Raynaud’s Phenomenon
An Update
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The pathogenesis of primary Raynaud’s phenomenon remains an enigma. Most evidence favors a local abnormality in the digital arteries as opposed to an increased activity of the sympathetic nervous system. The local fault may involve the α₁-adrenergic receptors, which are most important in reflex sympathetic vasoconstriction. Cooling blood vessels increase the sensitivity of α₁-adrenergic receptors, increased levels of α₁-adrenergic receptors are present in primary Raynaud’s disease, and patients show an increased sensitivity to α₁-adrenergic receptor agonists on finger blood flow. Serotonin has also been implicated, but the evidence is not compelling. In secondary Raynaud’s phenomenon, vasospastic attacks can often be explained by a low arterial distending pressure, a thickened vessel wall, or absence of β-adrenergic receptor activity. Diagnosis of primary Raynaud’s disease relies on a typical history and normal physical examination, laboratory studies, and nailfold capillaroscopy. Finger systolic blood pressures during local cooling with ischemia may be helpful to document vasospastic attacks but does not distinguish primary from secondary Raynaud’s phenomenon. The treatment of Raynaud’s phenomenon is usually conservative. Pavlovian conditioning or biofeedback may be beneficial. When drug therapy is necessary, the calcium channel entry blocker nifedipine or sympatholytic agents have been shown to decrease the frequency and duration of vasospastic attacks in about two thirds of patients, although subjective improvement does not usually correlate with objective testing. Direct-acting vasodilators have not been shown to be of definite benefit. New therapies include prostaglandins, captopril, and the serotonergic antagonist ketanserin. Surgical sympathectomy has not been beneficial. (Hypertension 1991;17:593–602)
Increased activity of the sympathetic nervous system and a local fault in the digital arteries. Arguments for an increased sympathetic nerve activity include the ability to achieve normal hand or finger blood flow during body and hand heating in patients, the benefit of treatment with sympatholytic agents and the relief of vasospastic attacks of the toes by sympathectomy, and the induction of vasospastic attacks by emotional stimuli in some patients. Evidence against sympathetic nervous system overactivity is the direct measurement of normal cutaneous sympathetic nerve activity, local cooling of one hand does not increase reflex sympathetic vasoconstriction in the opposite hand, and normal plasma and urinary catecholamines have been found in primary Raynaud’s disease and scleroderma. The local fault theory or an increased sensitivity of digital blood vessels to cold is substantiated by the induction of vasospastic attacks in sympathetically denervated fingers, the induction of attacks in single fingers, an enhancement of reflex sympathetic vasoconstriction by local hand cooling, and a loss of digital systolic blood pressure with a local ischemia and cold stimulus.

The local fault at the digital artery level may involve the α2-adrenergic receptors. Cooling has been shown to increase the sensitivity of α2-adrenergic receptors but not α1-adrenergic receptors; this may be the mechanism of the enhancement of reflex sympathetic vasoconstriction by local hand cooling. Increased levels of α2-adrenergic receptors of platelets by binding capacity and affinity studies has been found in patients with primary Raynaud’s disease in contrast to control subjects and patients with Raynaud’s phenomenon. In normal subjects, the α2-adrenergic receptors are most important in the reflex sympathetic vasoconstriction induced by body cooling with α1-adrenergic receptors playing a much smaller role. The α2-adrenergic receptor antagonist yohimbine increases finger blood flow significantly in normal subjects during body cooling, whereas the α1-adrenergic receptor antagonist prazosin has only a small effect (Figure 1). Furthermore, patients with primary Raynaud’s disease have an increased sensitivity to intra-arterial infusions of clonidine, the α2-adrenergic receptor agonist, but not to phenylephrine, the α1-adrenergic receptor agonist.

Serotonin has been implicated in the pathophysiology of Raynaud’s phenomenon. S2-serotonergic receptors have been shown to be present in human hand and digital blood vessels by in vitro and in vivo studies. Intra-arterial 5-hydroxytryptamine produced a dose-related decrease in finger blood flow. The S2-serotonergic receptors are evidently involved in the digital vasoconstriction induced by reflex sympathetic stimulation. During reflex sympathetic vasoconstriction produced by body cooling, ketanserin, an S2-serotonergic receptor antagonist, produced a significant increase in finger blood flow (Figure 2). The increase in finger blood flow occurred during α1- and α2-adrenergic receptor blockade, ruling out a sympathetic effect of ketanserin. Patients with primary Raynaud’s disease show an increased sensitivity to intra-arterial 5-hydroxytryptamine infusions compared with normal subjects. One group has reported increased levels of plasma and platelet 5-hydroxytryptamine in patients with primary and secondary Raynaud’s phenomenon. Furthermore, the serotonergic antagonist ketanserin has been reported to benefit patients with Raynaud’s phenomenon. However, infusions of 5-hydroxytryptamine produce a reddish discoloration of the fingers and hand, and ketanserin fails to prevent induction of vasospastic attacks although it relieves induced attacks.

Other theories for digital artery vasospasm include platelet abnormalities and increased blood viscosity.
Factor VIII/von Willebrand factor antigen and von Willebrand factor activity have been found to be increased in blood of patients with primary Raynaud's disease and scleroderma. Elevation of these factors may reflect endothelial cell injury. Endothelial cell injury may develop before structural vascular disease, but its role in primary Raynaud's disease is unknown. Endothelial cell function has not been studied. Most investigators have reported platelet abnormalities in patients with secondary Raynaud's phenomenon, especially scleroderma, but results have been variable in primary Raynaud's disease. Usually 𝛽-thromboglobulin and platelet factor 4, measures of the platelet release reaction, have been normal in the primary disease. Abnormalities in levels of the prostaglandins and thromboxane B2 have been reported in scleroderma but not in primary Raynaud's disease. Usually 𝛽-thromboglobulin and platelet factor 4, measures of the platelet release reaction, have been normal in the primary disease. Abnormalities in levels of the prostaglandins and thromboxane B2 have been reported in scleroderma but not in primary Raynaud's disease. A role for platelets in the pathogenesis of Raynaud's phenomenon has not been defined. Antiplatelet drugs or drugs that block platelet vasoconstrictor products should be more effective in preventing digital vasospasm than shown so far if platelets were important. Measurements of blood and plasma viscosity have produced variable results in patients with primary Raynaud's disease from different investigators. In the connective tissue diseases with Raynaud's phenomenon, blood viscosity is usually increased. No changes were found in finger systolic pressure or its reaction to cold in patients with primary disease treated by venesection to lower blood viscosity. Treatment with stanozolol decreased fibrinogen and increased the hematocrit; it caused no change in whole blood viscosity even though hand blood flow showed an increase in 10 patients with primary or secondary Raynaud's phenomenon. Blood viscosity is probably not of primary importance in digital vasospasm but could be a contributing factor in slowing blood flow in vasoconstricted or structurally abnormal vascular beds.

Studies have shown that patients with primary Raynaud's disease have lower brachial artery, digital, and arteriolar systolic blood pressures than normal subjects (Figure 3). Patients with secondary Raynaud's phenomenon have systemic blood pressures similar to normal subjects. The lower dig-
ital pressures seen in the primary disease are not due to reflex sympathetic vasoconstriction since pressure and blood flow increase equally in normal subjects and patients with digital nerve blocks. The low arterial and arteriolar pressure would predispose to vasospasm since the transmural arterial distending forces are decreased and less external pressure is required to stop blood flow.

A significant correlation of Raynaud's phenomenon and migraine headaches in patients with variant angina pectoris has been documented. Raynaud's phenomenon involves spasm of digital arteries, a decrease in cerebral regional blood flow precedes migraine headaches, and coronary artery vasospasm has been demonstrated in patients with variant angina. The three syndromes occurring together suggest a systemic factor may cause vasospasm in the digital, cerebral, and coronary circulatory beds. It could be a blood-borne or neurological factor or a generalized abnormality of vascular smooth muscle. Another example of vasospasm in more than one circulatory bed is the occurrence of pulmonary hypertension with Raynaud's phenomenon but no underlying systemic disease. Although vasospasm has not been demonstrated in the pulmonary vasculature of these patients, pathological abnormalities to account for the pulmonary hypertension are absent. Furthermore, patients with scleroderma may have Raynaud's phenomenon, decreased renal cortical blood flow with cooling or a cold pressor stimulus, myocardial infarctions with normal coronary arteries, and left ventricular dysfunction with cold exposure.

A major difficulty with the theory of a generalized vascular abnormality in Raynaud's phenomenon is the difference in neurogenic control and reactions to drugs of different circulatory beds. Sympathetic control of the circulation is greatest in the digital arteries, less in the coronary arteries, and negligible in the cerebral vessels. The vessels in these areas could respond with vasospasm because of their type of receptor predominance or unknown local factors. It would be difficult to explain how β-adrenergic receptor blocking drugs and ergot preparations induce Raynaud's phenomenon and aggravate variant angina but benefit patients with migraine headaches.

Therefore, there are many factors that can be implicated in the pathogenesis of vasospastic attacks of the digits (Figure 4). Many of the secondary causes of Raynaud's phenomenon are associated with decreased blood flow and blood pressure in the digits. Arteriography often shows digital artery stenoses or obstructions in the connective tissue diseases, traumatic vasospastic disease, and some of the drug-induced syndromes. Proximal large vessel obstructions in obstructive arterial diseases also give a low distal pressure. The decreased intravascular pressures would lead to vessel closure with normal sympathetic stimuli or external pressure. Additional factors in connective tissue diseases may be a decreased vessel lumen due to thickening of the vascular walls and increased tissue pressure compressing small vessels. Hyperviscosity in the blood dyscrasias and connective tissue diseases would cause sludging of blood and decreased blood flow in the digits. Constant nerve irritation in the carpal tunnel syndrome or thoracic outlet syndromes may induce persistent sympathetic vasoconstriction; similarly, some drugs may induce persistent digital vasospasm. Although studies have not been performed, it is likely that endothelial damage is present in many of the second-
ary causes of Raynaud’s phenomenon, and abnormalities in the release mechanisms of endothelial relaxing and vasoconstrictor factors may be present. Low digital artery pressure, thickened vessel walls, increased blood viscosity, persistent vasoconstriction together with endothelial abnormalities and the release of vasoconstrictor agents from platelet breakdown could lead to closure of arteries or arterioles during a normal sympathetic stimulus with or without an increase in extravascular pressure. In primary Raynaud’s disease, the strongest evidence indicates a local sensitivity of the digital arteries to cold. The abnormality may lie with the \( \alpha \)-adrenergic receptors, but serotoninergic receptors and low intravascular pressure may be contributing factors. The role of the endothelium, platelet vasoactive factors, neuropeptides, and \( \beta \)-adrenergic receptors remains to be explored.

**Diagnosis**

Because there are few tests of diagnostic value in objectively documenting Raynaud’s phenomenon, the history of episodic attacks of well-demarcated color changes of the digits on exposure to cold is most important. The physical exam in patients with primary Raynaud’s disease is normal. Blood and urine examination is also normal. Because Raynaud’s phenomenon may precede diagnostic features of connective tissue diseases by many years, a modification of the criteria proposed by Allen and Brown\(^{39}\) is useful for the diagnosis of primary Raynaud’s disease.

1. Vasospastic attacks induced by cold exposure.
2. Bilateral involvement of the extremities.
3. Absence of gangrene or involvement of only the skin of the fingertips.
4. History of symptoms for at least 2 years.
5. No evidence of an underlying disease including absence of antinuclear antibodies, a normal erythrocyte sedimentation rate, and normal nailfold capillaroscopy and esophageal motility studies.

Nailfold capillaroscopy may be diagnostic of the connective tissue diseases, but polymyositis, thromboangiitis obliterans, Belchet’s disease, and diabetic vasospastic disease may show nailfold capillary abnormalities.\(^{40-43}\) Capillaroscopy is normal in primary Raynaud’s disease. Enlarged, deformed capillary loops surrounded by avascular areas may be seen in scleroderma, mixed connective tissue disease, and dermatomyositis. Abnormal capillary loops and a prominent subpapillary venous plexus may occur in lupus erythematosus, and bushy capillary formations are most common in mixed connective tissue disease.

The effect on finger systolic blood pressure of local cooling and ischemia has been used as a diagnostic objective test for Raynaud’s phenomenon.\(^{11}\) The digit is usually cooled by circulating water through a finger cuff around the proximal finger, and the finger is made ischemic by inflating a digital blood cuff to suprasystolic pressure at each temperature for 5 minutes. Cooling to 20°, 15°, 10°, and 5°C are the temperatures usually used. Patients with primary and secondary Raynaud’s disease have a greater reduction or loss of finger systolic pressure with cooling compared with normal subjects who show a gradual decrease. This test is more sensitive if the body is also cooled. Patients with secondary Raynaud’s phenomenon are more likely to have a positive test.\(^{44}\) This test does not differentiate primary from secondary causes of Raynaud’s phenomenon.

**Treatment**

Conservative measures will suffice for the majority of patients with primary or secondary Raynaud’s phenomenon. Most patients need reassurance that they will not lose digits; only rare patients with the primary disease develop small areas of gangrene at the fingertips. Patients must keep the hands and feet warm and dry; mittens are better than gloves so that the fingers may share their warmth. All parts of the body must be protected from cold exposure to prevent reflex sympathetic vasoconstriction of the digits. Stimuli that produce vasospastic attacks, usually cold plus pressure on the digits, must be avoided. There are a variety of battery-operated or chemical devices available for warming the hands or feet. Tobacco smoking should be stopped because nicotine stimulates the sympathetic nerves to effect vasoconstriction.\(^{45}\) Drugs that induce digital vasoconstriction such as \( \beta \)-adrenergic receptor antagonists and ergotamine preparations should be withdrawn if possible.

Biofeedback or Pavlovian conditioning has proved of benefit to some patients. One of the more successful regimens has been immersing the hands in 43°C water while the body is exposed to 0°C temperatures.\(^{46}\) After 3 weeks of daily sessions, improvement has been noted for several months.

When the vasospastic attacks interfere with patients’ ability to work or perform daily activities, or trophic digital lesions develop, drug therapy should be tried. Drugs used in the treatment of Raynaud’s phenomenon are nonspecific and produce many side effects; beneficial responses usually do not correlate with objective tests of the digital circulation. Only about two thirds of patients can be expected to respond to drug therapy.

**Calcium Entry Blockers**

*Nifedipine.* Nifedipine has been shown to decrease the frequency, duration, and intensity of vasospastic attacks in approximately two thirds of patients with primary or secondary Raynaud’s phenomenon.\(^{47-49}\) The movement of calcium ions in the slow channels is inhibited by calcium entry blockers, leading to a reduced influx of calcium into the cells and decreased smooth muscle contractility. Calcium entry blockers are particularly effective in inhibiting vascular responses evoked by \( \alpha \)-adrenergic receptor activity,\(^{50}\) and in some animal vessels, most of the contraction to serotonin is inhibited.\(^{51}\)

Nifedipine is currently the drug of first choice. Patients with primary Raynaud’s disease may show the most improvement, and digital ulcers have been re-
reported to heal in patients with scleroderma. Objective tests of digital circulation often do not show the basis for the drug's action, although a decrease in fingertip vascular resistance occurs with acute doses of nifedipine\(^4^9\) (Figure 5). Doses of 10–30 mg three times a day have been used. Frequent side effects of headache, dizziness, flushing, palpitations, dyspepsia, pruritus, and edema prevent the use of nifedipine in many patients. We have found that the new slow release preparation avoids some of these side effects and is effective treatment, but formal studies have not been performed in patients with Raynaud's phenomenon.

Diltiazem. Diltiazem, at doses of 30–120 mg three times a day, has been reported to benefit patients with primary or secondary Raynaud's phenomenon in three small double-blind, placebo-controlled studies.\(^52^-^54\) One study in patients with secondary Raynaud's phenomenon showed no decrease in frequency of attacks or general improvement with 60 mg three times a day.\(^55\) Side effects of diltiazem include headache, flushing, lightheadedness, nausea, and ankle edema but are less than with nifedipine. We have used diltiazem in patients who could not tolerate nifedipine, but results have been unsatisfactory.

Verapamil. Verapamil has been studied in patients with severe primary or secondary Raynaud's phenomenon at a dose of 80 mg four times a day.\(^56\) Subjective symptoms and objective findings showed no benefit.

Nicardipine and Nisoldipine. These two calcium channel blocking agents have been the subject of only a few studies in patients with Raynaud's phenomenon and results have been conflicting for both drugs. In one double-blind, placebo-controlled study,\(^57\) nicardipine (30 mg three times a day) significantly reduced the frequency of attacks in 27 patients with Raynaud's phenomenon but no effect on objective tests was apparent. However, in another study,\(^58\) the same dose of nicardipine failed to decrease the frequency or severity of attacks compared with placebo. Nisoldipine has also been reported to have favorable effects in one study\(^59\) but no effect in another.\(^60\)

**Sympatholytic Agents**

Reserpine and guanethidine. Reserpine and guanethidine have been used for many years in the treatment of Raynaud's phenomenon. Reserpine depletes norepinephrine from arteries and guanethidine interferes with the release of norepinephrine from sympathetic neuroeffector junctions. Both drugs have been shown to increase digital capillary blood flow in patients with Raynaud's phenomenon or scleroderma\(^61^-^62\) (Figure 6). Adequate control studies have not been performed with either agent. Intra-arterial reserpine has not been shown to be of more benefit than placebo injections.\(^63\) Reserpine is given in a dose of 0.125–1.0 mg daily and may produce nasal congestion, bradycardia, postural hypotension, dyspepsia, and edema. A dose of 0.25 mg intravenously is used to decrease sympathetic tone. Guanethidine is given intravenously as a dose of 0.125–1.0 mg. The use of guanethidine should be avoided in patients with Raynaud's phenomenon because of the increased risk of producing orthostatic hypotension. Both reserpine and guanethidine have been the subject of many studies. However, the results of these studies are conflicting and hard to interpret because of the many variables that affect the outcome of such studies.
fluid retention, lethargy, and depression. The dose of guanethidine is 10–50 mg daily and may induce postural hypotension, diarrhea, and impotence. It does not cause depression. Both drugs must be titrated to relief of symptoms or side effects.

Prazosin and Thymoxamine. Prazosin, an α1-adrenergic receptor antagonist, has been the subject of several placebo-controlled studies in patients with primary or secondary Raynaud's phenomenon, some positive and some negative. Although one study reported dissipation of the initial benefit with prolonged treatment, it appears that moderate benefit can be expected in about two thirds of patients in decreased frequency of vasospastic attacks and overall subjective good response. Objective tests of changes in finger hemodynamics with prazosin have also been conflicting. The dosage of prazosin is variable, ranging from 2 to 8 mg daily. With the higher doses, side effects of palpitations, nausea, headache, dizziness, fatigue, edema, dyspnea, rash, or diarrhea may limit its use.

Thymoxamine is also predominantly an α1-adrenergic receptor antagonist although it has some α2-adrenergic receptor blocking effect. At doses of 40–160 mg/day, one controlled study and one uncontrolled study have shown some benefit in relieving symptoms of vasospastic attacks and in objective tests of the finger circulation. Side effects are reported as less than with prazosin. More experience is needed with this agent; it is not available in the United States.

Methyldopa. Methyldopa was reported to subjectively improve 30 of 42 (75%) patients with primary or secondary Raynaud's phenomenon at a dose of 1–2 g daily in an uncontrolled study. There was an increased rate of rewarming of fingers after cold exposure. Methyldopa stimulates the central inhibitory α-adrenergic receptors, producing peripheral vasodilation. In a study comparing methyldopa with other drugs, no subjective or objective benefit was found in patients with Raynaud's phenomenon, but the average dose was only 704.3 mg daily. Side effects of methyldopa include drowsiness, headache, dry mouth, postural hypotension, nasal congestion, edema, and diarrhea. Fever and hemolytic anemia may occur. We have not had success in treating patients with primary or secondary Raynaud's phenomenon with methyldopa.

Phenoxybenzamine. Phenoxybenzamine is an α-adrenergic receptor antagonist that has been used in the treatment of Raynaud's phenomenon. Conflicting reports exist regarding its efficacy. The side effects of the recommended doses of 10–30 mg four times a day are often intolerable. These include postural hypotension, nasal congestion, palpitations, impotence, and gastrointestinal symptoms.

Direct-acting agents. Nitroglycerin preparations applied to the hands have been recommended for patients with Raynaud's phenomenon since 1948. Studies of various nitroglycerin preparations have shown variable results. One placebo-controlled study using 10 cm of 1% nitroglycerin three times a day for 6 weeks reported fewer and less severe vasospastic attacks and better healing of ulcers in patients with secondary Raynaud's phenomenon who were taking maximally tolerated doses of sympatholytic agents. Headache has been a major problem with the use of any nitroglycerin preparation. In our experience, patients receive little if any benefit from this agent.

Nicotinic acid and papaverine compounds have been studied in patients with Raynaud's phenomenon, but there is little evidence to recommend their use.

New Treatments

Prostaglandins. Prostacyclin and prostaglandins E1 and E2 have been studied in the treatment of Raynaud's phenomenon because of their vasodilatory action and ability to inhibit platelet aggregation. Several uncontrolled studies reported benefit with intravenous infusions of prostaglandin E1, but a large multicenter study comparing the agent with placebo infusions showed no improvement in frequency or severity of Raynaud's attacks, ulcer healing, skin temperature, or digital systolic pressure during cooling. Controlled studies with intravenous prostacyclin analogues and prostaglandin E1 ointment have shown more promise with the effect of intravenous infusions lasting several weeks. However, a study of intravenous iloprost compared with oral nifedipine showed no significant difference in the effect of the two agents on frequency, duration, or severity of attacks or healing of digital lesions. Hand temperature and digital circulation (laser Doppler and photoplethysmography) were increased with iloprost but not nifedipine. It was considered that side effects were less with iloprost than with nifedipine, but of course, the iloprost had to be given intravenously. Oral prostaglandin preparations are now being studied and may prove of value in the treatment of Raynaud's phenomenon.

Captopril. Captopril was reported to heal digital ulcers in patients with scleroderma. Because the acute vasodilator effect of captopril on the fingers was blocked by serine proteinase inhibitors and angiotensin II antagonists had no effect on finger blood flow, kinin accumulation was considered to be the mechanism of action. Uncontrolled studies performed with captopril showed significant improvement in both subjective and objective parameters. One study found that only patients with primary Raynaud's disease were benefited and not patients with scleroderma. The only placebo-controlled study did not find a significant decrease in the frequency or severity of attacks, although parameters of finger blood flow increased. Usual dosage has been 25 mg three times a day; side effects include rash, cough, taste impairment, deterioration in renal function, and neutropenia. The role of angiotensin converting enzyme inhibitors in the treatment of Raynaud's phenomenon remains to be determined.

Ketanserin. Ketanserin is a serotoninergic S2 antagonist that also has some α1-adrenergic receptor blocking activity. It would therefore inhibit the vasocon-
striction and platelet aggregation induced by serotonin. It has been shown to increase digital pulse volume and finger temperature when given intravenously to patients with Raynaud's phenomenon. Several small uncontrolled and placebo-controlled studies have reported conflicting results with oral ketanserin in the treatment of Raynaud's phenomenon. However, a very large double-blind, placebo-controlled trial in patients with primary and secondary Raynaud's phenomenon due to connective tissue disease showed a significant decrease in the frequency but not the duration or severity of the vasospastic attacks (Figure 7). The patients and their physicians considered there was significant improvement with the drug. Side effects of ketanserin include dizziness, sedation, edema, dry mouth or eyes, anxiety, and scotomas. The QT interval may be prolonged. Usual dosage has been 40 mg two or three times a day. Ketanserin is not available in the United States.

Sympathectomy. Cervicothoracic sympathectomy has been performed in patients with Raynaud's phenomenon. In the upper extremities, immediate results are sometimes excellent in patients with primary Raynaud's phenomenon but vasospastic attacks usually recur within 6 months to 2 years. Even less benefit is obtained in patients with secondary Raynaud's phenomenon. Complications include Horner's syndrome, dryness of the skin, excess perspiration of the trunk and thighs, pleural effusions, pneumothorax, neuralgia, and atrial fibrillation. However, lumbar sympathectomy for Raynaud's phenomenon of the toes has benefited more than 80% of patients and results are usually permanent.

The results of sympathectomy are difficult to evaluate because there are no controlled studies and usually only patients with very severe disease undergo surgery. The success rate is no better than conservative medical management. Sympathectomy should definitely not be performed in patients with secondary Raynaud's phenomenon, and it is of doubtful value in the primary disease.

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