

Ministry of Defence

Synopsis of Causation

Raynaud's Phenomenon

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. Raynaud's phenomenon (RP) is a reversible episodic constriction (spasm) of small blood vessels (microcirculation) in response to cold, local pressure and emotion. It classically affects the fingers and toes, but can also affect the nose, tips of ears and any extremity exposed to cold.
- 1.2. RP presents as pallor (blanching) of the digits, followed by a blue discoloration (cyanosis) and redness (rubor). The pallor reflects the constriction of the vessels, which prevents blood getting into the vessel. The blueness reflects the colour change undergone by red blood cells when they lose their oxygen while trapped in the vessel which is in spasm, and the redness is a consequence of the blood returning into the vessels during the recovery phase.
- 1.3. RP is the blanket term used for the above symptoms. RP is subdivided into secondary Raynaud's syndrome when there is an associated disorder and primary Raynaud's disease when there is not.¹

2. Clinical Features

- 2.1. Raynaud's phenomenon (RP) is usually typified by spasm in the small blood vessels which shows as blanching or whitening of the affected area, followed by a bluish discoloration and then redness and heat once the circulation starts to recover. Pain, numbness and coldness which are secondary to reduced blood flow can accompany the changes in the circulation seen in the first 2 stages. The recovery phase (with associated redness) is frequently accompanied by an uncomfortable burning and tingling sensation. In secondary Raynaud's phenomenon the lack of blood flow can be severe enough to result in digital ulceration and gangrene, and amputation may be required.
- 2.2. This typical triphasic colour change is not necessarily present in all patients, with some patients experiencing bi- or monophasic colour change. However, it is accepted that blanching must be present to allow a diagnosis of RP.
- 2.3. RP may affect as many as 20-30% of young women and has an overall prevalence in the population of between 3% and 10%² with a female:male ratio of 9:1.³ However, this ratio is reversed for occupational Raynaud's (see section 3.5.).
- 2.4. RP can occur in a single digit or affect all the fingers simultaneously. It can be unilateral or bilateral.
- 2.5. RP predominantly affects the hands and feet although other areas such as ears, nose, tongue and nipples can also be affected. Moreover, it is increasingly being recognised that the vasospasm is probably systemic in nature with decreased gullet (oesophageal), pulmonary and heart (myocardial) blood flow being seen in these patients after a cold challenge. A link between Raynaud's disease and migraine⁴ has been documented.
- 2.6. Although cold and emotional stress are the most likely triggers of an attack other stimuli such as physical traumatic stress (for example, pressure or, vibration exposure), smoking,⁵ and hormones (particularly the fluctuations seen during the menstrual cycle) have also been implicated.⁶
- 2.7. The duration of an attack varies from seconds to hours. The affected area normally returns to its normal colour and temperature after an attack. The most severely affected patients may experience marked, year round restrictions in their daily activities.
- 2.8. Detailed history and examination are vital to establish the diagnosis and to try to elicit whether the RP is primary or secondary, as this affects both prognosis and treatment.

3. Aetiology

- 3.1. The precise mechanism by which RP occurs is not entirely clear. However, vasoregulation is mediated by several structures the most important of which are the blood vessels themselves, the nervous system, the blood and inflammatory cells as well as the local substances produced by them. RP may be a consequence of an imbalance of these mechanisms. Raynaud's phenomenon is classified as primary or secondary.
- 3.2. **Primary Raynaud's disease.**
 - 3.2.1. Primary Raynaud's disease is idiopathic and by definition there is no known underlying cause, but it occurs spontaneously. It is frequently seen in young females (typically in their teens and second decade) and these cases account for the vast majority of Raynaud's patients presenting to their general practitioner. There is evidence of familial aggregation in this group of patients, although no particular genes have yet been identified.⁷ The disease course tends to be milder and does not result in digital ulceration or other complications. The exception to this is during long severe exposure to cold, for example mountaineering, when a prolonged primary Raynaud's spasm attack can cause tissue damage. In most cases there is little interference with daily activities.²
 - 3.2.2. In the context of the armed forces, if a person has pre-existing primary Raynaud's disease, or indeed any underlying vascular disease, it may affect the feet when exposed to cold damp conditions (trench foot) in addition to the hands, and may interfere with the ability to handle weapons etc. when the fingers are numb.
- 3.3. **Secondary Raynaud's syndrome.** This occurs less frequently; the age of onset is rarely before the second decade and it can be associated with a variety of other disorders. These are broadly divided into:
 - immune mediated
 - occupation related
 - drug induced
 - obstructive vascular diseases
 - infections
 - metabolic disorders
 - miscellaneous conditions

By virtue of a detailed history, examination, and in some cases diagnostic blood tests, it is usually possible to determine which form affects a sufferer.

3.4. Immune mediated.

- 3.4.1. These are the best recognised of the associated disorders together with the occupation related ones. This group comprises autoimmune multi-

systemic diseases that affect the connective tissue which surrounds the joints, muscles, blood vessels and internal organs. RP is believed to be present in 90% of patients with systemic sclerosis, 85% of those with mixed connective tissue disease, between 10% and 45% of patients with systemic lupus erythematosus, 33% of patients with Sjögren's syndrome and 20% of those with dermatomyositis/polymyositis.⁸ Cryoglobulinaemia and antiphospholipid syndrome are also frequently associated with RP. Antiphospholipid syndrome is especially important to identify as it can be associated with risk of thrombosis, migraine and recurrent miscarriage in women of child bearing age

- 3.4.2. These patients are likely to suffer from more severe and frequent attacks, digital ulcers, pitting scars over the finger pulps and other organ involvement. They may have abnormal nail fold vessels (wide and tortuous, or absent) on microscopy, and the diagnosis can often be confirmed by the presence of characteristic antibodies in the blood.
- 3.4.3. Other autoimmune conditions associated with RP are vasculitis, particularly Takayasu's arteritis and giant cell arteritis, but also thromboangiitis obliterans (Buerger's disease), a smoking related disorder. In these conditions the vessels are inflamed leading in some cases to arterial narrowing (stenosis) and tissue injury.

3.5. Occupation related

- 3.5.1. **HAVS** The most common form of occupational Raynaud's is hand arm vibration syndrome (HAVS), previously called vibration white finger syndrome. HAVS occurs in workers exposed to mechanical vibration such as that caused by pneumatic drills, chainsaws and grinders. Although Raynaud's phenomenon is the main clinical manifestation, it is also characterised by neurological symptoms such as paraesthesia (tingling) and numbness of the fingers as well as musculoskeletal features. All components may not be recognised in a patient at the same time.
- 3.5.2. The neurological symptoms and signs are thought to be due to direct vibration damage to the nerves and to vasospasm in the vasa nervorum, the small blood vessels supplying the nerves. The symptoms begin as diminished sensory perception, and can progress to impaired tactile discrimination and reduced manual dexterity. In the later stages it is the neurological symptoms which the patient finds most troublesome. These symptoms and signs may be confused with carpal tunnel syndrome (compression of the median nerve at the wrist which produces paraesthesia in the median nerve distribution) as carpal tunnel syndrome has also been linked to vibration exposure and may co-exist with HAVS. As the prognosis and treatment of these 2 conditions are different, care should be taken to distinguish between them.
- 3.5.3. Considerable variation has been observed between the first exposure to vibration tools and the onset of symptoms, the so called "latent period"; with reports ranging from 6 weeks to 14 years.⁹ However, the severity of the symptoms when they occur correlates with the duration of exposure.¹⁰ HAVS is graded using the Stockholm scale¹¹ and progression up the scale is used as a guide to advise patients on the desirability of continued vibration exposure.

- 3.5.4. Simple measures such as protective anti-vibration gloves¹² which must be kept dry, vibration-proof impact tools which are regularly serviced, and job modification may help reduce the symptoms and prevent progression. If a job change is effected in the early stages some resolution in symptoms may occur, but this is less likely to occur in severely affected patients.³ HAVS is a classified occupational disease and requires RIDDOR reporting in the UK. No links between military specific tasks and HAV have been identified.
- 3.5.5. **Other occupation related disorders** Other less common occupation related disorders include workers exposed to polyvinyl chloride, ammunition workers (after work) and RP secondary to cold injury. Handling weapons and exposure to ammunition residues presents no risk of the condition.
- 3.6. **Drug induced.** Several drugs have been implicated in the precipitation of vasospastic attacks. Beta-blockers (used for the treatment of angina and hypertension), anti-cancer agents and ergotamine derivatives (used for the treatment of migraine) are the most common ones. Resolution of the symptoms can be achieved by withdrawing the drug.
- 3.7. **Obstructive vascular disease.**
- 3.7.1. Atherosclerotic disease (hardening of the arteries) is the commonest cause of RP in those over 60 years old. In these patients other cardiovascular risk factors such as raised cholesterol, hypertension, diabetes and/or cigarette smoking are normally present. These risk factors should be treated aggressively to prevent heart attack or stroke, but such treatment does not usually resolve the Raynaud's which will still require the symptomatic treatment documented in section 4.1.
- 3.7.2. Obstruction caused by pressure from outside the vessels can cause RP, as in the case of thoracic outlet syndrome, where a cervical rib or other obstruction compresses the vessel. It is usually unilateral and may be associated with neurological symptoms. The symptoms are produced by a positional, intermittent compression of the brachial plexus and/or subclavian artery running through the thoracic outlet near the neck.
- 3.7.3. Walking crutch pressure in the armpit may have a similar effect, by compressing the axillary artery.
- 3.7.4. Microemboli from the heart or other arteries have also been described as an occlusive cause of secondary Raynaud's.
- 3.8. **Infections.** Parvovirus B19, cytomegalovirus, hepatitis B and C and helicobacter pylori infection have all been associated with RP. Although the exact reason is not known, some authors have postulated that these viruses may have the ability to produce vasoactive substances. These are rare.
- 3.9. **Metabolic disorders.** Conditions in which there is an excess or reduced production of hormones such as hypothyroidism (reduced thyroxine, a vasodilator), carcinoid syndrome (producing excess serotonin, a constrictor) and phaeochromocytoma (producing excess adrenalin, a constrictor) have also been associated with RP.

3.10. **Miscellaneous.** The incidence of these conditions is very low.

- 3.10.1. **Malignant disease and blood disorders** A number of other conditions have been linked to RP. The most important ones are; malignancies such as ovarian carcinoma and lymphoma, and conditions that increase the viscosity of blood such as paraproteinaemias (too much protein in the blood), polycythaemias (too many red blood cells in the blood) and cryofibrinogenaemias (a type of blood protein that solidifies in the cold). These latter can all be diagnosed by blood testing.
- 3.10.2. **Complex regional pain syndrome** (previously called reflex sympathetic dystrophy) can occur when there is trauma to a region, usually round the neck and upper body. This trauma may be trivial in itself but lead to a painful RP and associated skin and bone changes.
- 3.10.3. **Smoking** It is generally accepted that smoking seems to be associated with the severity of Raynaud's symptoms rather than susceptibility. However, other studies have failed to confirm the association between tobacco use and RP.¹³
- 3.10.4. **Others** Advancing age (probably reflecting increasing atherosclerosis), and low body weight (for example, anorexia, where there is little fat insulation).¹⁴

4. Treatment and Prognosis

4.1. **Treatment.** The treatment of RP takes 3 directions: firstly to withdraw (or limit) predisposing factors, such as cold, vibration exposure, atherosclerosis and vasoconstrictor drugs. The second is to provide warmth with items such as gloves (standard or artificially heated), and hand/feet/body warmers etc. The third is symptomatic treatment with drugs that act as vasodilators. These drugs improve circulation to the affected areas but their use may be inhibited by side-effects such as headache, nausea and fluid retention. There is evidence for efficacy of calcium channel blockers (nifedipine or amlodipine).¹⁵ In addition angiotensin blocking agents (perindopril or enalapril), serotonin uptake inhibitors (fluoxetine) or nitrate patches may be used with variable success in patients with both primary and secondary Raynaud's phenomenon. More severe forms of Raynaud's may require patients to be admitted for intravenous infusions of iloprost, a vasodilator working through endothelial cell activity and requiring treatment over several consecutive days. There are many reports of anecdotal response to a variety of herbal supplements including ginger extract, cayenne and extract of Ginkgo biloba. All treatments are aimed towards relief of symptoms of Raynaud's rather than cure. As RP is a cold related disorder, Raynaud's sufferers may only require drug therapy in colder weather when symptoms are usually worse.

4.2. Prognosis.

4.2.1 The prognosis of RP is largely dependent on the underlying cause. In those cases where the condition has developed from exposure to drugs, toxins or specific employments, symptoms may improve or completely resolve after discontinuation of the cause. In the early stages of HAVS, however, a more limited vibration exposure may be permitted with regular monitoring of the condition to detect progression.

4.2.2 On the other hand if the RP is secondary to chronic conditions, as is the case with the connective tissue diseases, symptoms rarely settle completely although they can be improved with treatment.

4.2.3 In a recent prospective study looking at the natural history of predominantly primary RP in the community, only a third of females and males were still symptomatic at 7 years while two thirds had resolution of their Raynaud's symptoms.²

4.3 Further information.

4.3.1 Further information may be obtained by patients by contacting the Raynaud's and Scleroderma Association (tel 01270 872776) or by e mail info@raynauds.org.uk or on the website <http://www.raynauds.org.uk>

5. Summary

- 5.1. RP is an episodic reversible peripheral ischaemia usually provoked by cold, local pressure or emotion. Classically, the spasm of the small digital vessels leads to pallor of the digits followed by bluish discoloration and then redness once the circulation starts to recover. RP is subdivided into secondary Raynaud's syndrome when there is an associated disorder and primary Raynaud's disease when there is not.
- 5.2. RP is a common and mild disease in the majority of cases, when the diagnosis is usually primary Raynaud's disease. In a minority of cases, particularly in those with secondary Raynaud's syndrome such as connective tissue diseases and HAVS, it can lead to considerable morbidity.
- 5.3. It is particularly important to establish the underlying cause in secondary Raynaud's syndrome as symptoms can be improved by avoiding the offending cause or with preventive and pharmacological measures. Symptoms may be attenuated, but not cured, by judicious use of vasoactive drugs, combined with heated aids.

6. Related Synopses

Work-related Upper Limb Disorders

7. Glossary

autoimmune disorders	Disorders caused when the immune system causes illness by mistakenly attacking the body's own tissues.
brachial plexus	Nerve network controlling movement and sensation in the arm.
cervical rib	Extra rib or tight fibrous band connecting the seventh cervical vertebra with the breastbone.
cyanosis	Bluish discoloration of the skin or lips caused by lack of oxygen in the blood.
idiopathic	Occurring without known cause.
median nerve	The nerve that travels through the carpal tunnel of the wrist and supplies the thumb and first 3 fingers of the hand.
microemboli	Blood clots that travel through the circulatory system and can obstruct blood vessels.
oesophageal	Relating to the oesophagus (the gullet), the passage between the pharynx and the stomach.
paraesthesia	Pins and needles or tingling.
subclavian artery	The subclavian artery is a major artery of the upper chest that mainly supplies blood to the head and arms. It is located below the clavicle (collar bone), hence the name.
systemic	Spread throughout the body; affecting many or all body systems or organs.
vasoactive	Affecting the dilation or constriction of blood vessels.
vasoregulation	Regulation of blood vessels' calibre by dilatation or constriction.
vasospasm	Sharp and often persistent contraction of a blood vessel reducing its calibre and blood flow.

8. References

1. Al-Allaf W, Belch JJ. Systemic sclerosis: Raynaud's phenomenon. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, editors. *Rheumatology*. 3rd ed. London: Weisman MH; 2003. p. 1507-12.
2. Suter LG, Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum* 2005 Apr;52(4):1259-63.
3. Belch JJ, Ho M. Vasospastic disorders and vasculitis. In: Beard JD, Gaines PA, editors. *A companion to specialist surgical practice: vascular and endovascular surgery*. 2nd ed. London: WB Saunders Co; 2001. p. 201-24.
4. de Trafford JC, Lafferty K, Potter CE, Roberts VC, Cotton LT. An epidemiological survey of Raynaud's phenomenon. *Eur J Vasc Surg* 1988 Jun;2(3):167-70.
5. Belch JJ. Raynaud's phenomenon. *Cardiovasc Res* 1997 Jan;33(1):25-30.
6. Greenstein D, Jeffcote N, Ilsley D, Kester RC. The menstrual cycle and Raynaud's phenomenon. *Angiology* 1996 May;47(5):427-36.
7. Freedman RR, Mayes MD. Familial aggregation of primary Raynaud's disease. *Arthritis Rheum* 1996 Jul;39(7):1189-91.
8. Porter JM, Rivers SP, Anderson CJ, Baur GM. Evaluation and management of patients with Raynaud's syndrome. *Am J Surg* 1981;142:183-189.
9. Friden J. Vibration damage to the hand: Clinical presentation, prognosis and length and severity of vibration required. *J Hand Surg (Br)* 2001 Oct;26(5):471-4
10. Mirbod SM, Yoshida H, Nagata C, Inaba R, Komura Y, Iwata H. Hand-arm vibration syndrome and its prevalence in the present status of private forestry enterprises in Japan. *Int Arch Occup Environ Health* 1992;64(2):93-9.
11. Brammer AJ, Taylor W, Lundborg G. Sensorineural stages of the hand-arm vibration syndrome. *Scand J Work Environ Health* 1987 Aug;13(4):279-83.
12. Koton J. Prevention of hand arm vibration syndrome by using antivibration gloves. *Med Pr* 2002;53(5):423-31.
13. Herrick AL. Pathogenesis of Raynaud's phenomenon. *Rheumatology* 2005 May;44(5):587-96.
14. Maricq HR, Carpentier PH, Weinrich MC, Keil JE, Palesch Y, Biro C, et al. Geographic variation in the prevalence of Raynaud's phenomenon: a 5 region comparison. *J Rheumatol* 1997 May;24(5):879-89.
15. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology* 2005 Feb;44(2):145-50.