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Raynaud Phenomenon

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Updated: Jun 3, 2009

Introduction

Background

Raynaud phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure. The phenomenon is named for Maurice Raynaud, who, as a medical student, defined the first case in 1862 as "episodic, symmetric, acral vasospasm characterized by pallor, cyanosis, suffusion, and a sense of fullness or tautness, which may be painful."[1]

Secondary Raynaud phenomenon should be distinguished from primary Raynaud phenomenon (Raynaud disease). They are distinct disorders that share a similar name. Raynaud disease is characterized by the occurrence of the vasospasm alone, with no association with another illness. Secondary Raynaud phenomenon is a designation usually used in the context of vasospasm associated with another illness, most commonly an autoimmune disease.

There are several diagnostic criteria for primary Raynaud phenomenon, including attacks triggered by exposure to cold and/or stress, symmetric bilateral involvement, an absence of necrosis, no detectable underlying cause, normal capillaroscopy findings, normal laboratory findings for inflammation, and an absence of antinuclear factors.[2]

Young female patients who have had Raynaud phenomenon alone for more than 2 years and have not developed any additional manifestations are at low risk for developing an autoimmune disease. The same should not be said for older patients and male patients with Raynaud phenomenon, as vasospastic symptoms may predate systemic disease by as many as 20 years. In some studies, 46%-81% of affected patients have secondary Raynaud phenomenon.

Although Raynaud phenomenon has been described with various autoimmune diseases, the most common association is with progressive systemic sclerosis (90% in individuals with scleroderma) and mixed connective-tissue disease (85% prevalence). Raynaud phenomenon has also been described with such diverse diseases as systemic lupus erythematosus and other disorders not classified as autoimmune, including frostbite, vibration injury, polyvinyl chloride exposure, and cryoglobulinemia.

Pathophysiology

In individuals with Raynaud phenomenon, one or more body parts experience intense vasospasm with associated pallor and, often, cyanosis. This is often followed by a hyperemic phase with associated erythema. The affected body parts are usually those most susceptible to cold injury. A clear line of demarcation exists between the ischemic and unaffected areas. These effects are reversible, and they must be distinguished from irreversible causes of ischemia such as vasculitis or thrombosis. Rarely, tissue necrosis occurs distal to the affected vessel, usually in the periphery of the vasculature. It most commonly affects the digits of the fingers but may affect the toes, nose, and ears. Occasionally, even the tongue is involved.

Despite several years of research, the full understanding of the pathophysiology of Raynaud phenomenon remains to be elucidated.

Primary Raynaud phenomenon is related to functional alterations alone. In contrast, secondary Raynaud phenomenon also reflects structural microvascular abnormalities. Herrick (2005) reviewed the pathogenesis of Raynaud phenomenon and describes the mechanisms under 3 categories: vascular, neural, and intravascular abnormalities.[3]

Vascular abnormalities

- Endothelial dysfunction
  - A deficiency of vasodilatory mediators, including nitric oxide, has been implicated in the pathogenesis of Raynaud phenomenon.[4]
  - Endothelin-1, a potent vasoconstrictor found in the endothelium, has been found to be circulating in high levels in patients with secondary Raynaud phenomenon.[5]

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Vascular abnormalities

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    - A deficiency of vasodilatory mediators, including nitric oxide, has been implicated in the pathogenesis of Raynaud phenomenon.[4]
    - Endothelin-1, a potent vasoconstrictor found in the endothelium, has been found to be circulating in high levels in patients with secondary Raynaud phenomenon.[5]
        - Release of endothelin-1 is triggered by vasoactive stimuli, including angiotensin, vasopressin, and transforming growth factor-beta (TGF-beta).[6]
        - A study by Rajagopalan et al (2003) reported increased levels of circulating endothelin-1 in patients with secondary Raynaud phenomenon.[4]
        - There have been conflicting results regarding the levels of endothelin-1 in patients with primary Raynaud phenomenon.
    - Angiotensin also has vasoconstrictive and profibrotic effects.[7]
        - A 2004 study by Kawaguchi et al revealed higher levels of angiotensin II in patients with diffuse cutaneous systemic sclerosis.[8]
        - Based on these results, treatment with angiotensin-converting enzyme (ACE) inhibitors needs further investigation.
- Structural abnormalities
    - In patients with systemic sclerosis, Raynaud phenomenon differs from primary Raynaud disease.[9]
    - It is related to fibrotic proliferation of the vasculature leading to reduced blood flow to the digits.

Neural abnormalities

- Central mechanisms
    - Edwards et al (1998) performed a series of experiments showing that patients with primary Raynaud phenomenon do not habituate to stressful stimuli in the same way as healthy control subjects. The ability to habituate is described as vasodilation in forearm muscles and vasoconstriction in the cutaneous circulation of skin.
    - Based on these data, it is presumed that patients with Raynaud phenomenon repeatedly undergo cutaneous vasoconstriction to many stressful stimuli. Healthy individuals are able to habituate, thus not displaying these responses.[10]
- Impaired vasodilation
    - An important neuropeptide, calcitonin gene-related peptide, is a potent vasodilator secreted by nerves that supply blood vessels.[11]
    - A diminished number of calcitonin gene-related peptide–releasing neurons has been found in skin biopsy samples of patients with primary Raynaud and systemic sclerosis.[12]
    - Neuropeptide Y, a potent vasoconstrictor, has been found in increased levels in Raynaud phenomenon secondary to systemic sclerosis.
- Impaired vasoconstriction

- α_{2C} -adrenoreceptors overactivity: α_{2C} -adrenoreceptors have been found to enable cold-induced vasoconstriction of the blood vessels.[13]
- Two studies by Furspan et alshowed that the enhanced contractile response to α_2 -adrenergic agonists and cooling in patients with primary Raynaud phenomenon may be linked to increased protein tyrosine kinase activity.[14]
- These data provide information regarding the possible benefits of protein tyrosine kinase inhibitors in the treatment of Raynaud phenomenon.

Intravascular abnormalities

- In primary Raynaud and systemic sclerosis, increased platelet activation and aggregation has been demonstrated.[15]
- An increased production of platelet thromboxane A_2, a potent vasoconstrictor, has been found in patients with Raynaud phenomenon.
- In patients with systemic sclerosis, an impaired fibrolytic system has been reported, probably contributing to vascular obstruction.[16]
- Oxidative stress by reactive oxygen species has also been implicated in the pathogenesis of Raynaud phenomenon.

Frequency

United States

- A 7-year study of Raynaud phenomenon in whites in the United States showed baseline prevalence rates of 11% in women and 8% in men and yearly incidence rates of 2.2% in women and 1.5% in men.[17]

International

- The prevalence of primary Raynaud phenomenon varies among different populations, from 4.9%-20.1% in women to 3.8%-13.5% in men.
- As in the United States, the prevalence of secondary Raynaud phenomenon depends on the underlying disorder.

Mortality/Morbidity

- Primary Raynaud phenomenon does not usually cause death or serious morbidity. However, in very rare cases, ischemia of the affected body part can result in necrosis.
- Secondary Raynaud phenomenon is important as a possible marker for other diseases that may lead to morbidity and mortality. Examples of this include scleroderma (progressive systemic sclerosis), systemic lupus erythematosus, and hyperviscosity syndromes.

Race

- Primary Raynaud phenomenon has no racial predilection.
- Secondary Raynaud phenomenon approximates the racial prevalence of the underlying disease, if any.

Sex

- The prevalence of primary Raynaud phenomenon varies in different populations, ranging from 4.9%-20.1% in women to 3.8%-13.5% in men.

Age

- Primary Raynaud phenomenon usually occurs in the second or third decade of life.
- Secondary Raynaud phenomenon begins in accordance with the underlying disorder.

Clinical

History

- Numbness and pain in the affected area or areas may be present.
- Affected areas show at least two color changes: white (pallor), blue (cyanosis), and red (hyperemia).
    - The color changes are usually in the order noted, but not always.
    - These changes should be reversible but may, in severe cases, lead to local ischemia and ulceration.
- Any history of associated symptoms should raise suspicion of an underlying disorder. History of other vasospastic symptoms such as migraines may be useful.
- Obtain occupational history.
    - Secondary Raynaud phenomenon has been associated with the frequent use of vibrating tools such as jackhammers and sanders.

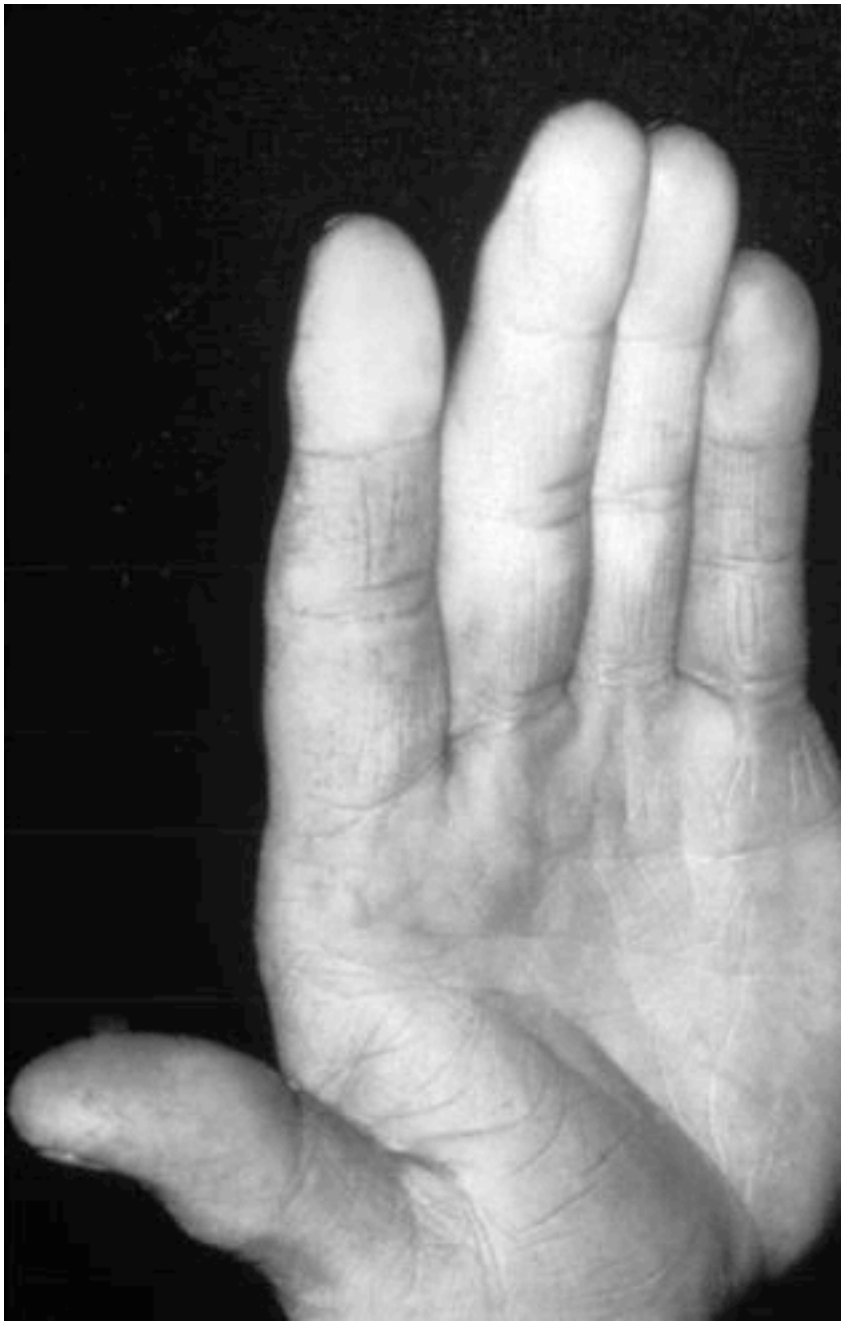


Photo of a patient with Raynaud phenomenon that resulted from working with a jackhammer. Courtesy of the CDC.

- Industrial exposure to polyvinyl chloride has been implicated.
- Any history of injury or frostbite may leave the involved limb vulnerable to vasospasm.

- Syndromes associated with Raynaud phenomenon include the following:
  - Autoimmune disorders
    - Progressive systemic sclerosis (scleroderma) including the diffuse and limited (formerly called CREST syndrome)

        - Systemic lupus erythematosus
        - Mixed connective-tissue disease (and other overlap syndromes)
        - Dermatomyositis and polymyositis
        - Rheumatoid arthritis
        - Sjögren syndrome
        - Vasculitis
        - Primary pulmonary hypertension
    - Infectious syndromes
        - Hepatitis B and C infections (especially associated with mixed or type 3 cryoglobulinemia)
        - *Mycoplasma infections* (with cold agglutinins)
    - Neoplastic syndromes
        - Lymphoma
        - Leukemia
        - Myeloma
        - Waldenström macroglobulinemia
        - Polycythemia
        - Monoclonal or type 1 cryoglobulinemia
        - Lung adenocarcinoma
        - Other paraneoplastic disorders
    - Environmental associations
        - Vibration injury
        - Vinyl chloride exposure
        - Frostbite
        - Lead exposure
        - Arsenic exposure
    - Metabolic/endocrine syndromes
        - Acromegaly
        - Myxedema
        - Diabetes mellitus
        - Pheochromocytoma
        - Fabry disease
    - Hematologic syndromes
        - Paroxysmal nocturnal hemoglobinuria
        - Polycythemia
        - Cryofibrinogenemia
    - Drug-related associations
        - Oral contraceptives
        - Ergot alkaloids
        - Bromocriptine
        - Beta-adrenergic blocking drugs
        - Antineoplastics (eg, vinca alkaloids, bleomycin, cisplatin)
        - Cyclosporine
        - Alfa-interferon
- Syndromes that may be confused with Raynaud phenomenon are as follows:
    - Anatomic syndromes
        - Carpal tunnel syndrome
        - Reflex sympathetic dystrophy syndromes
        - Thoracic outlet syndrome
    - Miscellaneous circulatory syndromes
        - Atherosclerosis

        - Thromboangiitis obliterans
        - Vasculitis
        - Thromboembolic disease
    - Vasospastic syndromes
        - Livedo reticularis
        - Acrocyanosis
        - Chilblains

Physical

- Carefully examine digits if either primary or secondary Raynaud is suspected.
    - Observe for sclerodactyly, calcinosis, or digital ulcers.
    - Examine nailfold capillaries under magnification from a dissecting microscope or ophthalmoscope to help diagnose underlying autoimmune disorders.
    - Abnormalities often appear in patients with early scleroderma. The normally regular pattern of capillary loops is replaced with abnormally large loops, alternating with areas without any capillaries.
- Evaluate any signs or symptoms of other syndromes associated with secondary Raynaud.
    - Bone pain may suggest a paraneoplastic syndrome associated with a hyperviscosity syndrome.
    - The presence of nephritis, malar erythema, and arthritis suggests systemic lupus erythematosus.
- Persistent cyanosis or necrotic distal tissue suggests an underlying disorder or permanent ischemia. Livedo reticularis suggests an autoimmune disorder or coagulation abnormality.
- Carpal tunnel syndrome has been associated with an increased frequency of Raynaud phenomenon.

Causes

- The cause of primary Raynaud phenomenon remains unknown.
- Possible causes for secondary Raynaud can be divided into several broad categories, including the following:
    - Occupational
    - Hematologic
    - Collagen-vascular (autoimmune)
    - Medication-induced
    - Miscellaneous syndromes such as Fabry disease, pheochromocytoma, lung adenocarcinoma, acromegaly, carpal tunnel syndrome, and myxedema
- Although the following entities do not usually have the same inciting causes, nor do they encompass the usual color changes associated with Raynaud phenomenon, they can easily be mistaken for Raynaud phenomenon:
    - Vasculitis
    - Carpal tunnel syndrome
    - Reflex sympathetic dystrophy
    - Thromboembolic disease
    - Thoracic outlet syndrome

Differential Diagnoses

Acromegaly	Localized Fibrosing Disorders: Linear Scleroderma, Morphea, Reg Fibrosis

Acute Myelogenous Leukemia
Antiphospholipid Antibody Syndrome and Pregnancy
Antithrombin Deficiency
Arteriovenous Fistulas
Atherosclerosis
Buerger Disease (Thromboangiitis Obliterans)
Carcinoid Lung Tumors
Cold Agglutinin Disease
Cryoglobulinemia
Dermatomyositis
Diabetes Mellitus, Type 1
Diabetes Mellitus, Type 2
Extremity Vascular Trauma
Frostbite
Graft Versus Host Disease
Heart-Lung Transplantation
Hemoglobinuria, Paroxysmal Cold
Hepatitis B
Hepatitis C
Hypothermia
Injecting Drug Use
Lung Cancer, Non-Small Cell
Lung Cancer, Oat Cell (Small Cell)
Lymphoma, B-Cell
Mixed Connective-Tissue Disease
Multiple Myeloma
Paroxysmal Nocturnal Hemoglobinuria
Peripheral Arterial Occlusive Disease
Pheochromocytoma
Polycythemia Vera
Polymyositis
Protein C Deficiency
Protein S Deficiency
Rheumatoid Arthritis
Scleroderma
Sjogren Syndrome
Stimulants
Systemic Lupus Erythematosus
Toxicity, Arsenic
Toxicity, Cocaine
Toxicity, Cyanide
Toxicity, Lead

Other Problems to Be Considered

Acrocyanosis

Alfa-interferon

Antineoplastics (eg, vinca alkaloids, bleomycin, cisplatin)

Beta-adrenergic blocking drugs

Bromocriptine

Carpal Tunnel Syndrome

Chilblains

Cryoglobulinemia, mixed or type 3, associated with hepatitis B and C

Cryoglobulinemia, monoclonal or type I

Cyclosporine

Ergot alkaloids

Fabry disease

Leukemia

Livedo reticularis

Lymphoma

Mycoplasma infection with cold agglutinins

Myeloma

Oral contraceptives

Overlap syndromes

Peripheral Vascular Disease

Scleroderma, diffuse and localized (CREST syndrome)

Thoracic Outlet Syndrome

Thromboembolic disease

Vasculitis

Vibration injury

Vinyl chloride exposure

Waldenström macroglobulinemia

Workup

Laboratory Studies

- Complete blood cell count - To evaluate for polycythemic disorders, underlying malignancies, or autoimmune disorders
- Blood urea nitrogen - To evaluate for possible renal impairment or dehydration
- Creatinine - To evaluate for possible renal impairment
- Prothrombin time - To observe for any evidence of hepatic dysfunction
- Activated partial thromboplastin time - To observe for any evidence of antiphospholipid antibody disorder or hepatic dysfunction
- Serum glucose - To evaluate patient for diabetic disease
- Thyroid-stimulating hormone - To observe for thyroid disorders
- Optional laboratory tests
    - Antinuclear antibody - May be positive in autoimmune disorders and should be obtained in patients with features of these disorders
    - Serum viscosity - Elevated in hyperviscosity syndromes such as paraproteinemias
    - Serum creatine kinase - Elevated in muscle damage such as polymyositis and dermatomyositis
    - Rheumatoid factor - May be elevated in rheumatoid arthritis, other autoimmune disorders, and some forms of cryoglobulinemia (monoclonal proteins in multiple myeloma and Waldenström macroglobulinemia have an increased frequency of rheumatoid factor activity)
    - Hepatitis panel - Positive for B or C infection in many patients with cryoglobulinemia
    - Cold agglutinins - Present in *Mycoplasma* infections and lymphomas
    - Heavy metal screen - To observe for patients with neuropathic pain due to poisoning
    - Growth hormone - To evaluate for acromegaly
    - Serum vanillylmandelic acid - To evaluate for pheochromocytoma
    - Metanephrine - To observe for pheochromocytoma in appropriate patients
    - Catecholamines - To observe for pheochromocytoma
    - Leukocyte alkaline phosphatase - To evaluate for leukemias in appropriate patients
    - Antiphospholipid antibodies studies - Including dilute Russell viper venom studies, anticardiolipin antibodies, and anti-beta-1-glycoprotein-2 antibodies.

Imaging Studies

- Thermography, isotope studies, and arteriography have all been used, but none has proven superior to clinical assessment in office practice.
- A fixed, nonreversible, cyanotic lesion requires further evaluation of the vasculature.

Other Tests

- Acid hemolysis test
- Sucrose lysis test

Procedures

- Serum protein electrophoresis
- Liver or kidney biopsy
- Measurement of digital blood pressures before and after immersion in cold water (The difference should be less than 30 mm Hg.).

Treatment

Medical Care

- General measures: These include education, warming of local body part, and cessation of vasoconstricting agents such as nicotine.
- Primary Raynaud phenomenon
    - Use calcium channel blockers, especially those that cause vasodilation. The most commonly used drug is nifedipine. Use the lowest dose of a long-acting preparation and titrate up as tolerated. If adverse effects occur, decrease dosage or use another agent such as nicardipine, amlodipine, or diltiazem.
    - ACE inhibitors and intravenous prostaglandins have been advocated, and clinical trials have indicated some benefit. The selective serotonin uptake inhibitor (SSRI) fluoxetine has also been shown effective in at least one study.
    - Therapy with antiplatelet agents has been attempted but has not been proven effective, and anticoagulation is not indicated. The angiotensin-receptor antagonist losartan at 50 mg/d has been found effective in patients with primary Raynaud phenomenon and scleroderma.
    - Topical nitroglycerin (1% or 2%) has been found to help if applied locally based on a limited number of controlled studies.[18]
- Secondary Raynaud phenomenon
    - Therapy must be tailored to the underlying disorder.
    - If associated with occupational or toxic exposure, the patient should avoid the inciting environment.
    - Patients with hyperviscosity syndromes and cryoglobulinemia improve with treatments that decrease the viscosity and improve the rheologic properties of their blood (eg, plasmapheresis).
    - Unfortunately, patients with autoimmune disorders and associated Raynaud phenomenon do not usually respond well to therapy.
    - Hepatitis B, hepatitis C, and *Mycoplasma* infections need to be addressed, if present.
    - In older patients with newly onset Raynaud phenomenon and no obvious underlying cause, malignancy must be considered.

Surgical Care

- Cervical sympathectomy is still considered controversial and may offer only temporary relief.
- Digital sympathectomy has been gaining support for severe or tissue-threatening disease. This may be used in patients with either primary or secondary Raynaud phenomenon, but it is more commonly necessary with the secondary forms.

Consultations

- Typically, primary Raynaud phenomenon does not require any consultations.
- Secondary Raynaud phenomenon may require consultations.
    - Consult a rheumatologist or hematologist to delineate associated syndromes.
    - Fixed (nonreversible) lesions are not Raynaud phenomenon and may require referral to a rheumatologist, vascular surgeon, orthopedist, or other specialist.

Diet

Fish oils containing omega-3-fatty acids may be beneficial in some patients with primary Raynaud phenomenon.

Activity

- Nondrug therapy may be all that is required for mild cases of primary Raynaud phenomenon. Therapies can include the following:
    - Biofeedback and relaxation
    - Avoiding inciting environmental factors such as direct contact with frozen foods or cold drinks
    - Insulation against cold and local warming, including electric and chemical warming devices
    - Removing any drugs from the medical regimen that may provoke vasospasm
    - Avoiding smoking
- With time, most patients learn to incorporate these therapies on their own.

Medication

Drugs should be used to vasodilate the affected circulation, as long as other tissues and systemic blood pressure are not compromised.

Calcium channel blockers

These agents are used for vasodilation and possible antiplatelet effects. The dihydropyridine class of agents contains potent vasodilators and is the first line of treatment after nondrug therapy.

Nifedipine (Adalat, Procardia)

Start with lowest dose available and titrate upward as tolerated. Result should be a diminution in the frequency or severity of attacks. Usually preparations that are not strong negative inotropes are preferred. ER dosage form is most commonly used. If this drug cannot be used, the alternative preparations (nicardipine, amlodipine, diltiazem) are worth considering.
On average, moderate reduction of up to 35% improvement can be expected.
Nifedipine among the dihydropyridines has been extensively studied; however, in the same category, felodipine, amlodipine, and isradipine seem to be equally effective.

Dosing

Adult

30 mg XL PO qd

Pediatric

Not recommended

Interactions

Caution with coadministration of any agent that can lower BP, including beta-blockers and opioids; H2 blockers (cimetidine) may increase toxicity

Contraindications

Documented hypersensitivity; systemic hypotension; possibly, esophageal reflux; aortic stenosis

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Teratogenic in rats and rabbits; blood pressure should be monitored; PT in patients on warfarin may be prolonged; may cause lower extremity edema; allergic hepatitis has occurred but is rare; possible increased cardiovascular risks with short acting preparations; may cause headache and reflex tachycardia, edema, and flushing

Nicardipine (Cardene, Cardene SR)

Used for vasodilatation and possible antiplatelet effects. Start with lowest dose available. Extended dose preparations and agents with fewer negative inotropic effects are preferred.

Dosing

Adult

20-30 mg PO tid or 30-60 mg PO bid (extended dose)

Pediatric

Not recommended

Interactions

Interactions with other agents that lower blood pressure

Contraindications

Documented hypersensitivity; systemic hypotension; possibly, gastroesophageal reflux; aortic stenosis

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Causes vasodilatation; may cause headache, tachycardia, edema, and flushing; possible increased cardiovascular risks with short-acting agents; used with caution in patients with intracerebral hemorrhage and hepatic metabolism, so caution should be used when using it in patients with impaired liver function

Amlodipine (Norvasc)

Relaxes coronary smooth muscle and produces coronary vasodilation, which in turn improves myocardial oxygen delivery. Benefits nonpregnant patients with systolic dysfunction, hypertension, or arrhythmias. Can be used during pregnancy if clinically indicated.

Dosing

Adult

2.5-5 mg/d PO; not to exceed 10 mg/d PO

Pediatric

Not recommended

Interactions

Fentanyl may increase hypotensive effects; may increase cyclosporin levels; H2 blockers (cimetidine) may increase toxicity

Contraindications

Documented hypersensitivity; systemic hypotension; aortic stenosis

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Adjust dose in renal/hepatic impairment; may cause lower extremity edema; allergic hepatitis has occurred but is rare

Diltiazem (Cardizem CD, Cardizem SR, Dilacor, Tiamate, Tiazac)

During depolarization, inhibits calcium ions from entering the slow channels and voltage-sensitive areas of vascular smooth muscle and myocardium. Causes some vasodilatation but not as potently as nifedipine.

Dosing

Adult

Cardizem SR: 60-120 mg PO bid

Pediatric

Not established

Interactions

May increase carbamazepine, digoxin, cyclosporine, and theophylline levels; when administered with amiodarone, may cause bradycardia and a decrease in cardiac output; when administered with beta-blockers may increase cardiac depression; cimetidine may increase diltiazem levels

Contraindications

Documented hypersensitivity; severe CHF, sick sinus syndrome, second- or third-degree AV block, and hypotension (<90 mm Hg systolic)

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in impaired renal or hepatic function; may increase LFT levels, and hepatic injury may occur

Angiotensin-converting enzyme inhibitors

These agents are used for vasodilation and possible antifibrotic and anti-inflammatory properties.

Benazepril (Lotensin)

Prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in lower aldosterone secretion. Should be used once a day. Should be started at the lowest possible dose and titrated upwards as tolerated. Desired effects include a decrease in frequency and severity of attacks of Raynaud phenomenon.

Dosing

Adult

10 mg PO qd

Pediatric

Not recommended

Interactions

May increase digoxin, lithium, and allopurinol levels; probenecid may increase benazepril levels; coadministration with diuretics increase hypotensive effects; the hypotensive effects of benazepril may be enhanced when administered concurrently with diuretics and NSAIDs

Contraindications

Documented hypersensitivity; chronic cough; systemic hypotension; hyperkalemia; NSAIDs

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Use lowest effective dose and monitor serum potassium level; caution in renal impairment, valvular stenosis, or severe congestive heart failure

Angiotensin II receptor antagonists

Used for vasodilation and for their possible antifibrotic and anti-inflammatory effects.

Losartan (Cozaar)

Nonpeptide angiotensin II receptor antagonist that blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II. May induce a more complete inhibition of the renin-angiotensin system than ACE inhibitors. Does not affect the response to bradykinin and is less likely to be associated with cough and angioedema. For patients unable to tolerate ACE inhibitors. Less effective in patients with scleroderma

than with primary Raynaud phenomenon. May modify some serum markers of vascular damage and possibly modulate some of the underlying tissue damage in scleroderma.

Dosing

Adult

50 mg PO qd

Pediatric

Not recommended

Interactions

Ketoconazole, sulfaphenazole, and phenobarbital may decrease effects; cimetidine may increase effects of losartan; may interact with other drugs that increase potassium concentrations and produce hyperkalemia

Contraindications

Documented hypersensitivity to angiotensin II preceptor antagonists

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Caution in patients with unilateral or bilateral renal artery stenosis; may cause hyperkalemia

Endothelin inhibitors

These agents inhibit vessel constriction and elevation of blood pressure by competitively binding to endothelin-1 (ET-1) receptors ETA and ETB in endothelium and vascular smooth muscle.

Bosentan (Tracleer)

Endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension in patients with WHO class III or IV symptoms to improve exercise ability and to decrease rate of clinical worsening. This leads to significant increase in cardiac index (CI) associated with significant reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP). Recently, prevention of digital ulcers was demonstrated in a randomized prospective, placebo-controlled trial that involved 122 patients with scleroderma.
Case series also reported complete cessation of Raynaud symptoms in 4 patients.

Dosing

Adult

<40 kg: 62.5 mg PO bid; not to exceed 125 mg/d

>40 kg: 62.5 mg PO bid for 4 wk initially, then increase to 125 mg PO bid

Pediatric

Not established; 62.5 mg PO bid recommended if <40 kg, or >12 years; not to exceed 125 mg/d

Interactions

Toxicity may increase when administered concomitantly with inhibitors of isoenzymes CYP450 2C9 and CYP450 3A4 (eg, ketoconazole, erythromycin, fluoxetine, sertraline, amiodarone, and cyclosporine A); induces isoenzymes CYP450 2C9 and CYP450 3A4, causing decrease in plasma concentrations of drugs metabolized by these enzymes, including glyburide and other hypoglycemics, cyclosporine A, hormonal contraceptives, simvastatin, and, possibly, other statins; hepatotoxicity increases with concomitant administration of glyburide

Contraindications

Documented hypersensitivity; coadministration with cyclosporine A or glyburide

Precautions

Pregnancy

X - Contraindicated; benefit does not outweigh risk

Precautions

Causes at least 3-fold elevation of liver aminotransferases (ie, ALT, AST) levels in about 11% of patients; may elevate levels of bilirubin (serum aminotransferase levels must be measured prior to initiation of treatment and then monthly); caution in patients with mildly impaired liver function (avoid in patients with moderate or severe liver impairment); not recommended while breastfeeding; monitor hemoglobin levels after 1 and 3 mo of treatment and every 3 mo thereafter; exclude pregnancy before initiating treatment and prevent thereafter with use of reliable contraception; headache and nasopharyngitis may occur

Serotonin reuptake inhibitors

Serotonin is a potent vasoconstrictor that is released from nerve endings and during platelet activation, explaining why SSRIs are believed to be helpful in the treatment of Raynaud phenomenon. Fluoxetine (20 mg) versus nifedipine (40 mg) in patients with primary and secondary Raynaud phenomenon showed that fluoxetine statistically improved the frequency and severity of Raynaud attacks, while nifedipine did not reach statistical significance. A better response was seen in patients with Raynaud disease versus patients with Raynaud phenomenon.

Fluoxetine (Prozac)

Selectively inhibits presynaptic serotonin reuptake with minimal or no effect in the reuptake of norepinephrine or dopamine.
May cause more gastrointestinal adverse effects than other SSRIs now currently available, which is the reason it is not recommended as a first choice. May be given as a liquid or a capsule.
May give as 1 dose or divided doses. Presence of food does not appreciably alter levels of the medication.
May take up to 4-6 weeks to achieve steady state levels of the medication, as it has longest half-life (72 h).
Long half-life is both an advantage and a drawback. If it works well, an occasional missed dose is not a problem; if problems occur, eliminating all active metabolites takes a long time. The choice depends on adverse effects and drug interactions. Adverse effects of SSRIs seem to be quite idiosyncratic; thus, relatively few reasons exist to prefer one over another at this point if dosing is started at a conservative level and advanced as tolerated.

Dosing

Adult

10 mg PO upon waking; can be increased q2wk; not to exceed 60 mg/d

Pediatric

Not established

Interactions

Increases toxicity of diazepam and trazodone by decreasing clearance; also increases toxicity of MAOIs and highly protein-bound drugs; serotonin syndrome (ie, myoclonus, rigidity, confusion, nausea, hyperthermia, autonomic instability, coma, eventual death) occurs with simultaneous use of other serotonergic agents (eg, anorectic agents, tramadol, buspirone, trazodone, clomipramine, nefazodone, tryptophan; discontinue other serotonergic agents at least 2 wk prior to SSRIs)

Contraindications

Documented hypersensitivity; concurrent or recent (within 2 wk) use of MAOIs; coadministration with thioridazine

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in hepatic impairment and history of seizures; MAOIs should be discontinued at least 14 d before initiating fluoxetine therapy

Prostaglandins

Agents in this class have potent vasodilatory effects.

Epoprostenol (Flolan)

Analogue of PGI2 has potent vasodilatory properties, immediate onset of action, and half-life of approximately 5 min. In addition to vasodilator properties, also contributes to inhibition of platelet aggregation and plays role in inhibition of smooth muscle proliferation.
Continuous chronic infusion should be administered through central venous catheter.

Dosing

Adult

Acute dose: 2 ng/kg/min continuous IV; increase by 2 ng/kg/min q15min or longer until dose-limiting effects are elicited (eg, chest pain, anxiety, dizziness, changes in heart rate, dyspnea, nausea, vomiting, headache, hypotension, flushing)
Continuous chronic infusion: Initial: 4 ng/kg/min IV less than maximum-tolerated infusion rate determined during acute dose
If maximum-tolerated infusion rate is <5 ng/kg/min IV, chronic infusion rate should be half maximum-tolerated acute infusion rate
Dosage adjustments: Dose adjustments in chronic infusion rate should be based on persistence, recurrence, or worsening of patient symptoms of pulmonary hypertension; if symptoms persist or reoccur after improving, infusion rate should be increased by 1-2 ng/kg/min q15min or more; following establishment of new chronic infusion rate, patient should be observed and vital signs monitored
Studies used dosing regimens of 6-10 ng/kg/min for 72 h

Pediatric

Interactions

Coadministration with anticoagulants may increase bleeding risk because of shared effects on platelet aggregation

Contraindications

Documented hypersensitivity to epoprostenol or structurally related compounds; chronic use in patients with CHF due to severe left ventricular systolic dysfunction

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Coadminister whenever possible with anticoagulants to reduce risk of thromboembolism; sudden discontinuation or reduction in therapy may result in rebound pulmonary hypertension

Iloprost (Ventavis)

Synthetic analogue of prostacyclin PGI_2 that dilates systemic and pulmonary arterial vascular beds. Indicated for pulmonary arterial hypertension (WHO Group I) in patients with NYHA class III or IV symptoms to improve exercise tolerance and symptoms and to delay deterioration.

Dosing

Adult

Inhalation: Initial: 2.5 mcg/dose; if tolerated, increase to 5 mcg/dose; administer 6-9 times/d (dose at intervals 2 h while awake); 5 mcg/dose for maintenance dose; 45 mcg maximum daily dose

Pediatric

Interactions

May increase hypotensive effect of vasodilators and antihypertensives; may increase bleeding risk when coadministered with anticoagulants

Contraindications

Documented hypersensitivity to iloprost or any component of formulation

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Intended for inhalation administration using Prodose ADD drug-delivery system; monitor vital signs during initiation; avoid use in patients with hypotension (systolic BP <85 mm Hg); use caution with concurrent conditions or medications that may increase risk of syncope; dosage or therapy adjustment may be required if exertional syncope occurs; may reflect therapeutic gap or insufficient efficacy; if pulmonary edema occurs during administration, discontinue therapy; use caution in hepatic dysfunction; safety not established in patients with other concurrent pulmonary diseases (eg, COPD, severe asthma, acute infections); safety and efficacy not established in pediatric patients

Phosphodiesterase type 5 enzyme inhibitors

Agents in this class have potent vasodilatory effects.

Sildenafil (Revatio)

Phosphodiesterases are a complex group of enzymes that help to tightly regulate the degradation of intracellular cyclic nucleotides. Intracellular responses to both NO and prostacyclin are mediated by the cyclic nucleotides cGMP and cyclic-AMP (cAMP) respectively. So, by bolstering the vasodilatory effect of both NO and prostacyclin, these agents may be useful in the treatment of Raynaud phenomenon.

Dosing

Adult

50 mg PO bid

Pediatric

Not established

Interactions

Potentiates vasodilatory effect of NO, resulting in potentially fatal drop in blood pressure; coadministration with ketoconazole, erythromycin, or cimetidine increases plasma sildenafil concentrations; coadministration with rifampin decreases plasma levels of sildenafil; coadministration with bosentan increases bosentan levels by 50% and reduces sildenafil levels by 63%

Contraindications

Documented hypersensitivity; concurrent or intermittent using of organic nitrates in any form

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Adverse effects include headaches (16%), flushing (10%), upset stomach (7%), nasal congestion (4%), and a blue haze at the periphery of vision (3%); adverse effects occur more often in men taking the 100-mg dose; serious adverse effects occur in patients with severe heart disease and those who are taking nitrates; rates of MI were 1.7 and 1.4 per 100 man-years for sildenafil and placebo groups; sudden vision loss caused by nonarteritic anterior ischemic optic neuropathy (NAION) has been associated with PDE-5 inhibitors following use for ED, analysis is ongoing to determine causality; sudden decreases or loss of hearing has been reported

Vasodilators

These agents are used for their local vasodilatory effects.

Nitroglycerin (Nitro-Bid)

Decreases coronary vasospasm, which increases coronary blood flow. Also induces vessel dilatation, decreasing cardiac workload.

Dosing

Adult

0.5 inch (1%-2%) applied locally upon rising and 0.5 inch 6 h later; may double dose as needed

Pediatric

Not established

Interactions

Aspirin may increase nitrate serum concentrations; marked symptomatic orthostatic hypotension may occur with coadministration of calcium channel blockers (dose adjustment of either agent may be necessary)

Contraindications

Documented hypersensitivity; severe anemia, shock, postural hypotension, head trauma closed angle glaucoma, or cerebral hemorrhage

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in coronary artery disease, and low systolic blood pressure

Follow-up

Further Inpatient Care

- Primary Raynaud phenomenon is usually treatable on an outpatient basis.
- Although the same drugs and maneuvers are used for the phenomenon itself, treatment of secondary Raynaud phenomenon depends on the underlying disease.

Further Outpatient Care

- Patients should check their systemic blood pressure regularly and may want to keep a log of the number and severity of attacks. This may help in evaluating the efficacy of therapeutic management.

Transfer

- Transfer is not usually necessary.

Deterrence/Prevention

- Avoid cold and stressful situations that precipitate attacks.

Complications

- Rarely, digital ulceration and tissue loss result from primary Raynaud phenomenon.
- The complications associated with secondary Raynaud are usually related to the underlying disease. The direst of these include loss of tissue pulp in the distal phalanx, ulceration, and digital gangrene.
- Critical digital ischemia necessitates aggressive management. It is considered a medical emergency that requires hospitalization. Warm temperature and bed rest are used to decrease trauma and activity and to control pain.
    - Local infiltration of lidocaine or bupivacaine at the base of the involved digits decreases sympathomimetic input, reduces ischemic pain, and improves blood flow.
    - Rapidly advancing ischemic tissue anticoagulant therapy may be necessary. No algorithms or studies exist for the use of heparin.
    - Intravenous iloprost, alprostadil, or epoprostenol can be used if anticoagulant therapy fails or if the ischemia rapidly worsens.
    - Failure of all these therapies might warrant surgical intervention with distal digital sympathectomy and arterial reconstruction.
    - Further workup for vasculitis, thrombosis, arthrosclerosis, among other conditions, must be performed while treatment is in place.

Prognosis

- The prognosis of primary Raynaud phenomenon is usually very good, with no mortality and little morbidity.
- The prognosis of secondary Raynaud phenomenon is related to the underlying disease. The prognosis for the involved digit or digits in these patients is related to the severity of the ischemia and the effectiveness of maneuvers to restore blood flow.

Patient Education

- Patients with Raynaud phenomenon should avoid situations that precipitate their attacks, and they should insulate their hands from the cold.
- Smoking should be prohibited.
- If ulcerations develop, patients need to keep them sterile and to treat any infections aggressively that may intercede. All of this should be done under the supervision of a physician.
- If ulcerations or gangrene occur, a consultation with a wound care specialist may be useful.

- For excellent patient education resources, visit eMedicine's Circulatory Problems Center. Also, see eMedicine's patient education article Raynaud Phenomenon.

Miscellaneous

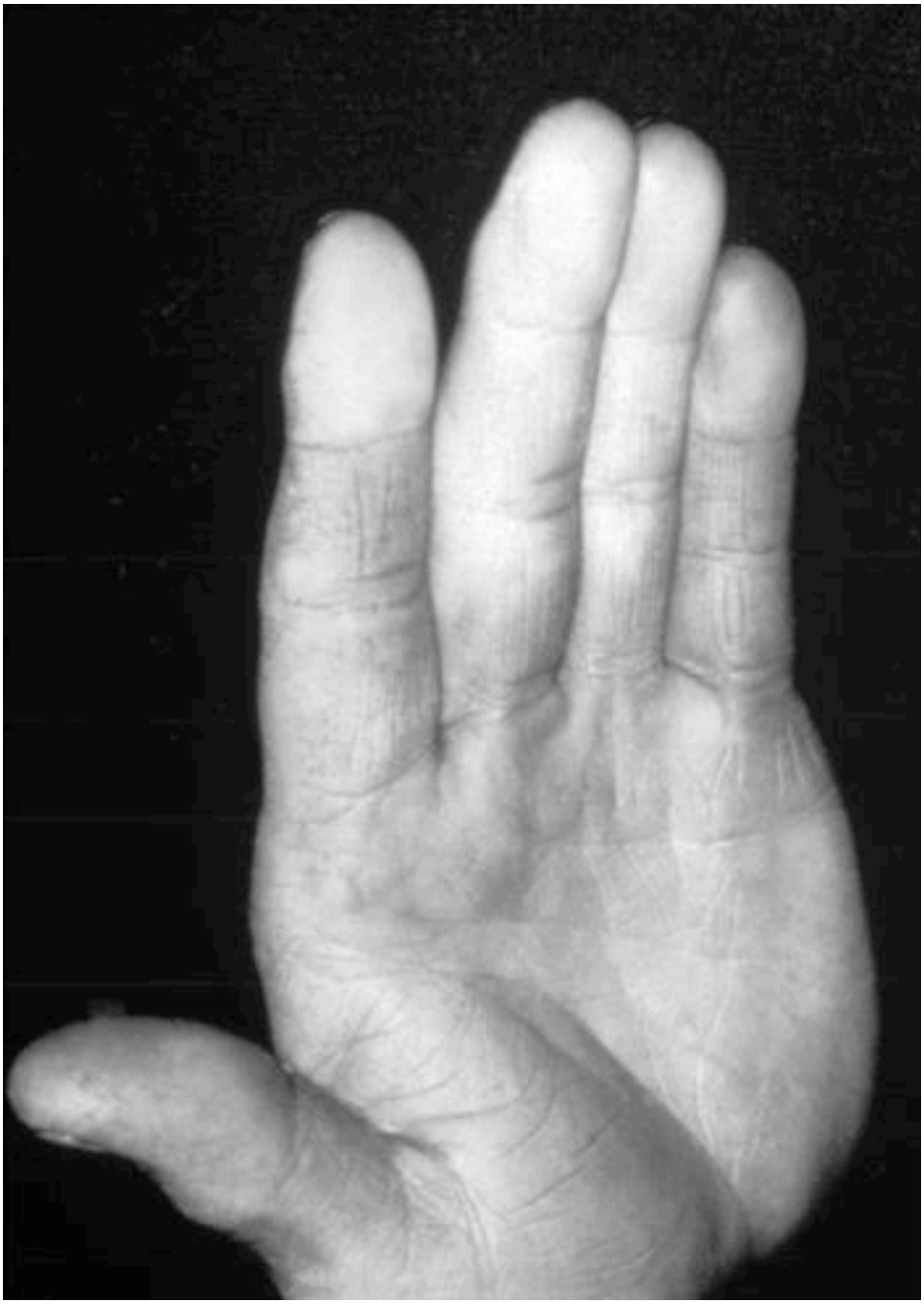
Medicolegal Pitfalls

- Failure to appropriately diagnose a secondary disorder

Special Concerns

- Caution should be taken to not overlook an underlying disorder.
- Wounds need to be treated appropriately.

Multimedia



Media file 1: Photo of a patient with Raynaud phenomenon that resulted from working with a jackhammer. Courtesy of the CDC.

References

75. Bakst R, Merola JF, Franks AG Jr, Sanchez M. Raynaud's phenomenon: pathogenesis and management. *J Am Acad Dermatol*. Oct 2008;59(4):633-53. [Medline].
76. Gayraud M. Raynaud's phenomenon. *Joint Bone Spine*. Jan 2007;74(1):e1-8. [Medline].
77. Herrick AL, Illingworth K, Blann A, Hay CR, Hollis S, Jayson MI. Von Willebrand factor, thrombomodulin, thromboxane, beta-thromboglobulin and markers of fibrinolysis in primary Raynaud's phenomenon and systemic sclerosis. *Ann Rheum Dis*. Feb 1996;55(2):122-7. [Medline]. [Full Text].

78. Rajagopalan S, Pfenninger D, Kehrer C, Chakrabarti A, Somers E, Pavlic R. Increased asymmetric dimethylarginine and endothelin 1 levels in secondary Raynaud's phenomenon: implications for vascular dysfunction and progression of disease. *Arthritis Rheum*. Jul 2003;48(7):1992-2000. [Medline]. [Full Text].
79. Kirchengast M, Munter K. Endothelin-1 and endothelin receptor antagonists in cardiovascular remodeling. *Proc Soc Exp Biol Med*. Sep 1999;221(4):312-25. [Medline].
80. Sakurai T, Goto K. Endothelins. Vascular actions and clinical implications. *Drugs*. Nov 1993;46(5):795-804. [Medline].
81. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. *J Hypertens*. Jun 2006;24(6):983-91. [Medline].
82. Kawaguchi Y, Takagi K, Hara M, et al. Angiotensin II in the lesional skin of systemic sclerosis patients contributes to tissue fibrosis via angiotensin II type 1 receptors. *Arthritis Rheum*. Jan 2004;50(1):216-26. [Medline].
83. Wigley FM, Flavahan NA. Raynaud's phenomenon. *Rheum Dis Clin North Am*. Nov 1996;22(4):765-81. [Medline].
84. Edwards CM, Marshall JM, Pugh M. Lack of habituation of the pattern of cardiovascular response evoked by sound in subjects with primary Raynaud's disease. *Clin Sci (Lond)*. Sep 1998;95(3):249-60. [Medline].
85. Bunker CB, Goldsmith PC, Leslie TA, Hayes N, Foreman JC, Dowd PM. Calcitonin gene-related peptide, endothelin-1, the cutaneous microvasculature and Raynaud's phenomenon. *Br J Dermatol*. Mar 1996;134(3):399-406. [Medline].
86. Bunker CB, Terenghi G, Springall DR, Polak JM, Dowd PM. Deficiency of calcitonin gene-related peptide in Raynaud's phenomenon. *Lancet*. Dec 22-29 1990;336(8730):1530-3. [Medline].
87. Chotani MA, Flavahan S, Mitra S, Daunt D, Flavahan NA. Silent alpha(2C)-adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. *Am J Physiol Heart Circ Physiol*. Apr 2000;278(4):H1075-83. [Medline].
88. Furspan PB, Chatterjee S, Freedman RR. Increased tyrosine phosphorylation mediates the cooling-induced contraction and increased vascular reactivity of Raynaud's disease. *Arthritis Rheum*. May 2004;50(5):1578-85. [Medline].
89. Lau CS, McLaren M, Saniabadi A, Belch JJ. Increased whole blood platelet aggregation in patients with Raynaud's phenomenon with or without systemic sclerosis. *Scand J Rheumatol*. 1993;22(3):97-101. [Medline]. [Full Text].
90. Herrick AL. Pathogenesis of Raynaud's phenomenon. *Rheumatology (Oxford)*. May 2005;44(5):587-96. [Medline]. [Full Text].
91. Suter LG, Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum*. Apr 2005;52(4):1259-63. [Medline].
92. Generali J, Cada D. Nitroglycerin (topical): Raynaud's phenomenon. *Hospital Pharmacy*. 2008;43:980-981. [Full Text].
93. Al-Allaf AW, Belch J. Raynaud's phenomenon. In: Hochberg et al, eds. *Practical Rheumatology*. 3rd ed. Philadelphia, Pa: Mosby; 2004:467-472.
94. Belch JJ, Newman P, Drury JK, et al. Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome. A double-blind controlled trial. *Lancet*. Feb 12 1983;1(8320):313-5. [Medline].
95. Bennett RM, O'Connell DJ. Mixed connective tisssue disease: a clinicopathologic study of 20 cases. *Semin Arthritis Rheum*. Aug 1980;10(1):25-51. [Medline].
96. Challenor VF. Angiotensin converting enzyme inhibitors in Raynaud's phenomenon. *Drugs*. Dec 1994;48(6):864-7. [Medline].
97. Cherniack MG. Raynaud's phenomenon of occupational origin. *Arch Intern Med*. Mar 1990;150(3):519-22. [Medline].

98. [Best Evidence] Chung L, Shapiro L, Fiorentino D, Baron M, Shanahan J, Sule S, et al. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. *Arthritis Rheum*. Mar 2009;60(3):870-7. [Medline].
99. Coffman JD, Cohen AS. Total and capillary fingertip blood flow in Raynaud's phenomenon. *N Engl J Med*. Jul 29 1971;285(5):259-63. [Medline].
100. De Angelis R, Cerioni A, Del Medico P, Blasetti P. Raynaud's phenomenon in undifferentiated connective tissue disease (UCTD). *Clin Rheumatol*. Apr 2005;24(2):145-51. [Medline].
101. Destors JM, Gauthier E, Lelong S, Boissel JP. Failure of a pure anti-platelet drug to decrease the number of attacks more than placebo in patients with Raynaud's phenomenon. *Angiology*. Aug 1986;37(8):565-9. [Medline].
102. DiGiacomo RA, Kremer JM, Shah DM. Fish-oil dietary supplementation in patients with Raynaud's phenomenon: a double-blind, controlled, prospective study. *Am J Med*. Feb 1989;86(2):158-64. [Medline].
103. Dowd PM, Martin MF, Cooke ED, et al. Treatment of Raynaud's phenomenon by intravenous infusion of prostacyclin (PGI2). *Br J Dermatol*. Jan 1982;106(1):81-9. [Medline].
104. Dziadzio M, Denton CP, Smith R, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum*. Dec 1999;42(12):2646-55. [Medline].
105. Flatt AE. Digital artery sympathectomy. *J Hand Surg* [Am]. Nov 1980;5(6):550-6. [Medline].
106. Freedman RR. Quantitative measurements of finger blood flow during behavioral treatments for Raynaud's disease. *Psychophysiology*. Jul 1989;26(4):437-41. [Medline].
107. Freemont AJ, Hoyland J, Fielding P, Hodson N, Jayson MI. Studies of the microvascular endothelium in uninvolved skin of patients with systemic sclerosis: direct evidence for a generalized microangiopathy. *Br J Dermatol*. Jun 1992;126(6):561-8. [Medline].
108. Furtado RN, Pucinelli ML, Cristo VV, Andrade LE, Sato EI. Scleroderma-like nailfold capillaroscopic abnormalities are associated with anti-U1-RNP antibodies and Raynaud's phenomenon in SLE patients. *Lupus*. 2002;11(1):35-41. [Medline].
109. Gasser P, Muller P, Mauli D, Staubli C. Evaluation of reflex cold provocation by laser Doppler flowmetry in clinically healthy subjects with a history of cold hands. *Angiology*. May 1992;43(5):389-94. [Medline].
110. Gerbracht DD, Steen VD, Ziegler GL, Medsger TA Jr, Rodnan GP. Evolution of primary Raynaud's phenomenon (Raynaud's disease) to connective tissue disease. *Arthritis Rheum*. Jan 1985;28(1):87-92. [Medline].
111. Goodfield MJ, Hume A, Rowell NR. The acute effects of cigarette smoking on cutaneous blood flow in smoking and non-smoking subjects with and without Raynaud's phenomenon. *Br J Rheumatol*. Apr 1990;29(2):89-91. [Medline].
112. Grader-Beck T, Wigley FM. Raynaud's phenomenon in mixed connective tissue disease. *Rheum Dis Clin North Am*. Aug 2005;31(3):465-81, vi. [Medline].
113. Harper FE, Maricq HR, Turner RE, Lidman RW, Leroy EC. A prospective study of Raynaud phenomenon and early connective tissue disease. A five-year report. *Am J Med*. Jun 1982;72(6):883-8. [Medline].
114. Heslop J, Coggon D, Acheson ED. The prevalence of intermittent digital ischaemia (Raynaud's phenomenon) in a general practice. *J R Coll Gen Pract*. Feb 1983;33(247):85-9. [Medline].
115. [Best Evidence] Ingegnoli F, Boracchi P, Gualtierotti R, Lubatti C, Meani L, Zahalkova L, et al. Prognostic model based on nailfold capillaroscopy for identifying Raynaud's phenomenon patients at high risk for the development of a scleroderma spectrum disorder: PRINCE (prognostic index for nailfold capillaroscopic examination). *Arthritis Rheum*. Jul 2008;58(7):2174-82. [Medline].
116. Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist.