JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Review on Raynaud's Phenomenon

K. Tejaswini, V. Hema Kavya, V.L. Jyothsna, V.Manohar,

T. Rajya Lakshmi, P. Ujwala Rama Chandra

Pydah college of pharmacy, patavala, Kakinada-Yanam Road, Kakinada, A.P

Abstract: The pathogenesis of Raynaud's phenomenon remains incompletely understood, but significant strides in comprehension have occurred over the past two decades regarding various contributing mechanisms. It is crucial to note that Raynaud's phenomenon can manifest either as a primary (idiopathic) condition or as a secondary phenomenon linked to various underlying conditions. The pathogenesis and pathophysiology differ across these conditions. This review focuses on specific subtypes of Raynaud's phenomenon that are particularly relevant to rheumatologists: those associated with systemic sclerosis, primary Raynaud's phenomenon, and Raynaud's phenomenon secondary to hand–arm vibration syndrome.

This review aims on the primary mechanisms believed to play a significant role in pathophysiology, categorized broadly as 'vascular,' 'neural,' and 'intravascular.' While these distinctions are somewhat artificial because of their interrelated nature, they aid in discussing key elements: the blood vessel wall (especially the endothelium), neural regulation of vascular tone, and various circulating factors capable of impeding blood flow or causing endothelial injury. Vascular abnormalities encompass both structural and functional aspects. Neural abnormalities involve the deficiency of the vasodilator calcitonin gene-related peptide (released from sensory afferents), activation of α2-adrenoreceptors (potentially with up-regulation of the typically 'silent' α2C-adrenoreceptor), and a component related to the central nervous system. Intravascular abnormalities include platelet activation, impaired fibrinolysis, heightened viscosity, and likely oxidant stress.

Key words: Raynaud's phenomenon Prognosis, Raynaud's disease, mean platelet volume, peripheral vascular disease, platelet activation.

Introduction: In reaction to low temperatures, the body undergoes adaptive measures by constricting blood flow to the skin. This serves as a thermoregulatory mechanism aimed at preventing excessive loss of body heat and maintaining core body temperature. In cases such as Raynaud phenomenon, there is notable vasoconstriction observed in the digital arteries and cutaneous arterioles[(1)]. This phenomenon, initially identified by Maurice Raynaud in 1862 and later explored by sir Thomas Lewis in 1930, can be classified as either primary or secondary.

Raynaud's phenomenon is most accurately characterized as a reversible spasm affecting peripheral arterioles triggered by exposure to cold or stress(Refer to figure no-1). Typically, it manifests prominently in the distal digits but can extend to areas such as the nose, ears, and tongue[(2)]. An episode of Raynaud's phenomenon follows a distinct pattern with three phases:

- **Phase 1:** Pallor results from intense vasoconstriction of the pericapillary muscular arterioles.

❖ **Phase 2:** Cyanosis ensues due to the accumulation of deoxygenated venous blood.

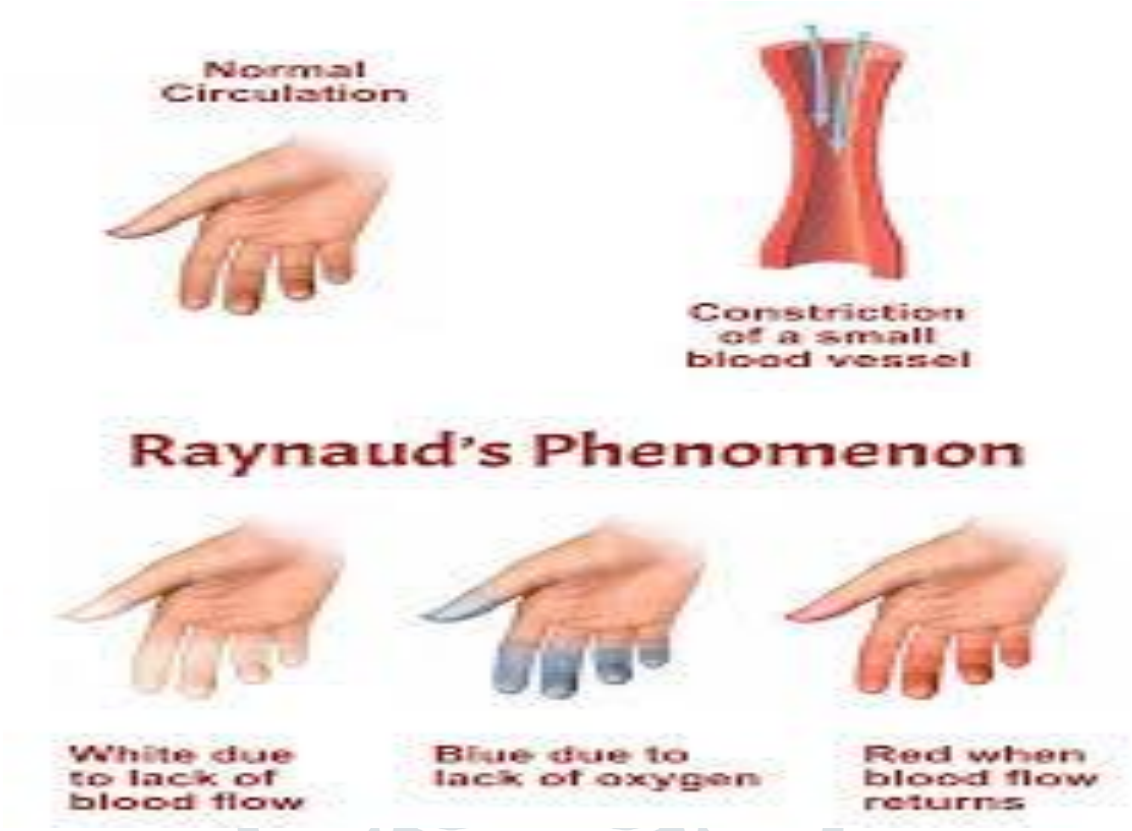

Figure no-1: Raynaud's Phenomenon

❖ **Phase 3:** Erythema appears as a response to a reactive increase in blood supply.

Raynaud's phenomenon can be comprehensively examined through three primary categories: vascular, neural, and intravascular abnormalities[3].

Raynaud's phenomenon can affect anyone, although certain individuals are more predisposed to developing it. There are two distinct types of Raynaud's phenomenon, each associated with different risk factors.

The primary form of Raynaud's phenomenon[4], characterized by an unknown cause, exhibits specific risk factors:

- **sex:** women are more prone to developing it compared to men.
- **Age:** typically, it manifests in individuals under the age of 30 and often initiates during the teenage years.
- **Family history:** the presence of Raynaud's phenomenon in a family member increases the likelihood of its occurrence in other family membersFamily history can play a crucial role in the development of Raynaud's phenomenon, as individuals with a family member affected by the condition face an increased risk of experiencing it themselves[5].

Raynaud's phenomenon is classified into two types:

❖ **Primary Raynaud's Phenomenon:** This type has no identified cause and represents the more prevalent form of the condition: (Refer to figure no-2).

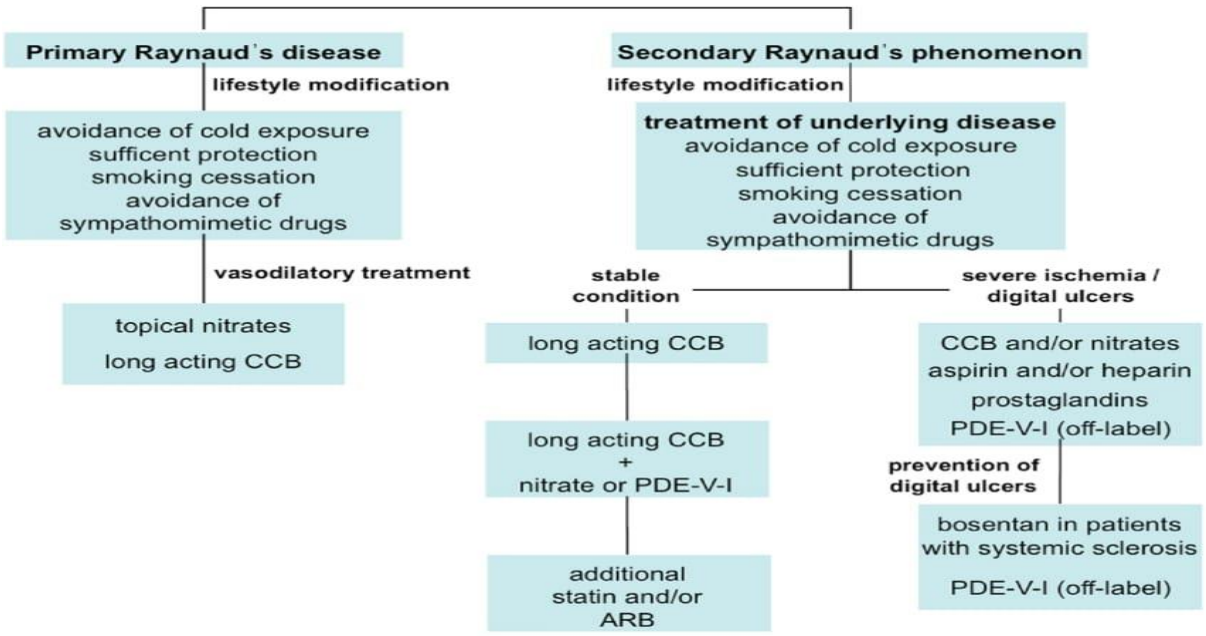

Figure no-2: Types of Raynaud's phenomenon

- **Secondary Raynaud's Phenomenon:** Associated with other underlying issues, such as rheumatic diseases like lupus or scleroderma. While less common[6], the secondary form tends to be more severe due to the damage inflicted on blood vessels: (Refer to figure no-2)

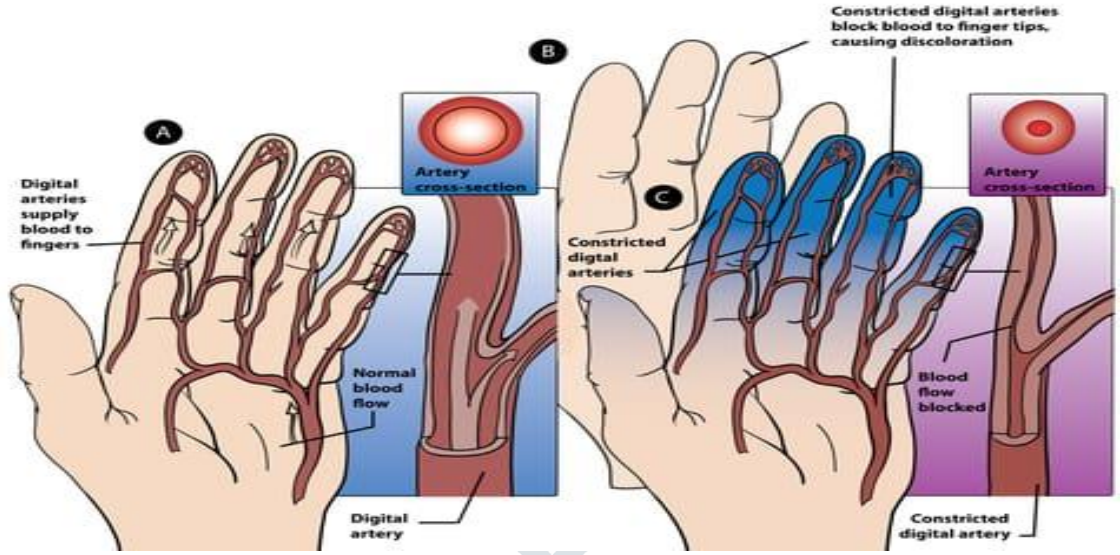

Figure no-3: Raynaud's phenomenon Harvard health

Factors linked to the development of secondary Raynaud's phenomenon encompass various diseases:

- Lupus and Scleroderma: Common rheumatic diseases associated with the secondary form.
- Inflammatory Myositis and Rheumatoid Arthritis: Conditions that may contribute to the occurrence of secondary Raynaud's phenomenon[7].
- Sjogren's Syndrome: Another rheumatic disease linked to the secondary type.(Refer to figure no-3)
- Certain Thyroid Disorders: Conditions affecting the thyroid have been associated with secondary Raynaud's phenomenon.
- Clotting Disorders: Conditions affecting blood clotting mechanisms.
- Carpal Tunnel Syndrome: Linked to the secondary form of Raynaud's phenomenon.
- Understanding the family history and distinguishing between primary and secondary forms is crucial for effective diagnosis and management of Raynaud's phenomenon[8]. Individuals with a familial

predisposition should be vigilant about potential symptoms and seek medical attention for timely intervention.

- Medication-Induced Symptoms: Certain medications prescribed for conditions such as high blood pressure, migraines, or attention deficit hyperactivity disorder (ADHD) may induce symptoms similar to those of Raynaud's phenomenon[9].
- Work-Related Exposures: Repeated use of vibrating machinery, such as jackhammers, or exposure to cold temperatures and certain chemicals at the workplace can lead to skin discoloration. This manifests as paleness or whitening, followed by a bluish tint as oxygen-depleted blood accumulates in the vessels[10]. Upon warming up, the blood vessels expand, and the skin flushes.

- **Causes of Raynaud's Phenomenon:** The exact cause of Raynaud's phenomenon is not fully understood. When exposed to cold, the body's response is to conserve heat, leading to the constriction (narrowing) of blood vessels in the skin's surface layer. This redirects blood from superficial vessels to deeper ones [11]. Primary Raynaud's phenomenon is more prevalent in women than men, suggesting a potential role of oestrogen and genetic factors, though specific genes remain unidentified.
- **Central Mechanism:** Many individuals with Raynaud's report stress-triggered vasospasms, indicating a potential role of the central nervous system, despite primary neural abnormalities being localized. Research in this area is challenging[12], and while evidence supporting central mechanisms is limited, studies have observed that patients with platelet-rich plasma do not habituate like healthy controls to stress-induced responses.(Refer to figure no-4) Persistent digital cutaneous vasoconstriction in platelet-rich plasma patients during a cool stimulus, linked to elevated endothelin-1 levels, suggests a combined impact of central mechanisms and locally released endothelin-1[13].

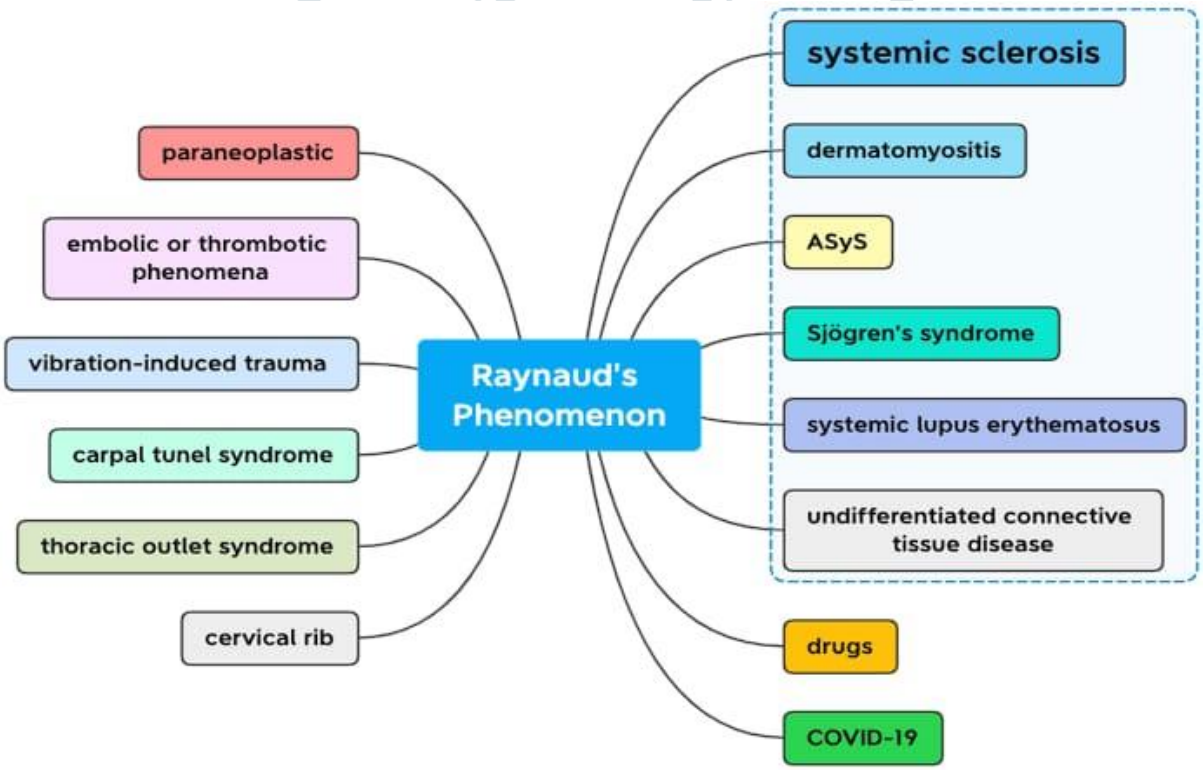

Figure no-4: Central mechanism of Raynaud's phenomenon

- **Pathophysiology:** Raynaud's phenomenon, first described in 1862 by Maurice Raynaud, involves "local asphyxia of the extremities" attributed to heightened central cord vascular innervation irritability. Its complex pathophysiology encompasses vascular, intravascular, and neural components, potentially differing between primary and secondary Raynaud's. Vascular abnormalities disrupt the vasoconstriction-vasodilation balance, involving factors like endothelin-1 and nitrous oxide[14]. Intravascular anomalies may promote vasoconstriction through platelet activation and thromboxane increase. Neural

irregularities, including calcitonin gene-related peptide deficiency, impair vasodilation.(Refer to figure no-5) Enhanced sympathetic adrenergic vasoconstriction targets proximal arteries, particularly in secondary Raynaud's, with additional factors like smoking, genetics, and hormonal influence playing significant roles. Studies highlight parallels in digital vascular reactivity between healthy controls during the pre-ovulatory period and Raynaud's patients[15].

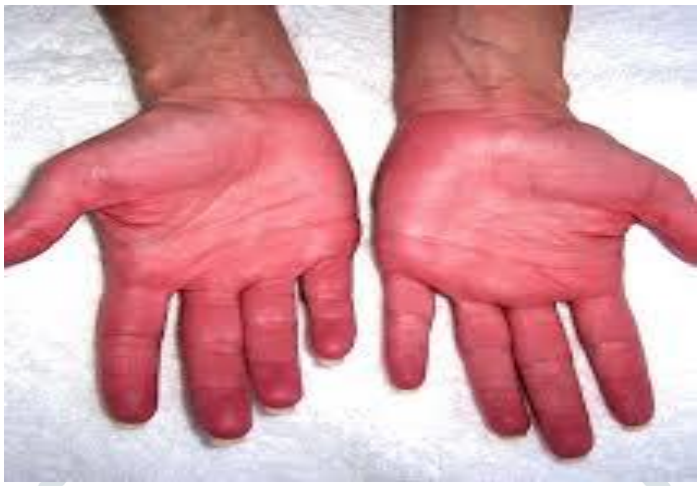

Figure no-5: difficulties in diagnosis and treatment of severe secondary phenomenon

- **Risk Factors:** Raynaud's phenomenon affects approximately 1 in 10 individuals, with the majority experiencing primary Raynaud's and only about 1 in 100[16], or fewer, developing secondary Raynaud's. Women face up to nine times higher risk than men.(Refer to figure no-6) Primary Raynaud's typically emerges between ages 15 and 25, while secondary Raynaud's tends to appear after 35, especially in individuals with conditions like rheumatoid arthritis, scleroderma, or lupus. Certain medications, used for cancer, migraines, or high blood pressure, and activities involving vibrating tools may increase the likelihood of Raynaud's[17].

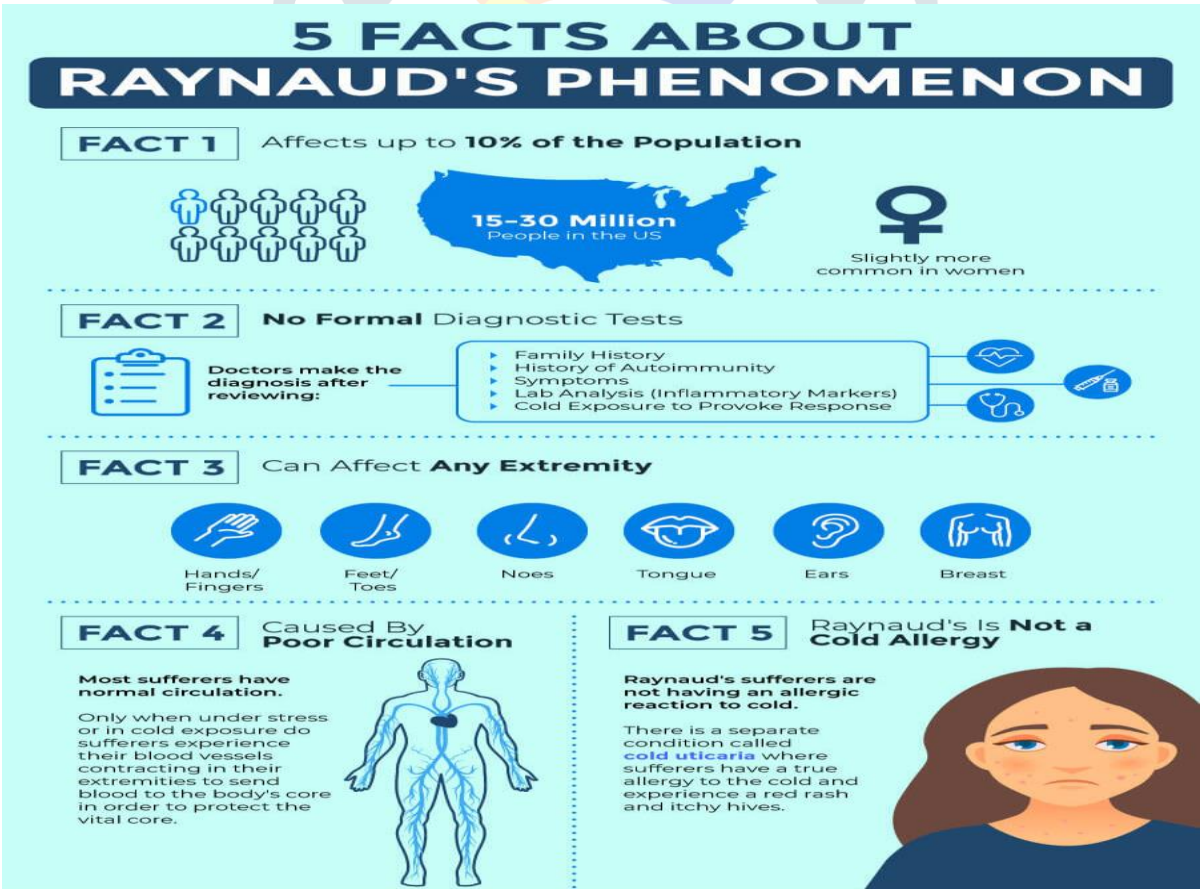

Figure no-6: Factors of Raynaud's phenomenon

- **Treatment:** As of now, medical treatment for Raynaud's phenomenon remains unsatisfactory. However, recent progress in understanding pathophysiological mechanisms has spurred further therapeutic approaches[18]. Clinical trials have shown promising results with various substances acting as vasodilators or inhibitors of increased vasoconstriction.

- Non-Medical Interventions: Effective management includes maintaining proper body insulation, avoiding cold exposure[19], discontinuing possible vasoconstrictive medications, and quitting smoking. These measures can be sufficient, particularly for patients with primary Raynaud's disease. In secondary Raynaud's, it is crucial to avoid triggering physical or chemical injuries and adequately treat the underlying disease[20].
- Calcium Channel Blockers: Calcium channel blockers induce relaxation of vascular smooth muscle cells by inhibiting voltage-gated channels, leading to peripheral vasodilation. Short-acting substances like nifedipine may cause side effects such as hypotension, reflex tachycardia, headache, or flush[21]The use of long-acting calcium channel blockers, such as felodipine, amlodipine, or nitrendipine, in patients with Raynaud's phenomenon remains controversial.
- Nitrates: Nitrates have been employed in both primary and secondary Raynaud's phenomenon through various administrations[22], including topical applications with transdermal patches, creams, gels, and oral forms. Sustained-release patches with glycerol trinitrate have demonstrated significant reduction in the severity and frequency of Raynaud attacks in both primary and secondary cases.

Symptoms of Raynaud's phenomenon:

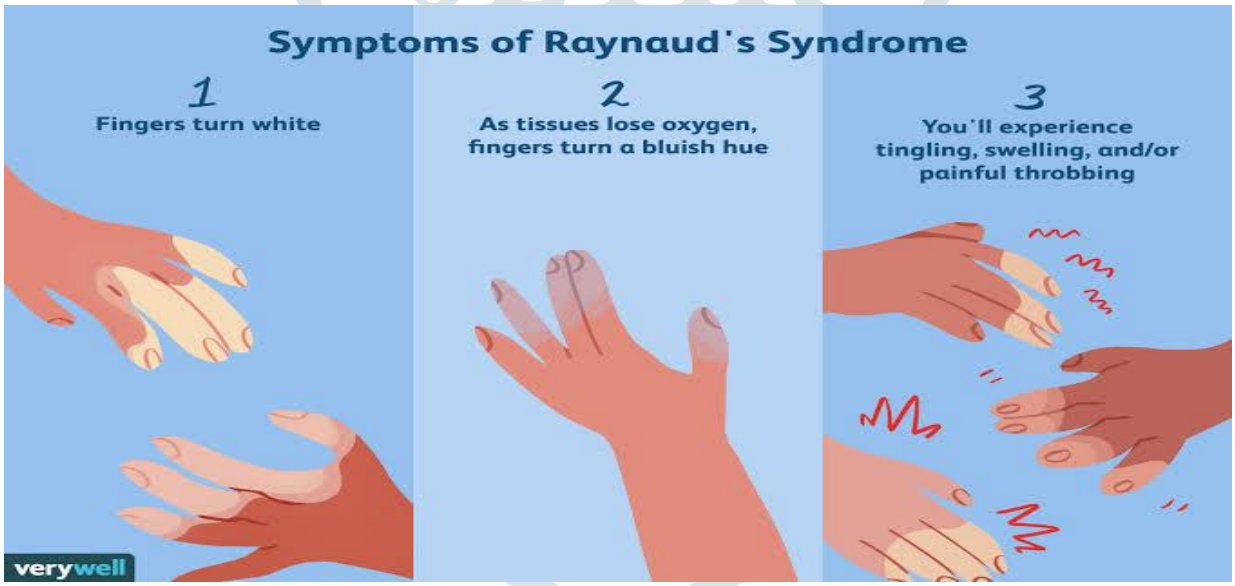

Figure no-7: Symptoms of Raynaud's phenomenon

Raynaud's phenomenon manifests as episodes or attacks that impact specific body parts, primarily the fingers and toes[23], resulting in sensations of coldness, numbness, and colour changes.(Refer to figure no-7) Exposure to cold, such as holding a glass of ice water or retrieving items from the freezer, serves as a primary trigger. Emotional stress[24], cigarette smoking, and vaping can also induce symptoms, extending to the ears and nose.

For individuals with severe Raynaud's phenomenon, the condition may progress to the development of small, painful sores, particularly at the fingertips or toe tips[25]. In rare instances, prolonged episodes spanning several days can cause a lack of oxygen to the tissues, leading to gangrene—a condition characterized by cellular death and decay of body tissues[26].

- **Conclusion:** Studying Raynaud's phenomenon poses significant challenges due to various factors. Firstly, it is crucial to acknowledge that Raynaud's is a complex symptom associated with diverse conditions, each with its distinct pathogenesis. Secondly, the intricacies of vascular physiology add to the complexity[27], with notable variations in both intra- and interindividual control of vascular tone, even in healthy individuals.

The pathophysiology of Raynaud's phenomenon involves numerous mechanisms[28]. While many align with Lewis's 'local fault' hypothesis, others, such as intravascular factors and a central nervous component of vasoconstriction, lean towards 'central' mechanisms, the definition of which varies. Contributing factors encompass heightened vasospasm, diminished vasodilation, structural abnormalities in both large and small vessels, and coagulopathy[29]. Key players in influencing these mechanisms include endothelin-1, NO, CGRP (and their balance), the α2-adrenoreceptor, free radicals (inducing oxidant stress), and platelet activation/aggregation. Advances in understanding the pathophysiology of Raynaud's phenomenon are steering the development of innovative treatment approaches[30].

Reference:

1.Ling SM, Wigley FM. Raynaud's phenomenon in older adults: diagnostic considerations and management. Drugs Aging. 1999; 15:183. [PubMed] [Google Scholar]

2. LeRoy EC, Medsger TA, et al. Raynaud's phenomenon: A proposal for classification. Clin Exp Rheumatol. 1992; 10:485. [PubMed] [Google Scholar]

3. Suter LG, Murabito JM, et al. The incidence and natural history of Raynaud's phenomenon in the community. Arthritis Rheum. 2005; 52:1259–1263. [PubMed] [Google Scholar]

4. Wigley FM. Clinical practice Raynaud's phenomenon. New Engl J Med. 2002 Sep 26; 347:1001–1008. [PubMed] [Google Scholar]

5. Koenig M, et al. Arthritis Rheum. 2008; 58:3902–12. [PubMed] [Google Scholar]

6. Spencer Green G. Outcomes in primary Raynaud's phenomenon. Arch Intern Med. 1998; 158:595–600. [PubMed] [Google Scholar]

7. Zufferey P, Depairon M, et al. Prognostic significance of nailfold capillary microscopy in patients with Raynaud's phenomenon and scleroderma-pattern abnormalities: a six-year follow-up study. Clin Rheumatol. 1992; 11:536–541. [PubMed] [Google Scholar]

8. Coffman JD, Doohen AS. Total and capillary fingertip blood flow in Raynaud's phenomenon. N Engl J Med. 1971; 285:259–263. [PubMed] [Google Scholar]

9. LeRoy EC, Downey JA, Cannon PJ. Skin capillary blood flow in scleroderma. J Clin Invest. 1971; 50:930–939. [PMC free article] [PubMed] [Google Scholar]

10. Bailey SR, Eid AH, et al. Rho kinase mediates cold-induced constriction of cutaneous arteries; role of a2c adrenoreceptor translocation. Circ Res. 2004; 94:1367–74. [PubMed] [Google Scholar]

11. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: meta-analysis. Rheumatology. 2005; 44:145–150. [PubMed] [Google Scholar]

12. Ennis H, Anderson ME, Wilkinson J, Herrick AL. Calcium channel blockers for primary Raynaud's phenomenon. Cochrane Library. 2014; 1:1–47. [Google Scholar]

13. Dziadzio M, Denton C, et al. Losartan therapy for Raynaud's phenomenon and scleroderma. Arthritis Rheum. 1999; 42:2646–2655. [PubMed] [Google Scholar]

14. Pope J, Fenlon D, et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev. 2000;(2):CD000953. [PMC free article] [PubMed] [Google Scholar]

15. Matucci-Cerinic M, et al. Ann Rheum Dis. 2011;70:32–8. [PMC free article] [PubMed] [Google Scholar]

16. Fries R, Shariat K, et al. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation. 2005 Nov 8;112(19):2980–5. [PubMed] [Google Scholar]

17. Caglayan E, et al. Arch Intern Med. 2012;172:1182–4. [PubMed] [Google Scholar]

18. Shenoy PD, et al. Rheumatol. 2010; 49:2420–8. [PubMed] [Google Scholar]

19. Abou-Raya A, Abou-Raya S, Helmi M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. J Rheumatol. 2008 Sep;35(9):1810–8. [PubMed] [Google Scholar]

20.Ventura I, Reid P, Jan R. Approach to Patients with Suspected Rheumatic Disease. Prim Care. 2018 Jun;45(2):169-180. [PubMed]

21.Pauling JD, Reilly E, Smith T, Frech TM. Evolving Symptom Characteristics of Raynaud's Phenomenon in Systemic Sclerosis and Their Association with Physician and Patient-Reported Assessments of Disease Severity. Arthritis Care Res (Hoboken). 2019 Aug;71(8):1119-1126. [PubMed]

22.Fernández-Codina A, Walker KM, Pope JE., Scleroderma Algorithm Group. Treatment Algorithms for Systemic Sclerosis According to Experts. Arthritis Rheumatol. 2018 Nov;70(11):1820-1828. [PubMed]

23.Wollina U, Koch A, Langner D, Hansel G, Heinig B, Lotti T, Tchernev G. Acrocyanosis - A Symptom with Many Factette's. Open Access Maced J Med Sci. 2018 Jan 25;6(1):208-212. [PMC free article] [PubMed]

24.Ruaro B, Sulli A, Smith V, Pizzorni C, Paolino S, Alessandri E, Cutolo M. Microvascular damage evaluation in systemic sclerosis: the role of nailfold video capillaroscopy and laser techniques. Rheumatism. 2017 Dec 21;69(4):147-155. [PubMed]

25.Belch J, Carlizza A, Carpentier PH, Constans J, Khan F, Wautrecht JC, Visona A, Heiss C, Brodeman M, Pécsvárady Z, Roztocil K, Colgan MP, Vasic D, Gottsäter A, Amann-Vesti B, Chraim A, Poredoš P, Olinic DM, Madaric J, Nikol S, Herrick AL, Sprynger M, Klein-Weigel P, Hafner F, Staub D, Zeman Z. ESVM guidelines - the diagnosis and management of Raynaud's phenomenon. Vasa. 2017 Oct;46(6):413-423. [PubMed]

26.Raynaud M. Local asphyxia and symmetrical gangrene of the extremities 1862. New researches on the nature and treatment of local asphyxia of the extremities 1874. Translated by Barlow. London: New Sydenham Society, 1888.

27.Lewis T. Experiments relating to the peripheral mechanism involved in spasmodic arrest of the circulation in the fingers, a variety of Raynaud's disease. Heart1929; 15:7–101.

28.Block JA, Sequeira W. Raynaud's phenomenon. Lancet2001; 357:2042–8.

29.Al-Allaf A-W, Belch JJF. Raynaud's phenomenon. In: Hochberg MC, Silman AJ, Smolen JS et al., eds. Rheumatology, 3rd edn. Elsevier, Edinburgh, 2003;1507–1512.

30.Kaheleh B, Matucci-Cerinic M. Raynaud's phenomenon and scleroderma. Dysregulated neuroendothelial control of vascular tone. Arthritis Rheum1995; 38:1–4.