin. For example, vasodilatation in arteriovenous anastomoses could alleviate attacks by facilitating upstream dilatation of digital arteries but might not increase nutritional blood flow.[16] This is especially important in patient with secondary forms of Raynaud's phenomenon, such as scleroderma, in whom impairments in endothelial dysfunction and microvascular structure severely limit nutritional blood flow especially during cold exposure, which precipitates tissue injury and ischemic ulceration.[16]

In advanced stages of scleroderma, the digital vasculature appears to be a passive conduit that is devoid of protective autoregulation.[39] Under these conditions, vasodilator-induced decreases in blood pressure could reduce an already-compromised nutritional blood flow. Therefore, special care should be taken when administering general vasodilators in this population. Current strategies in patients with secondary Raynaud's phenomenon should be to determine and treat the underlying disease process while addressing the vascular disease process by not only enhancing vasodilatation but also inhibiting vasoconstriction, reducing inflammation, and inhibiting thrombosis and thus serving to prevent tissue injury.

Endothelin-1 is a powerful vasoconstrictor, inflammatory, and fibrotic mediator.[16,17] Endothelial generation of endothelin-1 occurs in patients with scleroderma but not in those with primary Raynaud's phenomenon and is most prominent in the superficial microvascular system, which suggests that any pathogenetic role for endothelin-1 would be restricted to the nutritional microcirculation in patients with scleroderma.[16] Indeed, a combined endothelin-1 ET_A and ET_B receptor antagonist (bosentan) did not reduce the frequency of vasospastic attacks among patients with Raynaud's phenomenon but decreased the development of new digital ulcers in those with scleroderma.[40,41] Therefore, endothelin-1 may contribute to reduced nutritional blood flow in patients with scleroderma. The use of the endothelin-receptor antagonist bosentan is approved in Europe for the treatment of scleroderma with recurrent digital ischemic ulcers but is not recommended for the treatment of Raynaud's phenomenon alone. Another dual-receptor endothelin-1 inhibitor (macitentan) did not reduce the number of new digital ulcers in a placebo-controlled trial involving patients with scleroderma,[42] and a pilot study of a selective ET_A inhibitor (ambrisentan) did not increase blood flow to the digits.[43]

Statins have direct vascular-protective effects that are independent of their ability to lower the level of low-density lipoprotein cholesterol. These agents are known to reverse endothelial dysfunction in patients with other vascular diseases, and their protective effects include increased production of nitric oxide, decreased generation of endothelin-1, and protection of the endothelial monolayer.[16] Statins would be expected to be an effective treatment for Raynaud's phenomenon, including secondary Raynaud's phenomenon. There is preliminary evidence that statins have beneficial effects in patients with scleroderma, including reducing the severity of vasospastic attacks, reducing the number of digital ulcers and the formation of new ulcers, and increasing functionality.[44-46]

Direct vascular protective effects of statins are mediated predominantly by the inhibition of Rho and Rho kinase signaling. This signaling pathway contributes to endothelial dysfunction, including impaired nitric-oxide activity, and cold-induced amplification of α_2-adrenoceptor reactivity (Fig. 4).[16,17] A pilot study of short-term treatment with a Rho kinase inhibitor did not show a significant effect on thermal recovery of digital skin temperature after a cold challenge in patients with scleroderma.[47] However, Rho kinase inhibition reduced cold-induced vasoconstriction in healthy participants.[48,49]

A soluble guanylate cyclase stimulator (riociguat) increases the level of cyclic GMP and causes vasodilatation independently of nitric oxide.[50] Its role in treating Raynaud's phenomenon is now under study.

Cold-induced cutaneous vasoconstriction is mediated by sympathetic adrenergic nerve activity acting predominantly on cold-sensitive α_2-adrenoceptors.[16] Although this response may be amplified in patients with secondary Raynaud's phenomenon by altered activity of endothelial mediators, the inhibition of sympathetic vasoconstriction should prevent vasospastic episodes and microvascular insufficiency.[16] Unfortunately, blockade of prejunctional α_2-adrenoceptors in the central and peripheral nervous systems amplifies sympathetic vasoconstriction.[16] A recent trial targeting cold-sensitive α_{2C}-adrenoceptors was disappointing.[51] There is preliminary evidence that local injection of botulinum toxin, which probably inhibits sympathetic nerve activity,[16] has beneficial effects in the treatment of Raynaud's phenomenon and digital ischemic complications. However, its use is based mostly on open-label, uncontrolled studies,[52] and more rigorous clinical analysis is needed.

Multiple antithrombotic agents, including aspirin, dipyridamole, anticoagulants, and thrombolytic therapy, have been used in patients with Raynaud's phenomenon in whom ulceration and

thrombosis have occurred. The benefit of antiplatelet therapy is not well studied, but such therapy is often used in cases of secondary Raynaud's phenomenon when there is a risk of thrombosis. Long-term anticoagulation in the absence of a hypercoagulable state is not recommended. However, a small, placebo-controlled study that used low-molecular-weight heparin in patients with severe Raynaud's phenomenon showed a reduction in severity after 4 weeks and 20 weeks of therapy.[53]

Inflammatory diseases such as vasculitis, which precipitate vascular injury, may cause vasospasm and critical-tissue ischemia and mimic Raynaud's phenomenon. Although treatment of the precipitating disease process with an appropriate antiinflammatory or immunosuppressive agent is important, the role of antiinflammatory or immunosuppressive therapy is unknown in patients with autoimmune disease to treat associated typical Raynaud's phenomenon.

Although vasoactive agents can help alleviate the effects of Raynaud's phenomenon, the response of the thermosensitive vascular system to cold is intense and difficult to completely overcome with any drug intervention. Maurice Raynaud's text[1] reminds us of the importance of warmth in managing Raynaud's phenomenon: "different remedies produced no manifest improvement but during their employment the external temperature rising the cyanosis became less and less marked, and no longer appeared when the atmosphere became warm."

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