



# Office evaluation and treatment of Raynaud's phenomenon

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- **BACKGROUND** Raynaud's phenomenon, an episodic vascular disorder induced by cold temperatures or stress and characterized by white, blue, and red discoloration of the fingers and toes, may affect up to 20% of the general population.
- **KEY POINTS** Raynaud's phenomenon may exist independently (primary) or in association with an underlying disease (secondary), most commonly systemic sclerosis. The pathophysiologic features include vasospasm, endothelial cell changes, vessel obstructive features, and hemorrheologic factors. Raynaud's phenomenon is the initial manifestation of disease in 70% of patients with systemic sclerosis, in whom it may be present for many years before the development of the connective tissue disease. Patients with primary Raynaud's phenomenon need only conservative management and should be reassured that digital ischemia and loss of tissue occur extremely rarely. Pharmacologic agents that have been studied include vasodilators, platelet inhibitors, serotonin antagonists, and fibrinolytics.
- **CONCLUSIONS** For prognostic and therapeutic reasons, it is important to determine if Raynaud's phenomenon is associated with an underlying condition and if the patient may develop a connective tissue disease.

- INDEX TERMS: RAYNAUD'S DISEASE
- CLEVE CLIN J MED 1995; 62:51-61

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**R**AYNAUD'S phenomenon (RP), or digital vasospasm, initially described by Maurice Raynaud in 1888,<sup>1</sup> is characterized by episodic, triphasic discoloration of the fingers, toes, and, rarely, of the nose, lips, and ears upon exposure to cold or to emotional stress. The classic white, blue, and red discolorations occur, however, in only a minority of patients. The changes typically begin with well-demarcated white discoloration, representing vasospasm of the digital artery. This is followed by blue changes related to the presence of desaturated venous blood. Finally, hyperemia occurs with the return of blood flow, manifesting itself as erythema. This final recovery phase is associated with paresthesia or pain.

RP may occur in an otherwise healthy person or in association with an illness. Primary RP (Raynaud's disease) is not associated with an underlying disorder. Secondary RP can occur with connective tissue diseases, occupational exposures, structural arterial disease, medication effects, neoplasms, or hemorrheologic abnormalities (Table 1). A common

**TABLE 1**  
CAUSES OF SECONDARY RAYNAUD'S PHENOMENON

|                                            |
|--------------------------------------------|
| Connective tissue diseases                 |
| Systemic sclerosis                         |
| Polymyositis or dermatomyositis            |
| Undifferentiated connective tissue disease |
| Mixed connective tissue disease            |
| Systemic lupus erythematosus               |
| Rheumatoid arthritis                       |
| Sjögren's syndrome                         |
| Systemic vasculitis                        |
| Occupational diseases                      |
| Vibration disease                          |
| Vinyl chloride exposure                    |
| Structural arterial disease                |
| Thromboangiitis obliterans                 |
| Arteriosclerosis obliterans                |
| Atheroembolic disease                      |
| Thoracic outlet syndrome                   |
| Takayasu's disease                         |
| Medications                                |
| Vinblastine, bleomycin, and cisplatin      |
| Neoplasms                                  |
| Carcinoid syndrome                         |
| Pheochromocytoma                           |
| Paraneoplastic syndromes                   |
| Hemorrhheologic causes                     |
| Leukemia                                   |
| Cryoglobulinemia                           |
| Polycythemia                               |
| Thrombocytosis                             |
| Cold agglutinin disease                    |
| Paraproteinemia                            |
| Miscellaneous                              |
| Reflex sympathetic dystrophy syndrome      |
| Hypothyroidism                             |
| Arteriovenous fistula                      |

clinical challenge involves patients presenting with RP and no apparent associated condition who may be experiencing the first symptom of a connective tissue disease. This review focuses on how to diagnose RP, distinguish primary RP from secondary RP, and treat both forms.

#### EPIDEMIOLOGY

Between 5% and 20% of the general population has RP.<sup>2-4</sup> RP affects women more than men: Silman<sup>2</sup> determined a prevalence of 11% in men and 19% in women through a postal survey, and a prevalence of 16% in men and 21% in women attending a physician's office. Maricq et al<sup>3</sup> screened a random sample of 1752 South Carolina adults with a questionnaire; 10% reported cold sensitivity of their fingers, and 4.6% reported white or blue color changes in addition to cold sensitivity. In another study,



**FIGURE 1.** Top, blanching phase in a patient with Raynaud's phenomenon. Bottom, fingertip cyanosis with demarcation in a patient with Raynaud's phenomenon. From Maricq and Weinrich, reference 4, with permission.

Maricq et al<sup>4</sup> estimated the prevalence of RP to be 16.8% in Tarentaise, Savoie, France (which has a cool climate) and 5% in Charleston, SC (which has a warm climate).<sup>4</sup>

#### DIAGNOSIS

Accurate diagnosis begins with a carefully elicited history of episodes of cold- or stress-induced demarcated color changes, most often involving the fingers. Photographic color charts<sup>5</sup> and physiological tests such as photoelectric plethysmography<sup>6</sup> or the Nielsen test<sup>7</sup> help to substantiate the diagnosis.

Maricq and Weinrich<sup>4,5</sup> have developed a two-

part color chart used in conjunction with a standardized questionnaire to help identify RP in the clinic and in epidemiologic studies. The color charts, which carry color scales and photographs of actual finger blanching and cyanosis (Figure 1), provide a high degree of sensitivity and specificity and are a useful adjunct to the clinicians' evaluation, particularly in mild cases of RP.<sup>4,5,8</sup> Attempts to reproduce a patient's symptoms in the office by means of cold exposure of the hands or body, no matter how elaborate, are unreliable, as signs and symptoms of RP may not occur in an artificial environment.

Photoelectric plethysmography, a physiologic test that indicates digital vessel volume changes, demonstrates abnormally reduced amplitudes in patients with RP.<sup>6</sup> The Nielsen test, a more elaborate physiologic method, involves measuring finger systolic pressure after cooling the finger and body.<sup>7</sup> Finger cooling is achieved by a water-perfused double-inlet-plastic cuff. Patients with RP typically demonstrate greater decreases in finger systolic pressures than control subjects do and frequently demonstrate total occlusion of the digital artery. The purpose of the Nielsen test is not to produce an attack, but rather to analyze abnormal responses of digital systolic pressures to cooling. Although useful in research and in diagnosis, the Nielsen method and photoelectric plethysmography require special equipment and therefore are not practical for everyday office evaluation. They cannot differentiate primary RP from secondary RP.<sup>9</sup>

### Nailfold microscopy

Wide-field nailfold microscopy, a noninvasive means of examining capillary changes reflective of systemic disease, is useful for determining if a patient has an increased likelihood of developing a connective tissue disease.<sup>10-12</sup> It is best performed by placing a drop of immersion oil on the nailfold and using a 12× to 15× magnification for a wide viewing field. The overall capillary pattern and the individual capillary loops can then be evaluated.<sup>10,13</sup> Estimates of capillary density and dilation obtained with this method correlate well with information obtained from histologic evaluation of nailfold biopsy specimens.<sup>14</sup>

Characteristic nailfold capillary changes are seen in systemic sclerosis (scleroderma) and dermatomyositis, and less specific changes are seen in systemic lupus erythematosus (SLE) and rheumatoid arthritis. The nailfold changes in systemic sclerosis

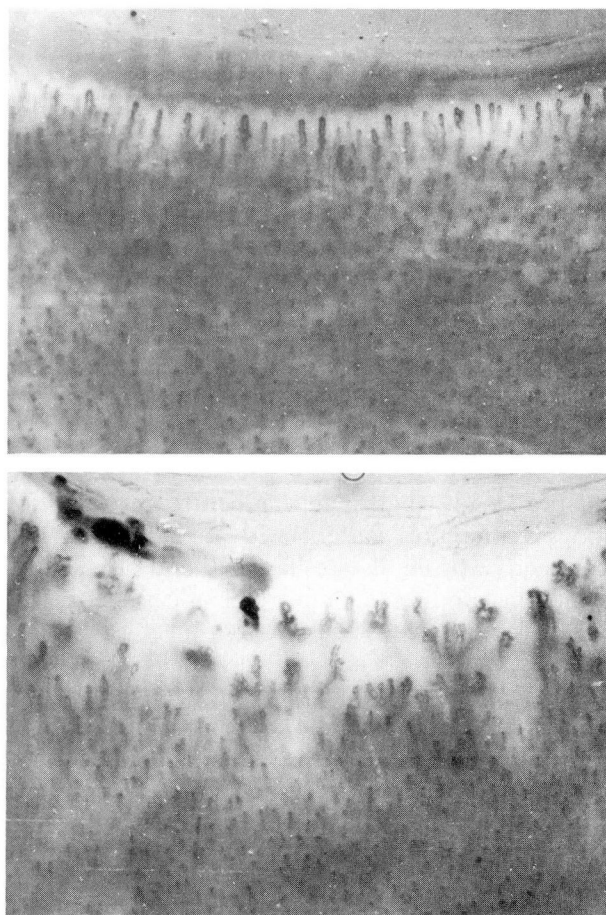


FIGURE 2. Top, normal nailfold capillaries. Bottom, an example of an active scleroderma pattern of nailfold capillaries in a patient with undifferentiated connective tissue disease. Capillary enlargement with avascularity is demonstrated. From Maricq, reference 15, with permission.

include capillary dilation with or without adjacent avascularity (Figure 2).<sup>10</sup> An "active pattern," reflecting disease activity, consists of capillary dilation but with a predominance of capillary loss, or avascularity. On the other hand, a "slow pattern" denotes dilation of capillaries with minimal loss and is seen in patients with less active disease.<sup>13,15-17</sup> Patients presenting with apparent primary RP and evidence of nailfold capillary dilation may actually be in the early stages of a connective tissue disease.<sup>11,12,18,19</sup>

Patients with other connective tissue diseases also have characteristic nailfold microscopic abnormalities. Dermatomyositis produces nailfold capillary changes that resemble those seen in systemic sclerosis; however, there is usually more extensive

**TABLE 2**  
**DIAGNOSTIC CRITERIA**  
**FOR PRIMARY RAYNAUD'S PHENOMENON\***

|                                                                          |
|--------------------------------------------------------------------------|
| Episodic attacks of acral pallor or cyanosis                             |
| Strong and symmetric peripheral pulses                                   |
| No evidence of digital pitting, ulcerations, or gangrene                 |
| No sclerodactyly                                                         |
| Normal nailfold capillaries                                              |
| Antinuclear antibody titer less than 1:160 for all patterns and epitopes |
| Erythrocyte sedimentation rate (Westergren) less than 20 mm/hour         |

\*Adapted from LeRoy and Medsger, reference 27, with permission

dilation, and a bushy appearance to the capillary loops is common.<sup>10</sup> Patients with an undifferentiated connective tissue disease have RP and other signs, symptoms, and serologic markers of connective tissue diseases; however, they do not meet established diagnostic criteria of a specific disorder.<sup>20</sup> Many have capillary dilation with or without avascularity similar to that seen in systemic sclerosis.

In SLE, nailfold changes primarily include capillary tortuosity.<sup>21,22</sup> Caspary and colleagues<sup>22</sup> found that patients with SLE and RP had increased capillary diameters, particularly if they had frequent attacks of RP (more than one per week).<sup>22</sup> Patients with rheumatoid arthritis and RP demonstrate few nailfold capillary changes but may have other subtle changes, including a visible superficial and deep venous plexus.<sup>10</sup>

#### PRIMARY RP

#### Clinical characteristics of primary RP

Primary RP most frequently arises between the second and fourth decades, more commonly in women. Some define it as the presence of RP for longer than 2 years without an associated illness; however, secondary disorders may become evident even after 10 to 15 years of symptoms.<sup>19,23–26</sup> This is an important distinction because primary RP is predominantly benign. LeRoy and Medsger<sup>27</sup> have proposed a classification system with guidelines to distinguish primary RP from secondary RP.<sup>27</sup> To be classified as having primary RP, a patient must have symmetrical pulses, normal nailfold capillaries, no evidence of tissue necrosis, no sclerodactyly, a negative antinuclear antibody (ANA) test, and a normal Westergren sedimentation rate (Table 2).

#### Pathophysiology of primary RP

The pathophysiologic effects of primary RP are attributed to vasospasm, which may be due to a central or a local process.<sup>28</sup> Compared with healthy control subjects, patients with primary RP may have diminished or similar digital blood flow rates; however, the range of blood flow values is great and this measure is therefore not diagnostic.<sup>29</sup> Primary RP patients may, however, attain a significant increase in digital blood flow in response to body heating, as do healthy controls.<sup>30</sup> Fixed obstructive and endothelial cell changes, present in secondary RP, are not seen in primary RP.<sup>31,32</sup> Arteriographic examinations in patients with primary RP are likewise normal.<sup>9</sup>

Enhanced sympathetic activity or vessel responsiveness to adrenergic stimuli may be important. Freedman et al<sup>30</sup> have provided evidence for enhanced peripheral alpha-adrenergic receptor sensitivity or density in patients with primary RP compared with normal controls. Local effects of prostaglandins and serotonin may also have a role.<sup>28</sup>

#### SECONDARY RP

#### Clinical characteristics of secondary RP

RP is a common symptom of connective tissue disease, occurring in 95% of patients with systemic sclerosis, 40% of patients with SLE, and 35% of patients with polymyositis or dermatomyositis.<sup>22,33–35</sup> It is the initial manifestation of disease in 70% of patients with systemic sclerosis,<sup>35</sup> in whom RP may be present for many years before the development of the connective tissue disease, particularly in limited cutaneous systemic sclerosis (also known as the CREST syndrome—calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasia).<sup>33</sup> Interestingly, the 5% of systemic sclerosis patients who do not experience RP have a worse prognosis with reduced survival.<sup>36</sup>

In addition, secondary RP may occur with underlying disorders other than connective tissue diseases (Table 1). Occupational hazards include the use of vibratory tools and exposure to vinyl chloride. When evaluating a patient for RP, one should seek physical findings suggestive of structural arterial disease. Hemorrhologic factors contributing to RP symptoms may be suggested by elevated peripheral blood counts and serum total protein concentrations, or the presence of cryoglobulins or cold agglutinins. The association of RP with certain medications, neoplasms, and hemorrhologic fac-

tors has generally not been well studied and seems to exist only in relatively small numbers of patients.

Distinguishing primary RP from secondary RP is important for choosing treatment and determining prognosis. Primary RP exists, by definition, in people without associated signs or symptoms of an underlying disease. RP may, however, be the initial symptom of a connective tissue disease, and a prolonged latency phase may elapse before other manifestations of a secondary disorder arise.<sup>18,19,23-26</sup> It would be beneficial if we could identify those patients who have only RP symptoms but who have an increased likelihood of developing a connective tissue disease, ie, of having secondary RP.

Gerbracht et al<sup>23</sup> found that an underlying connective tissue disease may not be evident within the first 10 years after the development of RP symptoms. Four (5%) of 87 patients acquired a definite connective tissue disease (CREST syndrome) approximately 8 to 17 years after the onset of RP.<sup>23</sup> Fitzgerald and colleagues<sup>25</sup> followed 58 patients who had only RP and found that 11 (19%) acquired a connective tissue disease at a mean of 9 years after the onset of RP symptoms. All 11 patients had systemic sclerosis (three diffuse, eight CREST syndrome). Baseline abnormalities on nailfold microscopy and pulmonary function testing were associated with the subsequent diagnosis of systemic sclerosis.<sup>25</sup>

In another study, 19% of 73 RP patients who did not have an obvious connective tissue disease at presentation developed one at a mean of 11.5 years after the onset of RP symptoms.<sup>24</sup> A connective tissue disease was the most common underlying disorder in secondary RP. Positive predictors were a positive ANA test, abnormal nailfold capillaries, and abnormal hand and chest radiographs. Predictive findings in other studies included evidence on history and physical exam of connective tissue disease, certain serologic abnormalities, advanced age at onset of RP, and severe RP as measured by photoelectric plethysmography.<sup>6,18,19,25-26,35,37-40</sup>

LeRoy and Medsger<sup>27</sup> have proposed a classification system in which RP patients are considered to have secondary RP associated with an undifferentiated connective tissue disease if they have any of the following: a positive ANA test, abnormal nailfold capillaries, digital pitting or gangrene, and certain abnormalities of the esophagus, small intestine, colon, lungs, heart, or kidneys (*Table 3*). Symptoms and signs found during a thorough history and physi-

**TABLE 3**  
SECONDARY RAYNAUD'S PHENOMENON:  
FEATURES ASSOCIATED WITH UNDIFFERENTIATED  
CONNECTIVE TISSUE DISEASE\*†

|                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Abnormal nailfold capillary pattern                                                                                                                                                            |
| Positive antinuclear antibody tests                                                                                                                                                            |
| Digital pitting, ulceration or gangrene                                                                                                                                                        |
| Esophageal abnormalities                                                                                                                                                                       |
| Prolonged transit time                                                                                                                                                                         |
| Abnormal motility studies                                                                                                                                                                      |
| Stricture                                                                                                                                                                                      |
| Barrett's metaplasia                                                                                                                                                                           |
| Small-intestinal abnormalities                                                                                                                                                                 |
| Dilation on roentgenography                                                                                                                                                                    |
| Malabsorption                                                                                                                                                                                  |
| Abnormal motility                                                                                                                                                                              |
| Atrophy on biopsy                                                                                                                                                                              |
| Colonic abnormalities (abnormal motility or pressure-volume relationships)                                                                                                                     |
| Pulmonary abnormalities                                                                                                                                                                        |
| Interstitial changes on roentgenography                                                                                                                                                        |
| Alveolitis by lavage or high-resolution computed tomography                                                                                                                                    |
| Restrictive changes by pulmonary function testing, especially diffusion capacity                                                                                                               |
| Cardiac abnormalities on chest roentgenography, electrocardiography, Holter monitoring, echocardiography with Doppler, stress thallium scanning, ventriculography (multigated angiogram scans) |
| Renal abnormalities (systemic hypertension, proteinuria (> 300 mg/24 hours), reduced renal blood flow or creatinine clearance (< 60 mL/minute))                                                |

\*Adapted from LeRoy and Medsger, reference 27, with permission

†Indicates the absence of a diagnosis of a well-defined connective tissue disease

cal exam should indicate which diagnostic tests to subsequently perform. The patients so identified may not meet the full diagnostic criteria for a connective tissue disease, but they have an increased likelihood of subsequently developing one. This risk has important prognostic implications.

### Pathophysiology of secondary RP

Secondary RP is multifactorial; vasospasm, structural abnormalities, and hemorrhologic factors may all contribute (*Table 1*).<sup>41</sup> Many physiological studies of secondary RP have included only patients with systemic sclerosis, a disease characterized by microvascular injury and end-organ fibrosis. The arteries in systemic sclerosis show evidence of endothelial damage and intimal proliferation,<sup>32,33,37</sup> changes believed to contribute a fixed obstructive feature to the pathogenesis of RP (*Figure 3*). Patients with systemic sclerosis have both fixed and reversible de-

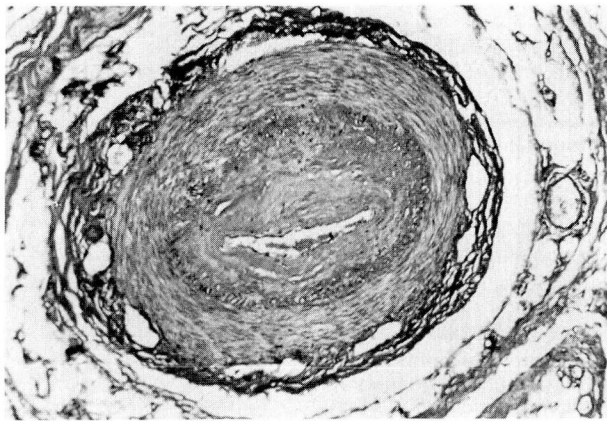


FIGURE 3. Photomicrograph showing the histopathologic changes (trichrome stain) in a cross section of a digital artery from a patient with systemic sclerosis and long-standing Raynaud's phenomenon. There is extensive intimal hyperplasia with a reduction in the lumen diameter of more than 75%. Provided by Richard M. Silver.

fects of digital blood flow, and their skin has abnormal thermal properties.<sup>29,31,42</sup>

Wigley and colleagues<sup>31</sup> used a laser Doppler flowmeter to demonstrate diminished digital perfusion at baseline in 21 patients with RP associated with systemic sclerosis. After blood flow was occluded, this group also had a lower peak blood flow and a longer time before peak blood flow returned than did both primary RP and control subjects. The vasodilator carboprostacyclin did not improve the baseline blood flow or the prolonged time to reactive hyperemia in the systemic sclerosis patients, lending further support for an element of a fixed obstructive defect in the digital vasculature.<sup>31</sup>

Studies using xenon 133 to measure skin blood flow found lower xenon-133 clearance after cooling in patients with systemic sclerosis than in healthy controls. Clearance subsequently returned to normal with rewarming, providing evidence of a reversible blood flow deficit in systemic sclerosis. Additionally, patients with systemic sclerosis have thermal abnormalities of the skin; with rewarming, their skin temperatures do not rise as high as in control subjects.<sup>42</sup>

Hematologic factors implicated in secondary RP include cryoglobulinemia, cold agglutinins, thrombocytosis, and polycythemia.<sup>32</sup> In systemic sclerosis, there may be enhanced platelet activation,<sup>43</sup> reduced fibrinolysis<sup>44</sup> and increased blood viscosity.<sup>45</sup> Peptides mediating vessel-wall reactivity may have a

role in precipitating RP attacks. For example, serotonin, a potent vasoconstrictor, is released upon platelet activation.<sup>28</sup> Endothelin, another peptide that mediates vasoconstriction, has been found to be elevated in patients with systemic sclerosis.<sup>46</sup>

#### RP AND INTERNAL ORGANS

Cold-induced vasospasm of the blood vessels supplying the lungs, heart, and kidneys has also been demonstrated. Diffusion capacity on pulmonary function testing has been found to diminish in response to cold and to increase during the hyperemic phase of primary or secondary RP.<sup>47</sup> Pulmonary capillary blood volume has also been shown to decline in association with cold-induced digital RP, supporting the idea of concurrent pulmonary vasospasm.<sup>48</sup>

Left ventricular dyskinesia is a cardiac manifestation of RP. In one study, regional left ventricular wall-motion abnormalities, as measured by radionuclide ventriculography, were seen with cooling and subsequently improved or resolved with rewarming in patients with secondary RP and systemic sclerosis. Pretreatment with nifedipine blunted the cold-induced wall-motion abnormalities, thus providing further evidence of cold-induced myocardial vasospasm.<sup>49</sup>

Renal manifestations of RP include the increased occurrence of renal scleroderma crises during the winter.<sup>50,51</sup> Cold-induced reductions in renal cortical perfusion have been measured by xenon washout during episodes of digital RP in systemic sclerosis patients.<sup>51</sup>

#### THERAPY

The goals of therapy are to reduce the number and the severity of RP attacks and to prevent digital ischemia and tissue loss. Conservative measures should be instituted in all patients with RP (Table 4). All patients should be taught the importance of keeping the extremities and trunk warm. Wearing protective clothing during the winter is only common sense, but precautions should also be taken with exposure to air conditioning. Additional conservative measures include stopping cigarette smoking<sup>52</sup> and discontinuing medications that induce or exacerbate RP. Typically, patients with primary RP do not require further intervention and should be reassured that digital ischemia and loss of tissue occur extremely rarely.

Pharmacologic agents used include vasodilators, platelet inhibitors, serotonin antagonists, and fibrinolytics (Table 4). Vasodilators are a good first choice for patients with primary or secondary RP. Topical nitroglycerin, applied in small amounts to the base of the fingers, reduces the frequency and severity of vasospastic attacks and the size of digital ulcers, presumably because its vasodilatory action improves digital capillary blood flow. Franks<sup>53</sup> gave methyldopa or guanethidine (sympatholytic agents) and topical nitrates to patients with systemic sclerosis and speculated that the resulting benefits may have been due to the combination of medications. In an earlier study, 1 to 2 g/day of methyldopa reduced the frequency of attacks, prevented cold-induced pain, and increased the digital blood flow and rate of rewarming in patients with primary RP (but not in secondary RP, presumably because of an additional structural obstructive component in the latter).<sup>54</sup>

### Calcium-channel blockers

Many studies have examined the efficacy of calcium-channel blockers, which relax smooth muscle and, thus, are vasodilators.<sup>55,56</sup> Nifedipine has been studied most extensively.<sup>57-59</sup> In these trials, patients taking nifedipine experienced a significant and sustained decrease in the number of RP attacks, although the intensity of the attacks was not significantly different from that in the placebo group.<sup>57,59</sup> Additionally, no significant difference in the mean cold-induced decline in digital artery systolic pressure was documented between the nifedipine and the placebo groups.<sup>58</sup> Side effects included headache, dizziness, edema, palpitations, and pruritus; however, none were intolerable. The extended-release form of nifedipine appears to be better tolerated, but it has not been tested in double-blind, placebo-controlled studies in the treatment of RP.

Sublingual nifedipine administration has produced acute vasodilation, as reflected by digital blood flow and digital temperature, in several studies.<sup>60-63</sup> This suggests a potential use for nifedipine as a prophylactic measure before planned, unavoidable cold exposure. The immediate effects of sublingual nifedipine administration, however, did not predict its long-term efficacy during daily oral administration.<sup>61,62</sup>

Diltiazem has decreased the frequency and severity of attacks in short-term trials.<sup>64,65</sup> Side effects, similar to those caused by nifedipine, also were not

**TABLE 4**  
THERAPEUTIC OPTIONS  
FOR RAYNAUD'S PHENOMENON

|                                                                                          |
|------------------------------------------------------------------------------------------|
| Conservative                                                                             |
| Warm protective clothing for trunk and extremities                                       |
| Discontinue tobacco use                                                                  |
| Discontinue implicated medications (beta blockers, ergotamines, methysergide, clonidine) |
| Biofeedback                                                                              |
| Pharmacologic                                                                            |
| Vasodilators                                                                             |
| Topical nitrates                                                                         |
| Calcium-channel blockers (nifedipine, diltiazem, felodipine, verapamil)                  |
| Iloprost                                                                                 |
| Sympatholytic agents                                                                     |
| Methyldopa                                                                               |
| Guanethidine                                                                             |
| Platelet inhibition                                                                      |
| Salicylates                                                                              |
| Dipyridamole                                                                             |
| Nifedipine                                                                               |
| Nicardipine                                                                              |
| Iloprost                                                                                 |
| Others                                                                                   |
| Pentoxifylline                                                                           |
| Ketanserin                                                                               |
| Captopril                                                                                |
| Prazosin                                                                                 |
| Reserpine                                                                                |
| Triiodothyronine                                                                         |
| Stanozolol                                                                               |
| Recombinant tissue plasminogen activator                                                 |
| Sympathectomy                                                                            |
| Pharmacologic                                                                            |
| Surgical                                                                                 |

severe. Felodipine has been well tolerated in patients with primary RP and has decreased the number and severity (as measured by plethysmography) of RP attacks.<sup>66</sup> Verapamil was no better than placebo in alleviating symptoms, increasing digital systolic pressure and blood flow, and speeding digital rewarming in a trial of 16 patients with severe RP.<sup>67</sup>

### Platelet inhibitors

In addition to their vasodilatory actions, some calcium-channel blockers (nifedipine and nicardipine) have been found to inhibit platelet activation in vitro and in vivo.<sup>68-71</sup> However, studies of nicardipine found no difference in the number or severity of attacks, digital blood flow, or response to cold challenge as compared with placebo.<sup>71</sup> Therefore, the role that platelet inhibition by calcium-channel blockers plays in RP is not clear; perhaps

the vasodilation and reduced vasospasm are the important events.

Aspirin, dipyridamole, and pentoxifylline have been tried as therapy for RP and have not improved the incidence or severity of symptoms.<sup>72,73</sup> Although skin perfusion improved in a study of pentoxifylline, RP symptoms and the occurrence of digital ulcerations were not altered.<sup>73</sup>

### Prostaglandins

Interest in the effects of prostaglandins on digital blood flow has prompted study of the prostacyclin analogue iloprost, which dilates arterioles and also inhibits platelet aggregation. Iloprost significantly decreased the frequency and severity of RP attacks and improved the daily function of patients with RP in several studies, with improvement persisting even 5 to 16 weeks after completion of therapy.<sup>74-76</sup> Digital ulcers also tended to heal better with iloprost, although the difference was not statistically significant.<sup>76</sup>

In a comparison trial of iloprost and nifedipine, both medications reduced the number, duration, and severity of RP attacks; however, three of 11 patients receiving nifedipine withdrew from the study because of side effects. The side effects of iloprost were self-limited and dose-related.<sup>75</sup>

A retrospective study of iloprost<sup>77</sup> in 84 patients with RP associated with connective tissue diseases (87% systemic sclerosis) revealed that 49 (58%) improved with iloprost infusion. Other pharmacologic measures had previously failed in 48 patients, yet 50% of these patients subsequently improved with iloprost.

Thus, iloprost may be useful in severe secondary RP and in patients for whom other treatments have failed. Limitations of iloprost include intravenous administration, restricted availability, and side effects (headache, flushing, nausea, and vomiting).<sup>74</sup>

### Other drugs

Other medications have been studied less extensively. Ketanserin, a serotonin receptor antagonist, improved digital blood flow as measured by photoplethysmography and increased skin temperature in patients with primary or secondary RP.<sup>78</sup> Captopril improved cutaneous blood flow in patients with primary RP, but the patients experienced no subjective improvement in RP attacks.<sup>79</sup> The physiologic mechanisms of the effects of captopril on blood flow are unclear.

Prazosin, a postsynaptic alpha-1 blocking agent, significantly decreased the number of attacks and reduced the digital artery resistance in both primary and secondary RP in a double-blind single-crossover study. However, these effects were not seen in secondary RP patients who had systemic sclerosis.<sup>80</sup> This raises the question of whether catecholamines contribute more in primary RP than in certain secondary forms. Side effects of prazosin included headache, rash, and dizziness. Reserpine given intra-arterially was ineffective in treating primary and secondary RP.<sup>81</sup>

A pilot study of triiodothyronine (T3) in nine patients with RP associated with connective tissue diseases demonstrated a subjective improvement in RP symptoms in all patients.<sup>82</sup> All side effects were dose-related and resolved with dosage reduction.

### Fibrinolytics

Another approach to therapy focuses on the altered fibrinolysis seen in secondary RP. Stanozolol, an anabolic steroid that normalizes an impaired fibrinolytic system, significantly improved digital blood flow and laboratory measures of fibrinolytic activity in patients with systemic sclerosis compared with control subjects.<sup>83</sup> These patients with secondary RP, however, did not experience a subjective improvement in their symptoms. Patients with primary RP experienced neither an objective nor a subjective improvement with stanozolol, and the anabolic steroid-related side effects limited continuation of the study for many patients. Patients with primary RP have not been shown to have the abnormal fibrinolysis seen in secondary RP. Thus, stanozolol is not indicated in primary RP.

Another agent that affects fibrinolysis, recombinant tissue plasminogen activator (rtPA), resulted in short-term improvements in digital blood flow in 10 patients with limited cutaneous systemic sclerosis (CREST syndrome).<sup>84</sup> Long-term improvements (5 days, 2 weeks, 1 month) were not demonstrated. Compared with placebo, rtPA increased mean fingertip temperature and whole-body warmth and improved laser Doppler and fibrinolytic parameters. However, even these changes were not sustained at 5 days. No adverse side effects occurred in this trial.

### Other approaches

Biofeedback may be an alternative to pharmacologic intervention. A retrospective review of 23 cases (11 primary and 12 secondary) demonstrated

greater improvement in baseline digital temperatures in secondary RP. Of the 18 patients available for follow-up 1 year after treatment, 13 (72%) experienced sustained subjective improvement. Four (44%) of the nine who had digital ulcers said they had fewer of them.<sup>85</sup>

Pharmacologic therapy has proven effective in reducing the frequency and severity of RP attacks but may be insufficient to produce adequate healing of digital ulcers with impending gangrene. Sympathetic nervous system blockade has been attempted both surgically and pharmacologically.<sup>86-90</sup> Surgical approaches have included preganglionic, digital, cervical, thoracic, and lumbar sympathectomies, with variable results. Pharmacologic sympathectomy may produce long-lasting improvement<sup>89,90</sup>; however, it is not a cure. The effects of sympathectomy are typically short-lived and should be reserved for the severe, acute threat of impending tissue loss.

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# SUMMARY

RP is an episodic cold- or stress-induced vascular disorder characterized by white, blue, and red discoloration of the fingers and toes. It may exist independently (primary RP) or in association with an underlying disease (secondary RP). For prognostic and therapeutic reasons, it is important to determine if a patient's RP is associated with an underlying condition and if the patient might develop a connective tissue disease. The pathophysiology of RP includes vasospasm, endothelial cell changes, vessel obstructive features, and hemorrheologic factors. The multiple mechanisms involved in the pathogenesis of RP form the basis for the various therapeutic approaches.

# ACKNOWLEDGMENT

We wish to thank Ms. Vicki Bradshaw for secretarial assistance in manuscript preparation.

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