This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

RAYNAUD’S PHENOMENON
FREDRICK M. WIGLEY, M.D.

A 37-year-old woman reports that her fingers turn blue when they are exposed to cold temperatures. She also has fatigue, arthralgias, and recurrent small, painful digital ulcers. How should she be evaluated and treated?

THE CLINICAL PROBLEM

In 1862, Maurice Raynaud recognized that some people who were exposed to cold temperatures had transient digital ischemia that he ascribed to an exaggerated response of the central nervous system. The term “Raynaud’s phenomenon” is now used to describe these episodic events, which represent vasoconstriction of the digital arteries, precapillary arterioles, and cutaneous arteriovenous shunts.

The ischemic phase of the attack is evidenced by demarcated pale or cyanotic skin limited to the digits (Fig. 1). It typically starts in one or several digits after exposure to the cold or a stressful situation and then spreads symmetrically to all fingers of both hands. The attack usually ends with a rapid reflow of blood into the digit, which is manifested by erythematous skin (reactive hyperemia). In over 80 percent of patients with Raynaud’s phenomenon who are seen by an internist, the condition is simply an exaggeration of the physiologic response to cold temperatures. However, it can also represent a clinical manifestation of a serious underlying disease or be the first sign of critical ischemia of a digit or limb. Depending on the severity of the vascular insult and the size of the vessel involved, superficial ulceration or deep-tissue necrosis with gangrene and amputation can result.

Reports of exaggerated sensitivity to cold temperatures are common among the general population. In a community-based survey of approximately 7000 people, almost 12 percent answered yes to the question “Are either your fingertips or toes unusually sensitive to cold temperatures?” Cool skin and non-demarcated mottling of the skin of the digits, hands, and limbs are considered a normal response to exposure to the cold. Raynaud’s phenomenon should be distinguished from acrocyanosis, a condition characterized by continuous cyanosis of the hands or feet that is aggravated by cold temperatures.

To be given a diagnosis of Raynaud’s phenomenon, a patient must have a history of sensitivity to the cold and have episodic pallor or cyanosis of the distal portions of the digits (or both) after exposure to the cold (Fig. 2). Photographs of the hands can be obtained during an attack and used to confirm the history. It is not necessary to perform a provocative test (e.g., immersion of the patient’s hand in ice water) to make a definitive diagnosis. Laboratory-based techniques to measure digital and cutaneous blood flow after a cold challenge can be used to distinguish patients with Raynaud’s phenomenon from cold-sensitive persons.

These tests are complex, require a carefully controlled ambient temperature to provide meaningful data, and are generally not used clinically.

According to population-based surveys of various ethnic groups, the prevalence of Raynaud’s phenomenon is approximately 3 to 5 percent. Geographic variations in the prevalence reflect differences in climate. The frequency and severity of the attacks are also influenced by the daily ambient temperature, with clear exacerbations during the winter.

STRATEGIES AND EVIDENCE

Primary versus Secondary Raynaud’s Phenomenon

Clinical criteria are used to distinguish patients with uncomplicated, or primary, Raynaud’s phenomenon from those with secondary Raynaud’s phenomenon (Table 1). The suggested criteria for primary Raynaud’s phenomenon are symmetric attacks; the absence of tissue necrosis, ulceration, or gangrene; the absence of a secondary cause on the basis of a patient’s history and general physical examination; normal nailfold capillaries; a negative test for antinuclear antibody; and a normal erythrocyte sedimentation rate. Clinicians can examine a patient’s cutaneous capillaries by placing a drop of grade B immersion oil on the patient’s skin at the base of the fingernail and viewing the area with a stereoscopic microscope or a hand-held ophthalmoscope set at 10 to 40 diopters. Normal capillaries appear as orderly, delicate vascular loops,
Figure 1. Active Raynaud’s Phenomenon.
Panel A shows sharply demarcated pallor resulting from the closure of digital arteries. Panel B shows digital cyanosis of the fingertips in a patient with primary Raynaud’s phenomenon.

Figure 2. Nail-Fold Capillaries in a Patient with the CREST Syndrome (Calcinosis Cutis, Raynaud’s Phenomenon, Esophageal Dysfunction, Sclerodactyly, and Telangiectasia), or Limited Scleroderma.
The capillaries are dilated and enlarged, and some areas are devoid of normal capillaries, a typical characteristic of scleroderma.
phenomenon is 14 years, and only 27 percent of cases are anatomically abnormal (Fig. 2).

whereas the capillaries of patients with an underlying rheumatic disease are frequently distorted or are anatomically abnormal (Fig. 2). The median age at the onset of primary Raynaud’s phenomenon is 14 years, and only 27 percent of cases begin at the age of 40 years or later. The symptoms are generally mild among patients with primary disease. In one study of 313 patients with primary Raynaud’s phenomenon, only 38 (12 percent) reported having severe attacks. About a quarter of patients with primary Raynaud’s phenomenon have a family history of Raynaud’s phenomenon in a first-degree relative.

If a patient meets the criteria for primary Raynaud’s phenomenon and is followed for a two-year period without the development of clinical or laboratory signs, then secondary disease is highly unlikely. In a meta-analysis involving 639 patients with presumed primary Raynaud’s phenomenon, a secondary disorder developed in 81 (12.6 percent), all but 1 of whom had a connective-tissue disease.

A secondary cause of Raynaud’s phenomenon is suggested by the following findings: an age at onset of more than 30 years; episodes that are intense, painful, asymmetric, or associated with ischemic skin lesions; clinical features suggestive of a connective-tissue disease (e.g., arthritis and abnormal lung function); specific autoantibodies; and evidence of microvascular disease on microscopy of nail-fold capillaries. In a large study, a connective-tissue disease developed in only 2 percent of patients with vasospastic disease alone who were seronegative for antinuclear antibodies and rheumatoid factor. The presence of antinuclear antibodies has relatively low positive predictive value for an associated connective-tissue disease (30 percent), whereas the presence of antibodies against a specific autoantigen is more highly suggestive of secondary disease.

For example, scleroderma is likely to be present or to develop in patients with anticentromere or antitopoisoerase antibodies. Approximately 15 to 20 percent of patients with Raynaud’s phenomenon who have autoantibodies, abnormalities of nail-fold capillaries, or both and who do not initially meet the criteria for a well-defined connective tissue disease ultimately will do so, usually within two years.

All patients with Raynaud’s phenomenon need to undergo a complete evaluation to rule out an underlying secondary cause, with specialized tests performed as appropriate on the basis of the clinical history (Fig. 3). The physician should determine whether the patient has symptoms of a connective-tissue disease (e.g., arthritis, myalgias, fever, dry membranes, rashes, and cardiopulmonary abnormalities); a history of or current drug use and exposure to toxic agents, especially chemotherapeutic agents; a history of repetitive trauma to the hands, such as that due to the use of vibrating tools; and a history of Raynaud’s events triggered by positional changes consistent with the presence of a thoracic outlet syndrome. Although nonselective beta-blockers have been reported to cause Raynaud’s phenomenon, this association is not supported by the findings of well-designed studies.

Carpal tunnel syndrome and other neuropathic conditions may cause sensitivity to the cold. A variety of uncommon conditions should also be considered in the differential diagnosis, especially cryoproteinemias, dysproteinemias, exposure to polyvinyl chloride, cancer, or hypothyroidism. If the patient’s symptoms are asymmetric, vascular studies may be useful to determine whether there is any evidence of large-vessel occlusive disease. The signs of atherosclerosis are unlikely to mimic those of typical symmetric Raynaud’s attacks but rather to consist of claudication of a limb on exercise, asymmetric abnormalities of a leg, or isolated and persistent digital ischemia. Vasculitis, emboli, or other vascular occlusive events cause critical ischemia but not typical Raynaud’s phenomenon. There is some evidence that Raynaud’s phenomenon is the clinical manifestation of a generalized vasospastic disorder.

This is especially true in patients who have Prinzmetal’s angina, migraines, or scleroderma.

**Nonpharmacologic Therapy**

The avoidance of cold temperatures is the best method to prevent an episode of Raynaud’s phenomenon. Keeping the whole body warm by wearing loose-fitting clothing, stockings, headwear, and gloves in cold weather is a key strategy. The digital arteries and thermoregulatory vessels of the skin are predominantly under sympathetic adrenergic control. Emotional stress alone can trigger digital vasospasm, and anxiety can exacerbate cold-induced Raynaud’s attacks. Therapies designed to reduce emotional stress may be helpful. Avoiding agents that cause vasoconstriction is also important (e.g., sympathomimetic

**TABLE 1. CRITERIA FOR THE DIAGNOSIS OF PRIMARY RAYNAUD’S PHENOMENON.***

<table>
<thead>
<tr>
<th>Criteria for Diagnosis</th>
<th>Primary Raynaud’s Phenomenon</th>
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<tbody>
<tr>
<td>Vasospastic attacks precipitated by cold or emotional stress</td>
<td>Symmetric attacks involving both hands</td>
</tr>
<tr>
<td>Symmetric attacks involving both hands</td>
<td>Absence of tissue necrosis or gangrene</td>
</tr>
<tr>
<td>Absence of tissue necrosis or gangrene</td>
<td>No history or physical findings suggestive of a secondary cause</td>
</tr>
<tr>
<td>No history or physical findings suggestive of a secondary cause</td>
<td>Normal nail-fold capillaries</td>
</tr>
<tr>
<td>Normal nail-fold capillaries</td>
<td>Normal erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Normal erythrocyte sedimentation rate</td>
<td>Negative serologic findings, particularly negative test for antinuclear antibodies</td>
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</tbody>
</table>

*Adapted from LeRoy and Medsger.10
Figure 3. Approach to the Diagnosis of Raynaud's Phenomenon.

POEMS denotes polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.
drugs, clonidine, ergotamine, and serotonin-receptor agonists). Smoking can reduce digital blood flow and should be avoided by patients with Raynaud’s phenomenon, but epidemiologic studies have not clearly demonstrated an association between smoking and Raynaud’s phenomenon. Temperature-related biofeedback is used in combination with various relaxation techniques to treat patients with Raynaud’s phenomenon, but the benefit remains unclear. In a controlled trial involving patients with primary Raynaud’s phenomenon who were followed for one year, the use of temperature-related biofeedback training did not reduce attacks significantly as compared with a control procedure.

### Calcium-Channel Blockers

Calcium-channel blockers are the most widely used agents for the treatment of Raynaud’s phenomenon (Table 2). Most clinical trials have evaluated nifedipine given in multiple daily doses for a relatively short period. The only long-term, placebo-controlled study of a sustained-release preparation of nifedipine (30 to 60 mg once daily) showed a 66 percent reduction in attacks in patients with primary Raynaud’s phenomenon. Side effects resulted in the discontinuation of nifedipine in 15 percent of participants, and those who continued vasodilator therapy reported sustained benefit during the one-year follow-up.

Clinical trials involving other members of the dihy-

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### Table 2. Pharmacologic Treatment of Raynaud’s Phenomenon.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium-channel blockers</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nifedipine</td>
<td>10–30 mg 3 times daily orally</td>
<td>Tachycardia, edema, flushing, headache, dizziness, constipation, orthostatic hypotension</td>
<td>Placebo-controlled trials indicate benefit</td>
</tr>
<tr>
<td>Sustained-release nifedipine</td>
<td>30–120 mg/day orally</td>
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<tr>
<td>Amlodipine</td>
<td>5–20 mg/day orally</td>
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<tr>
<td>Felodipine</td>
<td>2.5–10 mg twice daily orally</td>
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<tr>
<td>Isradipine</td>
<td>2.5–5.0 mg twice daily orally</td>
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<tr>
<td>Diltiazem*</td>
<td>30–120 mg 3 times daily orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained-release diltiazem*</td>
<td>120–300 mg/day orally</td>
<td></td>
<td></td>
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<tr>
<td><strong>Sympatholytic agent</strong></td>
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<tr>
<td>Prazosin</td>
<td>1–5 mg twice daily</td>
<td>Syncope, postural hypotension, dizziness, palpitations possible after first dose</td>
<td>Efficacy often transient, may wane after several weeks</td>
</tr>
<tr>
<td><strong>Angiotensin II–receptor type 1 antagonist</strong></td>
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<tr>
<td>Losartan</td>
<td>25–100 mg/day orally</td>
<td>Dizziness, headache, fatigue, diarrhea</td>
<td>One placebo-controlled trial indicated benefit</td>
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<tr>
<td><strong>Selective serotonin-reuptake inhibitor</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>20–40 mg/day orally</td>
<td>Insomnia, nausea, diarrhea, tremors</td>
<td>One placebo-controlled trial indicated benefit</td>
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<tr>
<td><strong>Vasodilator</strong></td>
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<tr>
<td>Nitroglycerin</td>
<td>¼–½ in. of 2% ointment applied topically per day</td>
<td>Headache, tachycardia, syncope, angina, rash, impotence, nausea, rebound hypertension</td>
<td>Popular therapy but little controlled data to support its use</td>
</tr>
<tr>
<td><strong>Other vasoactive drug</strong></td>
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<tr>
<td>Pentoxifylline</td>
<td>400 mg 3 times daily orally</td>
<td>Dyspepsia, nausea, vomiting</td>
<td>Popular therapy but little controlled data to support its use</td>
</tr>
<tr>
<td><strong>Prostaglandins</strong></td>
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<tr>
<td>Epoprostenol†</td>
<td>0.5–6 ng/kg of body weight/min intravenously for 6–24 hr for 2–5 days</td>
<td>Flushing, diarrhea, headache, hypotension, rash</td>
<td>Used for critical ischemia; in-hospital infusion recommended</td>
</tr>
<tr>
<td>Alprostadil</td>
<td>0.1–0.4 µg/kg/min intravenously for 6–24 hr for 2–5 days</td>
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<tr>
<td>Iloprost‡</td>
<td>0.5–2 ng/kg/min intravenously for 6–24 hr for 2–5 days</td>
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*Diltiazem is not as effective as the dihydropyridine class of calcium-channel blockers.

†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.
dropyridine class of calcium-channel blockers (e.g., isradipine, amlodipine, felodipine, and nisoldipine) have reported an approximately 50 percent reduction in the frequency of attacks and a significant reduction in the severity of attacks. There are no data to support the use of another calcium-channel blocker if the initial one is ineffective. A meta-analysis of placebo-controlled studies of calcium-channel blockers for the treatment of Raynaud’s phenomenon in patients with scleroderma found that such agents moderately reduced the severity and frequency of attacks (eight fewer attacks in a two-week period) among patients with severe attacks. Although calcium-channel blockers appear to be the best available vasodilator for the treatment of Raynaud’s phenomenon, only a few studies have compared calcium-channel blockers with other vasodilators.

Other Agents

Sympatholytic drugs are reported to be useful in the treatment of Raynaud’s phenomenon (Table 2). Of the currently available sympatholytic agents, only the α1-adrenergic-receptor blocker prazosin has been well studied. Two crossover trials found prazosin to be more effective than placebo. A single study of patients with scleroderma found that the angiotensin II-receptor type 1 antagonist losartan reduced the severity of attacks more than did sustained-release nifedipine. A controlled study found that fluoxetine, a selective serotonin-reuptake inhibitor, improved the symptoms of Raynaud’s phenomenon.

AREAS OF UNCERTAINTY

Value of Other Vasodilators

A variety of direct-acting vasodilators (nitroglycerine, hydralazine, papaverine, minoxidil, and niacin) are available but have not been well studied in patients with Raynaud’s phenomenon. The use of combinations of vasodilators (e.g., a calcium-channel blocker plus a nitroglycerine patch) has not been studied. Evidence that angiotensin-converting–enzyme inhibitors are useful in patients with this disorder is controversial, and data on the use of pentoxifylline are inconclusive.

Experimental Agents and Agents That Are Not Available in the United States

Although intravenous prostaglandin therapy appears to be effective, other prostacyclin preparations have also been reported to have beneficial effects, but whether intravenous alprostadil is among these agents remains in question.

Orally administered prostaglandins have not yet proved useful in the treatment of Raynaud’s phenomenon. Short-term administration of misoprostol (an oral preparation of prostaglandin E1) failed to reverse cold-induced vasospasm in patients with primary Raynaud’s phenomenon. A multicenter, placebo-controlled, double-blind study of patients with scleroderma found that orally administered iloprost had no benefit. Similar negative results have been reported for two other orally administered analogues of prostacyclin, cicaprost and beraprost.

Despite experimental evidence that nitric oxide and arginine can prevent vasospasm, a study of ambulatory patients found that orally administered arginine was no better than placebo. Although phosphodiesterase inhibitors (e.g., cilostazol and sildenafil) and the new endothelin-receptor inhibitors (e.g., bosentan) make sense as treatments for Raynaud’s phenomenon, the results of clinical trials with these agents are not yet available.

Sympathectomy

The role of proximal sympathectomy in the management of Raynaud’s phenomenon has not been established. In one study of 140 patients with Raynaud’s phenomenon, fewer than 20 percent claimed to derive lasting benefit from cervical sympathectomy and two thirds reported that the benefit lasted less than one year. Localized digital sympathectomy involving microsurgical techniques is considered safe and can improve digital blood flow immediately, but its use should be limited to patients with severe digital ischemia who have no response to medical treatment.

Acute Ischemic Crisis

In an acute ischemic crisis, a short-acting calcium-channel blocker such as nifedipine (10 to 30 mg every eight hours) should be started, as well as antiplatelet therapy with aspirin. A digital or wrist block with lidocaine or bupivacaine (without epinephrine) not only relieves pain but also produces a localized chemical sympathectomy that can reverse acute vasoconstriction. Intravenous iloprost (0.5 to 2 ng per kilogram of body weight per minute for up to five days) reverses acute critical ischemia, but this agent is no longer available in the United States (unless the patient imports it at his or her own expense). Short-term (48 to 72 hours) anticoagulation with heparin is used if there is persistent critical ischemia, evidence of large-artery occlusive disease, or both. Localized digital sympathectomy is used in refractory cases.
GUIDELINES

There are no formal guidelines for the evaluation and treatment of patients with Raynaud’s phenomenon.

CONCLUSIONS AND RECOMMENDATIONS

Any patient who presents with Raynaud’s phenomenon should be assessed for signs and symptoms suggestive of a secondary cause. Patients presenting before the age of 20 years who have no symptoms or signs (e.g., as evidenced by normal findings on nail-fold microscopy) of a secondary cause can be followed without undergoing other specialized tests (Fig. 3). Initial management should include the avoidance of cold temperatures; drug treatment should be added only if the attacks are poorly controlled and disabling.

The patient described in the clinical vignette has symptoms suggestive of an underlying connective-tissue disease, and testing for disease-specific autoantibodies is warranted. The presence of digital ulcers would dictate intervention with vasodilator therapy. Calcium-channel blockers are first-line therapy, and I would start with either 30 mg of sustained-release nifedipine per day or 5 mg of amldipine per day. The dose should be increased until benefit is noted or until a maximal tolerated dose is reached. If such agents are ineffective at full doses, I would add a nonspecific vasodilator such as 2 percent nitroglycerin ointment starting at a daily dose of ⅓ to ⅓ in. applied topically to the regimen, although data are lacking regarding the efficacy of combined therapy. Treatment of any underlying autoimmune disease may reduce the frequency and severity of attacks of Raynaud’s phenomenon, although the pattern or pace of attacks is often independent of overall disease activity.

Patients who have an acute ischemic crisis in a digit should quickly be evaluated to determine the underlying cause and should be given vasodilator therapy and aspirin. The success of this approach is determined by the degree of vasospasm vis-à-vis the amount of irreversible structural or occlusive disease. I now use intravenous epoprostenol for a refractory case, particularly if the ischemic crisis has not yet led to irreversible tissue injury or gangrene. The key to the treatment of critical ischemia is early intervention.

I am indebted to Sharon Monsky and the Scleroderma Research Foundation, Nancy and Joachim Bedlette, Nancy and Don Powell, Jack and Kathy Alfano, the Citibank Foundation, Nina and Albert Foundation, Nancy and Joachim Bechtle, Nancy and Don Powell, Mary Quirk, and Charles and Helen Schwab for their inspiration and support, and to Lisa Murray for assistance with the preparation of the manuscript.

REFERENCES


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