

Review Article

An Insight on Raynaud's Disease: Causes, Symptoms, Diagnosis, Treatment and Prevention

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ABSTRACT

Raynaud's disease is illustrated by a pale to blue to red series of color changes of the digits, most commonly after exposure to cold. Raynaud's phenomenon is a state of the flow that affects blood deliver to the skin and causes the extremities of the body to drop feeling and become numb also paroxysmal paleness and coldness of the extremities. Total 5-6% of global population is affected by this illness. Symptoms of Raynaud's phenomenon depend on the severity, incidence, and length of the blood-vessel spasm. There is no blood test for diagnosing Raynaud's phenomenon.

Certain Synonyms of Raynaud's phenomenon: systemic lupus erythematosus, microcirculation and vasoconstriction. Raynaud's disease is of two types: Primary Raynaud's phenomenon or idiopathic is considered the more frequent, milder condition. There is no underlying disease associated with the primary classification. About 75-80% of all cases diagnosed happen in women between 15 and 40years elderly. Another is Secondary Raynaud's phenomenon is not so frequent, but is considered the more severe of the two types. It is associated with an underlying disease, most commonly, one of the connective tissue diseases

The risk factors include: smoking, working with vibrating machinery - the fingers may go into spasm. This is due to an intermittent lack of blood supply to the fingers and emotional distress, exposure to the cold; women are affected more often than men. Management of Raynaud's disease is possible with medical, nursing, pharmacological, and surgical way.

Keywords: Raynaud's Disease, Reduced blood flow, Sympathetic Nervous System

INTRODUCTION

In medicine, Raynaud's phenomenon or Raynaud phenomenon repetitive episodes of biphasic colour change (at least 2 of pallor, cyanosis, erythema), in either cold or normal environment.

Raynaud's phenomenon is excessively reduced blood flow in response to cold or emotional stress, causing discoloration of the fingers, toes, and occasionally other areas. This condition may also cause nails to become brittle with longitudinal ridges. Named after French physician Maurice Raynaud (1834–1881), the phenomenon is believed to be the result of vasospasms that decrease blood supply to the respective regions.

Raynaud's phenomenon by itself is just a sign (hypoperfusion) accompanied by a symptom (discomfort). When linked to pathogenesis, it can be part of Raynaud's disease (also known as primary Raynaud's phenomenon), where the cause is unknown,^[1] or part of Raynaud's syndrome (secondary Raynaud's phenomenon), which is a syndrome caused by a known primary

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disease, most commonly connective tissue disorders such as systemic lupus erythematosus. Measurement of handtemperature gradients is one tool used to distinguish between the primary and secondary forms.^[2]



Fig.1: Maurice Raynaud (1834–1881)^[2]

It is a hyperactivation of the sympathetic nervous system causing extreme vasoconstriction of the peripheral blood vessels, leading to tissue hypoxia. Chronic, recurrent cases of Raynaud phenomenon can result in atrophy of the skin, subcutaneous tissues, and muscle. In rare cases it can cause ulceration and ischemic gangrene.^[3]

SIGNS AND SYMPTOMS

An image taken by a thermographic camera. The top hand belongs to a person who suffers from Reynaud's, the bottom hand does not. Red indicates a heat signature whilst green indicates little/no heat.

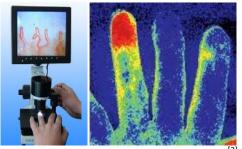


Fig.2: Image by thermographic camera^[3]

CLINICAL FEATURES

- Primarily affects fingers

- Can affect toes, thumbs, nipples, nose, earlobes

- Episodes precipitated by cold exposure and emotional stress

- Episodes accompanied by pain +/- numbness

- Pulses present

- Necrosis / tissue damage suggestive of secondary cause



Fig.3: Discoloration and numbness in hands ^[3]

The condition can cause pain within the affected extremities, discoloration (paleness), and sensations of cold and/or numbness. This can often be distressing to those who are not diagnosed, and sometimes it can be obstructive. If someone with Raynaud's is placed in too cold a climate, it could potentially become dangerous.

1. When exposed to cold temperatures, the blood supply to the fingers or toes, and in some cases the nose or earlobes, is markedly reduced; the skin turns pale or white (called pallor), and becomes cold and numb.



Fig.4: In RP temperature of hands down to 64 to $94^{\circ}F^{4}$

2. When the oxygen supply is depleted, the skin color turns blue (called cyanosis).



3. These events are episodic, and when the episode subsides or the area is warmed, the blood flow returns and the skin color first turns

red (rubor), and then back to normal, often accompanied by swelling, tingling, and a painful "pins and needles" sensation.



Pallor, cynosys and rubor of Hands in Raynaud's phenomenon Fig.5: Pallor, cyanosis and rubor of hands in Reynaud's phenomenon^[6]

All three color changes are observed in classic Raynaud's. However, not all patients see all of the aforementioned color changes in all episodes, especially in milder cases of the condition. Symptoms are thought to be due to reactive hyperemias of the areas deprived of blood flow.

In pregnancy, this sign normally disappears owing to increased surface blood flow. Raynaud's also has occurred in breastfeeding mothers, causing nipples to turn white and become extremely painful.^[4] Nifedipine, a calcium channel blocker and vasodilator, was recommended to increase blood flow to the extremities and noticeably relieved pain to the breast in an extremely small study group.^[5]

CAUSE

Primary

Primary (~10-15% of healthy population, female predominance) Raynaud's disease, or "Primary Raynaud's", is diagnosed if the symptoms are *idiopathic*, that is, if they occur by themselves and not in association with other diseases. Some refer to Primary Raynaud's disease as "being allergic to coldness." It often develops in young women in their teens and early

adulthood. Primary Raynaud's is thought to be at least partly hereditary, although specific genes have not yet been identified.^[6]

Smoking increases frequency and intensity of attacks, and there is a hormonal component. Caffeine also worsens the attacks. Sufferers are more likely to have migraine and angina.

Secondary

Raynaud's syndrome, or "Secondary Raynaud's," occurs *secondary to* a wide variety of other conditions. Secondary Raynaud's has a number of associations:

- Connective tissue disorders:
- Systemic sclerosis (scleroderma)^[7]
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Cold agglutinin disease
- Dermatomyositis
- Mixed connective tissue disease
- Polymyositis
- Sjögren's syndrome^[11]
- Ehlers-Danlos syndrome
- Eating disorders:
- Anorexia nervosa
- Obstructive disorders:
- Atherosclerosis



- Buerger's disease
- Haematological e.g. cold agglutinins
- Subclavian aneurysms
- Takayasu's arteritis
- Thoracic outlet syndrome
- Vascular occlusion e.g. vasculitis, thoracic outlet obstruction, Buerger's disease
- Drugs:
- Beta-Blockers
- Bromocriptine
- Cyclosporin

- Cytotoxic drugs - particularly chemotherapeutics and most especially bleomycin

- Ergotamine
- Sulfasalazine

- Anthrax vaccines whose primary ingredient is the anthrax protective antigen

- Stimulant medications such as those used to treat $\mathsf{ADHD}^{[8]}$

• Occupation:

- Jobs involving vibration, particularly drilling, suffer from vibration white finger

- Exposure to vinyl chloride, mercury

- Exposure to the cold (e.g. by working as a frozen food packer)

• Others:

- Carpal Tunnel Syndrome
- Chronic Fatigue Syndrome
- Cryoglobulinemia
- Eating disorders
- Hypothyroidism
- Lyme disease
- Magnesium Deficiency
- Malignancy
- Multiple Sclerosis

- Physical trauma, such as that sustained in auto accidents or other traumatic events

- Reflex Sympathetic Dystrophy

- Erythromelalgia (the opposite of Raynaud's, with hot and warm extremities) often co-exists in patients with Raynaud's^[9]

It is important to realize that Raynaud's can *herald* these diseases by periods of more than

twenty years in some cases, making it effectively their first presenting symptom. This may be the case in the CREST syndrome, of which Raynaud's is a part.

Patients with Secondary Raynaud's can also have symptoms related to their underlying diseases. Raynaud's phenomenon is the initial symptom that presents for 70% of patients with scleroderma, a skin and joint disease.

When Raynaud's phenomenon is limited to one hand or one foot, it is referred to as Unilateral Raynaud's. This is an uncommon form, and it is always secondary to local or regional vascular disease. It commonly progresses within several years to affect other limbs as the vascular disease progresses.^[10]

DIAGNOSIS

It is important to distinguish Raynaud's *disease* from *syndrome*. Looking for signs of arthritis or vasculitis as well as a number of laboratory tests may separate them.

Diagnostic Test

Diagnostic tests which doctors use to assess Raynaud's phenomenon include the:

* Antinuclear Antibody (ANA) lab test - are unusual antibodies, detectable in the blood, that have the capability of binding to certain structures within the nucleus of the cells.

* Erythrocyte Sedimentation Rate (ESR) blood test- This blood test determines the rate at which red blood cells settle to the bottom of a tube. A faster-than-normal rate may signal an inflammatory or autoimmune disease.

Nail fold Capillaroscopy Test– A drop of oil is put on the nail folds and then looked at under a magnifying glass to see whether there are changes in the capillaries which are indicative of connective tissue disease.

* **Cold Stimulation Test** - A heat sensor is taped to your fingers and the temperature is



recorded. Your hand is then immersed in ice water for 20 seconds

. Then it is removed from the bath and the temperature recorded every 5minutes until your finger temperature is the same as it was before the bath. This test should not be performed if you have a finger infection or problems with the blood supply to your fingers.

A careful medical history will often reveal whether the condition is primary or secondary. Once this has been established, an examination is largely to identify or exclude possible secondary causes.

- Digital artery pressure: pressures are measured in the arteries of the fingers before and after the hands have been cooled. A decrease of at least 15 mmHg is diagnostic (positive).

- Doppler ultrasound: to assess blood flow.

- Full blood count: this may reveal a normocytic anaemia suggesting the anaemia of chronic disease or renal failure.

- Blood test for urea and electrolytes: this may reveal renal impairment.

- Thyroid function tests: this may reveal hypothyroidism.

- An autoantibody screen, tests for rheumatoid factor, Erythrocyte sedimentation rate, and Creactive protein, which may reveal specific causative illnesses or a generalized inflammatory process.

- Nail fold vasculature: this can be examined under the microscope.

Diagnostic Criteria

The diagnostic criteria used to diagnose primary Raynaud's phenomenon include:

• Periodic vasospastic attacks of pallor (whiteness) or cyanosis (blueness) (note: some doctors include the additional criterion of the presence of these attacks for at least 2 years)

- · Normal nail fold capillary pattern
- · Negative antinuclear antibody test (ANA)
- · Normal erythrocyte sedimentation rate (ESR)

• Absence of pitting scars or ulcers of the skin, or gangrene (tissue death) in the fingers or toes

The diagnostic criteria used to diagnose Secondary Reynaud's phenomenon include:

- Periodic vasospastic attacks of pallor (whiteness) and cyanosis (blueness)
- · Abnormal nail fold capillary pattern
- · Positive antinuclear antibody test (ANA)

Abnormal erythrocyte sedimentation rate (ESR)

• Presence of pitting scars or ulcers of the skin, or gangrene in the fingers or toes

MANAGEMENT

Raynaud's syndrome (secondary Raynaud's) is managed primarily by treating the underlying cause and, as with Raynaud's disease (primary Raynaud's), avoiding triggers, such as cold, keeping a warm core body temperature and avoiding smoking (including passive smoking) and sympathomimetic drugs.^[11]

- General measures
- Maintenance of core temperature
- Avoidance of cold exposure
- Cessation of vasoconstrictive Rx e.g. β blockers
- Gloves (heated)
- Smoking cessation

Drugs can be helpful for moderate or severe RP. - Vasodilators - calcium channel blockers such as the dihydropyridines nifedipine, amlodipine diltiazem, preferably slow release or often first preparations are line treatment.^{[11][12]} They have the common side effects of headache, flushing, and ankle edema; but these are not typically of sufficient severity to require cessation of treatment.^[14] The limited evidence available shows that calcium channel blockers are only slightly effective in reducing how often the attacks happen.

- * Calcium channel blockers
- Dihydropyridine



Nifedipine better than amlodipine

- * Nitrates
- Transdermal or oral
- * Prostaglandins
- IV (disappointing results with oral preparation)
- * Phosphodiesterase V inhibitors
- Under investigation. Remain expensive.

- Patients with severe RP prone to ulceration or large artery thrombotic events may be prescribed aspirin. ^[11]

- Sympatholytic agents, such as the alphaadrenergic blocker prazosin may provide temporary relief.^[11]

- Losartan can, and topical nitrates may, reduce the severity and frequency of attacks, and the phosphodiesterase inhibitors sildenafil and tadalafil may reduce their severity. ^[11]

- Angiotensin receptor blockers or ACE inhibitors may aid blood flow to the fingers, ^[11] and there is some evidence that angiotensin receptor blockers (often losartan) reduce frequency and severity of attacks, and possibly better than nifedipine.

- The prostaglandin iloprost is used to manage critical ischemia and pulmonary hypertension in RP, and the endothelin receptor agonist bosentan is used to manage severe pulmonary hypotension and prevent finger ulcers in SSc. ^[11]

- Statins have a protective effect on blood vessels, and SSRIs such as fluoxetine may help RP symptoms but the data is weak.^[11]

Novel treatments

- Rho kinase inhibitors: Responsible for coldinduced expression of alpha-2 adrenoceptors

- Statins : In part due to Rho kinase inhibition

- Antiplatelet treatments: Current trial at RNHRD (for primary and secondary Raynaud's)

Nursing Management

 \cdot The client is encouraged to avoid exposure to cold.

• Avoid repetitive hand movements and stressful situations.

• Quit smoking and avoids secondary smoke as nicotine is potent vasoconstrictor.

· Stress management techniques ex. biofeedback

 \cdot Assist in alleviating some distress from the condition.

Medical Management

 Assessed regularly for symptoms of autoimmune diseases.

• Medication is administered if the symptoms are due to vasospastic disease.

• Biofeedback allows clients to voluntarily control the temperature of their hands.

 \cdot Avoiding particular stimuli (cold, tobacco) that provoke vasoconstriction.

• Calcium channel blockers-The first choice drugs for Raynaud's in Scleroderma patients.

• Vasodilators-Some doctors prescribe a vasodilator (a drug that relaxes blood vessels), such as nitroglycerine cream. You put the cream on your fingers to help heal skin ulcers.

Pharmacological Management

Nifedipine: calcium channel blockers nifedipine was found to reduce the frequency of ischemic episodes

Nursing considerations:

Don't give immediate-release form within 1 week of acute MI or in acute coronary syndrome. Monitor blood pressure regularly, especially in patients who take β -blockers or antihypertensive. Watch for symptoms of heart failure.

Captopril - ACE inhibitors

Indications: Hypertension, Diabetic nephropathy

Nursing considerations:

• Monitor patient's blood pressure and pulse rate frequently.



· Alert: Elderly patients may be more sensitive to drug's hypotensive effects.

· Assess patient for signs of angioedema.

 \cdot Drug causes the most frequent occurrence of cough, compared with other ACE inhibitors.

Diltiazem hydrochloride-slow channel blocker or calcium antagonist

Indications: indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Nursing considerations:

• Patients controlled on drug alone or with other drugs maybe switched to Cardizem LA tablets once a day at the nearest equivalent total daily dose.

• Monitor blood pressure and heart rate when starting therapy and during dosage adjustments.

 \cdot Maximum antihypertensive effect may not be seen for 14days.

Verapamil: calcium channel blockers

Indications:

Vasospastic angina (Prinzmetal's or variant angina); classic chronic, stable angina pectoris; chronic atrial fibrillation, to prevent paroxysmal supra ventricular tachycardia, supra ventricular arrhythmias.

Nursing considerations

• Patients with severely compromised cardiac function or those receiving beta blockers should receive lower doses of this drug.

• Instruct patient to take oral form of drug exactly as prescribed.

• Tell patient that long-acting forms shouldn't be crushed or chewed.

• Medication that aids in healing finger ulcers is iloprost aprostaglandin which is given IV and Ciprofloxacin (Cipro), an antibiotic. Chemotherapy drugs such as Bleomycin Sulfate (Blenoxane) and Cisplatin, also cause secondary Raynaud's disease.

Surgical Management¹²⁻¹³

• Nerve surgery. Through small incisions in the affected hands or feet, a doctor strips away these tiny nerves around the blood vessels. The surgery, called sympathectomy, may reduce the frequency and duration of attacks, but it's not always successful.

• Chemical injection. Doctors can inject chemicals to block sympathetic nerves in affected hands or feet. You may need to have the procedure repeated if symptoms return or persist.

• Amputation. Sometimes, doctors need to remove tissue damaged from a lack of blood supply. This may include amputating a finger or toe affected by Raynaud's in which the blood supply has been completely blocked and the tissue has developed gangrene.



Fig.6: Ambulatory Raynaud's monitor¹⁰

Space age bandage for RP monitoring: The Ambulatory Raynaud's Monitor wraps around a patient's finger and is secured with a bandage or medical tape. It contains two sensors that alternately record skin and ambient temperature - indicators of surface blood flow - every 36 seconds. A week's data is held by the monitor's electronics and is retained even if the device's power is unexpectedly interrupted. The monitoring system's batteries store enough energy to operate for several months, and devices can be cleaned and reinitialized for use with multiple patients.¹⁴

Surgery



- In severe cases, a sympathectomy procedure can be performed. Here, the nerves that signal the blood vessels of the fingertips to constrict are surgically cut. Microvascular surgery of the affected areas is another possible therapy. Infusions of prostaglandins, e.g. prostacyclin, may be tried, with amputation in exceptionally severe cases.

- A more recent treatment for severe Raynaud's is the use of Botox. The 2009 article studied 19 patients ranging in age from 15 to 72 years with severe Raynaud's phenomenon of which 16 patients (84%) reported pain reduction at rest. 13 patients reported immediate pain relief, 3 more had gradual pain reduction over 1-2 months. All 13 patients with chronic finger ulcers healed within 60 days. Only 21% of the patients required repeated injections. A 2007 article describes similar improvement in a series of 11 patients. All patients had significant relief of pain.

PRECAUTIONS TAKEN IN LIVE WITH RAYNAUD'S PHENOMENON

Precautions can be taken to reduce the number and intensity of attacks of white finger. These precautions include the following:

- Avoid exposing your hands to extreme cold -wear gloves when working in cold water or reaching into a freezer.

- Avoid tobacco and caffeine -- nicotine and caffeine can reduce blood circulation.

- Decrease stress and anxiety.



- Dress appropriately for cold weather by wearing layers, gloves, overcoat, hat and scarf.

- During an attack warm your fingers and toes (e.g. run warm water over your fingers, soak your feet in a bowl of warm water) and take time to relax.

- Exercise regularly and drink plenty of liquids to prevent dehydration.

- Protect the body from cold temperatures -turn down the air conditioner or wear a sweater.

- Protect your hands and feet from injury.



Fig.7: Precautions for Raynaud's disease^{6, 10}



GENERAL PRECAUTIONS

- If tingling, numbness or signs of white finger develop, promptly consult a physician.

- Keep warm at work -wear gloves and warm clothing when working in the cold.

- Massage and exercise your fingers during your breaks.

- Protect the hands from damage and extreme temperatures.

- Although significant advances have been made in reducing tool vibration, preventative measures to reduce this hazard are still necessary. Anti-vibration tools, anti-vibration gloves, and anti-vibration -- ----- shields may also help reduce exposure to vibration.

- In general, grinding, machining, and vibrating processes should be as fully automated as

possible. Workers should use vibrating tools only when necessary.

There are several ways to reduce the amount of vibration that passes from the tool to the hands.

- Use only well-maintained and properly operating tools.

- Hold vibrating tools as lightly as possible, consistent with safe work practices. Let the tool do the work.

- Rest vibrating tools on a support or work piece as much as possible.

- Store tools so that they do not have cold handles when next used.

- Use proper job design with scheduled breaks to reduce exposure to vibration.



Fig.8: Herbal products used in Raynaud's phenomenon^{13, 14}

In our diet we can add different variety of fruits and vegetables for prevention from Raynaud's disease which increases blood flow in extremities like: *Aloe vera, gingko biloba*, ginger, turmeric, onion, garlic, bitter guard, papaya, grapes, black currents, asparagus, apple, pitch, cocoa and even salmon and tuna fish etc.

It is important for workers to recognize if early symptoms of Raynaud's phenomenon have occurred, and then get appropriate advice to reduce further exposure to vibration.

Standards or laws regarding vibration exposure at work

British Columbia and New Brunswick are the only provinces in Canada that have specific standards for vibration exposure within their occupational health and safety regulations. Canadian (federal) legislation covers some vibration exposure situations.

Various agencies have proposed guidelines including the American Conference of Governmental Industrial Hygienists (ACGIH) which has published recommendations for



prevention of hand-arm (segmental) vibration syndrome.

Agencies associated with RD

- Raynaud's and Scleroderma Association: www.raynauds.org.uk
- Scleroderma Society:Sclerodermasociety.co.uk
- Arthritis Research UK (formerly ARC): arthritisresearchuk.org

CONCLUSION

Raynaud's disease is a general, painful state. It can be divided into primary and secondary

Raynaud's disease, and regular exercise and movement can help those who suffer from it. Raynaud's disease has a multifactorial aetiology, and a systematic approach with judicious use of investigations can help the physician to arrive at a correct diagnosis in the vast majority of cases.

There is currently no cure and treatments vary some suiting individuals better than others.

Continued investigation and research should show the way to newer and more efficient agents to treat this some- times devastating disease.

↓ REFERENCES

1. Raynaud's disease at Dorland's Medical Dictionary, 1988; 27th ed., p1495.

2. Anderson ME, Moore TL, Lunt M, Herrick AL. The distal-dorsal difference: a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. Rheumatology, March, 2007; 46 (3): 533–8.

3. Cotran, Ramzi S, Kumar, Vinay, Fausto, Nelson, Nelso Fausto, Robbins, Stanley L, Abbas, Abul K. Robbins and Cotran pathologic basis of disease. St. Louis, Mo: Elsevier Saunders, 2005; p. 542.

4. Holmen OL, Backe B. An underdiagnosed cause of nipple pain presented on a camera phone. BMJ, 2009; 339: b2553.

5. Anderson JE, Held N, Wright K. Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding. Pediatrics, April 2004; 113 (4): e360–4.

6. Pistorius MA, Planchon B, Schott JJ, Lemarec H. Heredity and genetic aspects of Raynaud's disease. Journal Des Maladies Vasculaires (in French), February 2006; 31 (1): 10–5.

7. Gayraud M. Raynaud's phenomenon. Joint, Bone, Spine, January 2007; 74 (1): e1-8.

8. Goldman, William, Ryan Seltzer, and Peter Reuman. Association between treatment with central nervous system stimulants and Raynaud's syndrome in children: A retrospective case–control study of rheumatology patients. Arthritis & Rheumatism, 58.2 (2008): 563-566.

9. Berlin AL, Pehr K. Coexistence of erythromelalgia and Raynaud's phenomenon. Journal of the American Academy of Dermatology, March 2004; 50 (3): 456–60.

10. Priollet P. Raynaud's phenomena: diagnostic and treatment study. La Revue du praticien (in French), October 1998; 48 (15): 1659–64.

11. Rathore KS, Rathore Swati, Pooja Bagdi, pharmainfo.net/reviews/overview-sjogren's-syndrome/, vol.6, issue5, 2008.

12. Mikuls, Ted R, Canella, Amy C, Moore, Gerald F, Erickson, Alan R, Thiele, Geoffery M, O'Dell, James R. Connective Tissue Diseases. Rheumatology. London: Manson Publishing. 2013; p. 117.

13. Kahan A, Weber S, Amor B, Saporta L, Hodara M, Degeorges M. Nifedipine and Raynaud's phenomenon. Annals of Internal Medicine, April 1981; 94 (4 pt 1): 546.

14. Josh Umbehr, medgadgets.com/medicine/johnhopkins, Feb5, 2007.