International Journal of Pharma Research and Health Sciences, 2022; 10(6): 3487-94.
DOI:10.21276/ijprhs.2022.06.01
Sharma *et al.*

CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Review article

Understanding Etiopathogenesis of Raynaud's Phenomenon Based on the Types of Abnormalities, Episodic Color Changes and Causes

Manisha Sharma[1,*], Payal Rani Chaudhary[1], Arya Mudgal[1], Diksha Pandey[2], Yogesh Joshi[1]

[1] Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun, Uttarakhand, India.
[2] Department of Pharmacy, Banasthali Vidyapeeth, Jaipur, Rajasthan, India.

ARTICLE INFO:
Received: 06 Oct 2022
Accepted: 12 Dec 2022
Published: 31 Dec 2022

Corresponding author *
Ms Manisha Sharma,
Pharm.D (PB), Research Scholar,
Department of Pharmacy Practice,
School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun-248001, Uttarakhand, India.
E-mail:
manisha.october@gmail.com

ABSTRACT:
Raynaud's phenomenon is an irregular vascular symptom. Recurrent finger and toe vasospasm, which is frequently linked to mental stress or exposure to low temperatures, is how it develops. A large number of people experience primary Raynaud's phenomenon, however it can also develop as a result of a wide range of associated medical disorders and medication treatments, such as systemic sclerosis. Approximately 3-5% of the general population suffers from primary Raynaud's syndrome. The systemic sclerosis related Raynaud's phenomenon can be extremely severe, progressing to digital ulcers in about 50% of patients, although being far more uncommon. Occupational or connective tissue conditions are some other causes of Raynaud's phenomenon. For treatment, the kind must be determined. The quality of life can be significantly impacted by Raynaud's phenomenon. The systemic sclerosis related variant of Raynaud's phenomenon, which is the well-studied and perhaps the most complicated to effectively treat, is the main aim of this review. Further discussion includes pertinent epidemiology and etiology connected to pathophysiology of Raynaud's phenomenon.
Keywords: Raynaud's, primary, secondary, systemic sclerosis.

1. INTRODUCTION

A common clinical symptom impacting the feet and hands is Raynaud's syndrome. Morris Raynaud, who described the first case of the condition as intermittent, bilateral, acral vasospasm characterized by pallor, cyanosis, and suffusion in 1862, gave the condition its name. Raynaud's phenomenon is defined by episodic digital ischemia, which is clinically manifested by the consecutive development of digital maceration, cyanosis, and rubor of the fingers or toes following cold exposure and subsequent rewarming. The colour changes are typically limited to the fingers or toes and are well defined. Usually, when a patient is exposed to a chilly environment or touches cold objects, one or more of their digits will turn white. The initial or idiopathic condition that most persons with Raynaud's phenomenon experience does not develop to tissue damage. However, Raynaud's phenomenon can also be a side effect of a wide range of various illnesses or ailments [1-4].

There are three answers to a typical episode in Raynaud's phenomenon:
Phase 1: Pallor due to massive precapillary muscle arteriole vasoconstriction;
Phase 2: Cyanosis because of venous blood accumulating with low oxygen content;
Phase 3: Reddening due to reactive increase in overall supply [5, 6].

Regardless of the underlying reason, Raynaud's phenomenon has a major negative impact on a person's quality of life and can lead to secondary types of chronic digital ischemia, including ulceration and gangrene [7-9].

2. EPIDEMIOLOGY

Although there are many conflicting statistics regarding the frequency and prevalence of Raynaud's phenomenon, it is generally agreed that 3 to 5 % of the general population suffers from this condition. According to the authors of a recent systematic review and analysis of the literature, the

prevalence and incidence of primary Raynaud's phenomenon were 4.85 percent and 0.25 percent, respectively. Meanwhile, according to some studies, primary Raynaud's phenomenon may be more common, affecting 2 to 20% of women and 1 to 12% of males. Notably among females and those with early beginning of Raynaud's phenomena, almost half of individuals with primary Raynaud's phenomenon have a family history of the condition. As per estimates, Raynaud's phenomena typically develop before the age of 30, although secondary Raynaud's phenomenon is more likely to emerge beyond the age of 40. In general, women are more likely than males to have the primary Raynaud's phenomenon. Men seem to be more prone to get Raynaud's phenomenon as they age, and it is more likely that this is because of occupational exposures (like using vibratory tools) or peripheral vascular disease (from atherosclerosis)[10-13].

3. ETIOPATHOGENESIS

According to Raynaud's initial explanation, the increased excitability of the central sections of the cord presiding over vascular innervation was the reason for local hypoxia of the extremities. Lewis T (1929) and Lewis T et al. (1934), observed that vasospastic attacks can still happen in Raynaud's phenomenon patients after local anesthetic of the digital sympathetic nerves or after sympathectomy almost 70 years after this initial finding. Based on their findings, they hypothesized that Raynaud's phenomenon was a local problem brought on by spasm of the digital arteries rather than a subsequent effect of a CNS disorder. The pathophysiology of Raynaud's phenomenon is still not fully understood more than 70 years later. Circulating hormones, neural signals, and mediators secreted from circulating cells and the blood vessel itself interact delicately to control blood vessel reactivity [14, 15].

On the basis of types of abnormalities

Herrick AL (2005), categorized the physiological and pathological processes of Raynaud's phenomenon into three categories: vascular, neural, and intravascular anomalies in a recent analysis of the pathophysiology of the condition[16, 17].

3.1. Vascular abnormalities: Nitric oxide deficiency, in particular, may be the main factor contributing to vascular anomalies. Additionally, people with secondary Raynaud's phenomenon have high amounts of vasoconstrictor medications such endothelin-1. Vasoactive stimuli, angiotensin, vasopressin, and beta-transforming growth factor all cause the release of endothelin-1. In contrast to primary Raynaud's phenomenon, patients with collagen vascular disorder have structural anomalies linked to fibrotic proliferation of the vasculature[6, 18-20].

3.2. Neural abnormalities: In Raynaud's syndrome, impaired vasodilation is frequently observed. A significant neuropeptide that is connected to the calcitonin gene is a powerful vasodilator released by nerves that supply blood vessels. Skin biopsies from patients with primary Raynaud's phenomenon and systemic sclerosis revealed a reduced number of calcitonin gene associated peptide releasing neurons. Alpha 2c adrenoceptor overexpression may be a contributing factor to increased vasoconstriction in Raynaud's phenomenon. It has been discovered that these adrenoceptors allow blood vessels to constrict in response to cold. Increased protein tyrosine kinase activity may be greater than the corresponding contractile response to alpha 2c adrenergic agonist and freezing in patients with primary Raynaud's syndrome. This supports the idea that inhibiting protein tyrosine may be useful in the management of Raynaud's phenomenon. A strong vasoconstrictor known as neuropeptide Y is present in people with Raynaud's syndrome owing to systemic sclerosis [21-26].

3.3. Intravascular abnormalities: The following intravascular anomalies are linked to the Raynaud's phenomenon:

- Primary Raynaud's syndrome and systemic sclerosis are both characterized by increased platelet activation and aggregation. Increased blood levels of thromboxane and β-thromboglobulin, which are produced from platelet granules, are evidence of platelet activation. The production of thromboxane, a powerful vasoconstrictor and platelet aggregator, is enhanced in systemic sclerosis patients, especially when they are chilled,and this may be a factor in the development of vasospasm. Expression of the gene that encodes thromboxane synthase was awhile back identified to be elevated in leucocytes from systemic sclerosis patients. Another vasoconstrictor made by platelets called serotonin has also been linked to the pathophysiology of Raynaud's [16, 27-29].
- In systemic sclerosis, the fibrinolytic system is disrupted. Tissue plasminogen activator antigen, a product of endothelial cells that may be produced in situations of endothelial activation, has been detected in systemic sclerosis at elevated levels, while other researchers have discovered elevated quantities of tissue plasminogen activator inhibitor. Although the issue is complicated and the findings are contradictory, it can be concluded that at least some systemic sclerosis patients have poor fibrinolysis, which sensitizes them to fibrin accumulation and vascular obstruction. Patients with systemic sclerosis were shown to have abnormalities in both fibrinolysis and coagulation, according to Ames et al [5, 30-32].
- Patients with systemic sclerosis, primary Raynaud's phenomenon, and hand-arm vibration syndrome have shown evidence of white blood cell activation, which

may be linked to the oxidative stress outlined below[33, 34].

- Oxidative stress is brought on by reactive oxygen species. Numerous mechanisms, such as the hypoxanthine-xanthine oxidase system and the stimulation of polymorphonuclear leucocytes, can result in the generation of free radicals. Oxidative stress has received less research than systemic sclerosis, but primary Raynaud's phenomenon and systemic sclerosis patients were included in a cross-sectional study that revealed some enhanced free radical markers and decreased levels of ascorbic acid, an antioxidant, in both groups. This implies that primary Raynaud's phenomenon may also experience oxidative stress [30, 35].

On the basis of episodic color change

Digital arteries and arterioles experience excessive vasoconstriction, which causes the Raynaud syndrome. Paroxysmal pallor or cyanosis of the hands or feet is brought on by these vascular abnormalities; occasionally, the lips, nose, or earlobes are also affected. Typically, proximal vasodilation, central vasoconstriction, and more distant cyanosis are linked with red, white, and blue colour changes in the affected digits from most proximal to most distal. Despite the fact that Raynaud's phenomenon is typically characterized by a triphasic colour reaction, some people may only complain pallor and cyanosis while others may only encounter cyanosis. Reactive hyperaemia has been shown to be less prevalent and cyanosis (without blanching) to be more prevalent in systemic sclerosis patients than in primary Raynaud's phenomenon patients. The occurrence of at least two (biphasic) changes in colour has historically been required by the most of classification schemes.

- Pallor phase: The maceration or pallor, which is induced by the digital arteries' vasospasm, is the ischemic phase of the phenomena.
- Cyanosis phase: Capillaries and venules dilate during the ischemic phase, and the deoxygenated blood that is contained in these vessels exacerbates cyanosis.
- Rubor phase: During the hyperemic phase, patients frequently report rubor and warmth in addition to a pulsating pain [3, 9, 36].

On the basis of causes

Raynaud's phenomenon can be a primary disease entity or a complication of a number of other conditions.

A) Primary causes:

The primary form affects more than half of Raynaud's patients. Women are affected five times more frequently than men, and the age of onset is typically between 20 and 40 years. An amplification of central and local vasomotor reactions to cold or emotional stress is shown in primary Raynaud's phenomenon. Except for late in the course, when intimal thickening may manifest, structural alterations in the artery walls are nonexistent. The duration of Raynaud's phenomenon is typically benign, but if it persists for a long time, it can cause atrophy of the muscles, skin, and subcutaneous tissues. Ischemic gangrene and ulceration are uncommon.In80 to 90% of individuals with systemic sclerosis (scleroderma), Raynaud's phenomenon occurs, and in 30% of cases, it is the presenting symptom. For many years, it might be the only sign of scleroderma [3, 36].

B) Secondary causes:

The term "Secondary Raynaud's phenomenon" describes vascular insufficiency in the extremities that results from arterial illness brought on by conditions such as systemic lupus erythematosus, scleroderma, buerger disease, or even atherosclerosis.The greatest research has been done on systemic sclerosis-related Raynaud's phenomenon out of all the secondary kinds of Raynaud's phenomenon. Numerous mechanisms work together. The main issue is a deficiency in thermoregulation and a fluctuation between vasoconstriction and vasodilation that encourages vasoconstriction. Any patient exhibiting new symptoms should be examined because Raynaud's phenomenon may be the first sign of such illnesses. 10% of these people will eventually show signs of an underlying problem [16, 36, 37].

➢ Collagen vascular disease

- According to medical professionals, Raynaud's phenomenon can occur in up to 12 out of every 100 RA patients. In the general population, 5 out of every 100 people have Raynaud's.
- It's unclear how Raynaud's syndrome and rheumatoid arthritis are related. It's possible that RA gradually impairs the blood vessels' capacity to dilate (expand and constrict). The nerves that regulate the blood vessels in the feet and hands are also harmed by RA.
- Additionally, Raynaud's may be more likely to occur in RA patients who simultaneously have lupus, scleroderma, Sjogren's disease, and arterial stiffening.
- Raynaud's phenomenon affects about 20% of people with systemic lupus erythematosus. Eventually, a condition known as chronic digital ischemia can form and lead to gangrene or ulceration. A proliferative endarteritis occludes the tiny arteries in the majority of severe cases.
- Across the range of rheumatic disorders, particularly undifferentiated connective tissue disease, scleroderma, and systemic lupus erythematosus, there is a correlation between Raynaud's phenomenon and the distinctive autoantibody in MCTD, anti-U1-RNP (ribonucleoprotein).
- About 30% of people with dermatomyositis or polymyositis experience Raynaud's syndrome [3, 38-41].

- Occlusive digital artery diseases

- 147 Raynaud's phenomenon patients' records, divided into those with and without occlusive digital artery disease based on the results of quantitative finger plethysmography, were examined in order to determine the relationship between occlusive digital artery disease and the existence or resulting presence of clinical manifestation in patients with Raynaud's phenomenon. Scleroderma patients were not allowed to participate in the trial. In 147 instances, occlusive digital artery disease was found in 62% of them.
- Even though thromboangiitis obliterans is a rare cause of Raynaud's phenomenon, it should be taken into account in young males, especially those who smoke cigarettes.
- Raynaud's phenomenon may be brought on by decreased intravascular pressure, activation of sympathetic fibres in the brachial plexus, or a combination of the two in patients with thoracic outlet compression syndrome [42].

- Blood dyscrasias

- There are numerous blood dyscrasias that could be related to Raynaud's syndrome. Patients with cold agglutinins, cryoglobulinemias, or cryofibrinogenemia may experience hyperviscosity, cold-induced precipitation of plasma protein, and aggregation of red cells and platelets.
- In the preliminary assessment of individuals with Raynaud's phenomenon, it is also important to take into account the hyperviscosity syndrome that is associated with myeloproliferative disease and lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) [3].

- Occupational disorders

Patients who work with vibrating hand instruments like chainsaws or jackhammers encourage future Raynaud's syndrome. In pianists and keyboard players, Raynaud's phenomenon also seems to appears to be more common [3].

- Environmental agents

Frostbite or electric shock damage to the hands could cause Raynaud's phenomenon later on [3].

- Drugs and toxins

- β-adrenoceptor blockers: Drug-induced Raynaud's phenomenon is known to be caused by β-adrenoceptor blockers, although there are few statistics on how common it is. The use of β-adrenoceptor blockers is the most frequent cause of secondary Raynaud's phenomenon (34.2% of secondary Raynuad's phenomenon), according to an observation of the Framingham Heart study data. Patients on beta-adrenoceptor blockers had a prevalence of 14.7%, according to a meta-analysis released in 2012 that comprised 13 research (1012 patients)[43].
- Clonidine: Cold-amplified 2c-adrenoceptors-mediated vasoconstriction is higher in Raynaud's phenomenon patients. It has been determined that the translocation of 2c-adrenoceptors to the surface of vascular smooth muscle cells, via a pathway involving RhoA-Rho kinase, mediates skin vasoconstriction in reaction to local cooling. In cold conditions, the typically expected central lowering of the adrenergic tone may become predominate due to clonidine direct 2c-vascular agonism [37, 44, 45].
- Ergot alkaloids: Due to the much-increased prevalence of Raynaud's phenomenon in the community of migraineurs, it is challenging to determine the role of ergot alkaloids in Raynaud's phenomenon. Additionally, the peripheral vasoconstriction brought on by ergot alkaloids is occasionally mistaken with Raynaud's phenomenon. Although 'ergotism' is infrequently seen (the frequency is estimated at 0.1%), the persistent vasoconstriction can cause gangrene [46-50].
- Dopaminergic agonist: Bromocriptine primarily acts as a dopaminergic agonist. It has vasodilative effects at low dosages, which are brought on by D1-receptor activation and result in the well-known orthostatic hypotensive state. High doses cause vasoconstriction due to its 1-adrenoceptor characteristicsand peripheral catecholamine release. Additionally, bromocriptine has been classified as directly activating 2-adrenoceptors, which could account for clonidine's ability to boost cold sensitivity.The long-term usage of bromocriptine may also cause microvascular damage. Apparently, two incidences of erythromelalgia associated with bromocriptine and calcium channel blockers have been reported [51-54].
- Selective serotonin re-uptake inhibitors (SSRIs): Fluoxetine, Fluvoxamine,Citalopram and Milnacipranare some examples of the selective serotonin re-uptake inhibitors (SSRIs) that some writers have reported as having a negative relationship with Raynaud's phenomenon and the improvement of erythromelalgia symptoms. Additionally, a case of developing Raynaud's phenomenon 2 days after starting treatment with the partial 5-HT4 serotonin receptor agonist tergaserod has been documented. This difference between vasoconstriction and vasodilatation is still not fully understood. According to some experts, the establishment of a vasoconstrictive effect when taking an SSRI requires endothelium damage [55-62].
- Stimulants: The peripheral release of catecholamines that causes vasoconstriction is caused by central activation of the dopaminergic and noradrenergic system. It has been documented that CNS stimulants can cause Raynaud's phenomenon in some people. Reboxetin, an inhibitor of norepinephrine re-uptake, has been implicated in two cases of Raynaud's phenomenon. Amphetamine-like medications and phentermine, a mild sympathomimetic substance most frequently used as an appetite suppressant in the obesity

treatment have both been linked to the development of Raynaud's phenomenon and vasculopathy [61, 63, 64].

- Ciclosporin: It is yet unknown how ciclosporin induces Raynaud's phenomenon. Cyclosporin has been demonstrated to have a vasospastic effect on both the macro and microcirculation, resulting in regular monitoring of hypertension or acute renal failure in the initial stages of treatment. Additionally, the use of ciclosporin can cause changes in the blood's viscosity, a reduction in the deformability of red blood cells, and an increase in platelet aggregation, all of which can contribute to Raynaud's phenomenon [65, 66].
- Sympathomimetics: In a patient with primary Raynaud's phenomenon, digital necrosis was reported as a result of localized lidocaine/epinephrine usage. There are few studies on sympathomimetic nasal decongestants (phenylephrine, pseudoephedrine). Therefore, based on their poor therapeutic efficacy and pharmacologic characteristics, these medications should be avoided in people with Raynaud's phenomenon caused by scleroderma [67, 68].
- Cancer chemotherapy: In a 1995 study of 90 patients with testicular cancer who had cisplatin-based chemotherapy for more than a year, 37% of them acquired Raynaud's phenomenon following four cycles of the chemotherapy drug combination of cisplatin, bleomycin, and vinblastine. However, following a single cycle of treatment with the drugs doxorubicin, bleomycin, vincristine, and dacarbazine and a cumulative dose of just 40 000 IU of bleomycin, severe Raynaud's phenomenon with digital necrosis has also been reported. Being that scleroderma is the primary cause of secondary Raynaud's phenomenon, it is worth noting that bleomycin is utilized to create a sclerodermic phenotype in animals [69-71].

➢ Other factors

- Estrogen: Raynaud's phenomenon is far more common in women than in males, which suggests that gender difference and hormonal factors have a role. Further evidence that hormones play a key role in the pathophysiology of this ailment comes from the increasing manifestation of this condition between menarche and menopause. There aren't many research looking at how sex hormones affect Raynaud's syndrome. Although, a latest population-based, age-controlled study discovered that postmenopausal women receiving unopposed estrogen replacement treatment had a higher prevalence of Raynaud's phenomenon than those who did not take hormones. In women using combined hormonal replacement, there was no discernible increase in the risk of Raynaud's phenomenon. Notably, fluctuations in blood flow have been reported during the menstrual cycle. Biological data suggests that estrogens may act as vasodilators, notwithstanding epidemiological research' findings that estrogen use is linked to Raynaud's phenomenon. NO synthesis and cytochrome P450 activity have been linked to estrogen-associated vasodilation [72-76].
- Genetic factors: It has long been recognized that the sickness is hereditary, which begs the essential question if the illness has a clear genetic foundation. Five candidate chromosomal areas with potential links were identified in a study of afflicted family members utilizing whole genome linkage analysis. The muscular acetylcholine receptor beta subunit and the serotonin 1B and 1E receptors are three likely candidate genes that the authors found. According to a different study, people with primary Raynaud's phenomenon were more likely to experience migraines, and this tendency was even more pronounced in those who had a family history of the condition. This data shows that main Raynaud's phenomenon is a genetically predisposed component of a more prevalent vascular tone problem. The pathophysiology of systemic sclerosis has also been linked to genetic variables [77-79].
- Smoking-Smoking may affect hand-arm vibration syndrome since it was linked to decreased finger systolic pressures in a study of 601 participants.A significant epidemiological investigation, however, found no connection between smoking and the Raynaud's phenomenon [80, 81].

4. CONCLUSION

The complex symptoms of vascular illness known as Raynaud's phenomenon. It is intricate, multifaceted, and still not truly addressed. The pathophysiology of Raynaud's phenomenon is now thought to involve numerous distinct pathways. Microvascular dysfunction is a crucial aspect of its pathophysiology. It makes sense that vasoconstrictors might cause or worsen Raynaud's syndrome. Increased sympathetic activity, as well as endothelia dysfunction or neurotoxicity, may be associated to increased vascular tone. There are additional mechanisms that contribute to increased blood viscosity, such as reduced red blood cell deformability and increased platelet aggregation. One distinguishing characteristic is that systemic sclerosis patients who have secondary forms of Raynaud's phenomenon may experience gangrene and digital ulcers. Any treatment must take into account the distinction between primary and secondary Raynaud's phenomenon. New methods to treatment are being motivated by advancements in understanding the pathophysiology of the Raynaud's phenomenon.

5. REFERENCES

1. Wigley FM, Flavahan NA. Raynaud's phenomenon. N Engl J Med. 2016; 375: 556-65.
2. Bakst R, Merola JF, Franks AG, Sanchez M. Raynaud's phenomenon: pathogenesis and management. J Am Acad Dermatol. 2008; 59:633-53.

3. Jameson JL, Kasper DL, LongoDL, Fauci AS, Hauser SL,LoscalzoJ.Harrison's principles of internal medicine (20th edition.). New York: McGraw- Hill Education. 2018; 6: 1928-29.
4. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol. 2012; 8: 469-79.
5. Herrick AL, Illingworth K, Blann A, Hay CR, Hollis S, Jayson MI. Von Willebrand factor, thrombomodulin, thromboxane, betathromboglobulin and markers of fibrinolysis in primary Raynaud's phenomenon and systemic sclerosis. Ann Rheum Dis. 1996; 55:122-7.
6. Sakurai T, Goto K. Endothelins. Vascular actions and clinical implications. Drugs. 1993; 46:795-804.
7. Bassel M, Hudson M, TailleferSS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. Rheumatology (Oxford) 2011; 50:762-7.
8. Fabian B, Fabian AK, Bugan A, Csiki Z. Comparison of mental and physical health between patients with primary and secondary Raynaud's phenomenon Category: Article. J Psychosom Res. 2019; 116: 6-9.
9. Pauling JD, Hughes M, Pope JE. Raynaud's phenomenon - an update on diagnosis, classification and management. Clin Rheumatol. 2019; 38: 3317-30.
10. Maundrell A,Proudman SM. Epidemiology of Raynaud's phenomenon. In: Wigley FM, Herrick AL and Flavahan NA (eds) Raynaud's phenomenon: a guide to pathogenesis and treatment. New York: Springer, 2015, pp. 21–35.
11. Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: Systematic review and meta-analysis of observational studies. BMJ Open 2015;5:6389
12. Belch J, Carlizza A, Carpentier PH,ConstansJ, Khan F, WautrechtJ, VisonaA, et al. ESVM guidelines - the diagnosis and management of Raynaud's phenomenon. Vasa 2017; 46: 413-23.
13. Cordeiro RA, de Andrade RM. Raynaud's phenomenon in the occupational context. Rev Assoc Med Bras. 2019; 65:131.
14. Lewis T. Experiments relating to the peripheral mechanisms involved in spasmodic arrest of the circulation in the fingers, a variety of Raynaud's disease. Heart. 1929;15:7-101
15. Lewis T, Pickering GW. Observations upon maladies in which the blood supply to the digits cease intermittently or permanently, and upon bilateral gangrene of digits; observations relevant to so-called Raynaud's disease. Clin Sci. 1934; 1:327.
16. Herrick AL. Pathogenesis of Raynaud's phenomenon. Rheumatology. 2005; 44: 587-96.
17. Rajagopalan S, Pfenninger D, Kehrer C, Chakrabarti A, Somers E, Pavlic R, et al. Increased asymmetric dimethylarginine and endothelin 1 levels in secondary Raynaud's phenomenon: implications for vascular dysfunction and progression of disease. Arthritis Rheum. 2003; 48: 1992-2000.
18. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. J Hypertens. 2006; 24: 983-91.
19. Kawaguchi Y, Takagi K, Hara M, Fukasawa C, Sugiura T, Nishimagi E, Harigai M, Kamatani N. Angiotensin II in the lesional skin of systemic sclerosis patients contributes to tissue fibrosis via angiotensin II type 1 receptors. Arthritis Rheum 2004; 50: 216-26.
20. Hughes M, Herrick AL. Raynaud's phenomenon. Best Pract Res Clin Rheumatol. 2016; 30:112-32.
21. 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) 1998; 95:249-60.
22. Bunker CB, Goldsmith PC, Leslie TA, Hayes N, Foreman JC, Dowd PM. Calcitonin gene-related peptide, endothelin1, the cutaneous microvasculature and Raynaud's phenomenon. Br J Dermatol. 1996; 134:399-406.
23. Bunker CB, Terenghi G, Springall DR, Polak JM, Dowd PM. Deficiency of calcitonin gene-related peptide in Raynaud's phenomenon. Lancet 1990; 336:1530-3.
24. 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. 2000; 278:H1075-83.
25. Furspan PB, Chatterjee S, Freedman RR. Increased tyrosine phosphorylation mediates the cooling-induced contraction and increased vascular reactivity of Raynaud's disease. Arthritis Rheum. 2004; 50:1578-1585.
26. 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; 22:97-101.
27. Reilly IA, Roy L, Fitzgerald GA. Biosynthesis of thromboxane in patients with systemic sclerosis and Raynaud's phenomenon. Br Med J. 1986; 292:1037-39.
28. Young V, Ho M, Vosper H, Belch JJF, Palmer CNA. Elevated expression of the genes encoding TNF- and thromboxane synthase in leucocytes from patients with systemic sclerosis. Rheumatology 2002; 41: 869-75.
29. Klimiuk PS, Grennan A, Weinkove C, Jayson MIV. Platelet serotonin in systemic sclerosis. Ann Rheum Dis. 1989; 48: 586-9.
30. Khouri C, Blaise S, Carpentier P, Villier C, Cracowski JL, Roustit M. Drug-induced Raynaud's phenomenon: beyond β-adrenoceptor blockers. Br J Clin Pharmacol. 2016; 82:6-16.

31. Marasini B, Cugno M, Bassani C, Stanzani M, Bottasso B, Agostoni A. Tissue-type plasminogen activator and von Willebrand factor plasma levels as markers of endothelial involvement in patients with Raynaud's phenomenon. Int J Microcirc Clin Exp. 1992; 11: 375-82.
32. Ames PR, Lupoli S, Alves J, Atsumi T, Edwards C, Iannaccone L, Khamashta MA, Hughes GR,Brancaccio V. The coagulation/fibrinolytic balance in systemic sclerosis: evidence for a haematological stress syndrome. Br J Rheumatol.1997; 36:1045-50.
33. Lau CS, O'Dowd A, Belch JJF. White blood cell activation in Raynaud's phenomenon of systemic sclerosis and vibration white finger. Ann Rheum Dis. 1992; 51: 249-52.
34. Lau CS, Bridges AB, Muir A, Scott N, Bancroft A, Belch JJF. Further evidence of increased polymorphonuclear cell activity in patients with Raynaud's phenomenon. Br J Rheumatol. 1992; 31: 375-80.
35. Herrick AL, Rieley F, Schofield D, Hollis S, Braganza JM, Jayson MIV. Micronutrient antioxidant status in patients with primary Raynaud's phenomenon and systemic sclerosis. J Rheumatol.1994; 21:1477-83.
36. RobbinsSL, Kumar V, Cotran RS. (2010). Robbins and Cotran pathologic basis of disease (8^{th} ed.). Philadelphia, PA: Saunders/Elsevier; 11: 518.
37. Flavahan NA. A vascular mechanistic approach to understanding Raynaud phenomenon. Nat Rev Rheumatol. 2015; 11: 146-58.
38. Hartmann P, Mohokum M, Schlattmann P. The association of Raynaud's syndrome with rheumatoid arthritis - a meta-analysis. Clin Rheumatol 2011;30:1013-9.
39. Tansey RJ, Wragg EA, Herrick AL. Raynaud's phenomenon and hand function in patients with rheumatoid arthritis. J Rheumatol. 2010; 37:1358-9.
40. Raynaud's. National Heart, Lung, and Blood Institute. Available at https://www.nhlbi.nih.gov/health-topics/raynauds (Accessed 2/1/2021).
41. Grader-Beck T, Wigley FM. Raynaud's phenomenon in mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31:465-81.
42. Zweifler AJ, Trinkaus P. Occlusive digital artery disease in patients with Raynaud's phenomenon. Am J Med. 1984; 77: 995-1001.
43. De Angelis R, Salaffi F, Grassi W. Raynaud's phenomenon: prevalence in an Italian population sample. Clin Rheumatol. 2006; 25: 506-10.
44. Freedman RR, Moten M, Migaly P, Mayes M. Cold-induced potentiation of alpha 2-adrenergic vasoconstriction in primary Raynaud's disease. Arthritis Rheum. 1993; 36: 685-90.
45. Roustit M, Cracowski JL. Assessment of endothelial and neurovascular function in human skin microcirculation. Trends Pharmacol Sci. 2013; 34: 373-84.
46. O'Keeffe ST, Tsapatsaris NP, Beetham WP. Association between Raynaud's phenomenon and migraine in a random population of hospital employees. J Rheumatol. 1993; 20: 1187-8.
47. Zahavi I, Chagnac A, Hering R, Davidovich S, Kuritzky A. Prevalence of Raynaud's phenomenon in patients with migraine. Arch Intern Med. 1984; 144: 742-4.
48. Quagliarello J, Barakat R. Raynaud's phenomenon in infertile women treated with bromocriptine. Fertil Steril 1987; 48: 877-9.
49. Zenone T, Durieu I, Nagnoug F, Castell P, Levrat R. Raynaud phenomenon with organic microangiopathy and prolonged treatment with bromocriptine. Rev Medecine Interne Fondee Par SocieteNatl Francaise Medecine Interne. 1996; 17: 948-50.
50. Cruaud D, Noel G, Daumont M.Raynaud's syndrome induced by bromoergocryptine. Nouv Presse Medicale 1977; 6: 2693.
51. Newman-Tancredi A, Cussac D, Audinot V, Nicolas J, Ceuninck FD, Boutin J, Millan MJ. Differential Actions of Antiparkinson Agents at Multiple Classes of Monoaminergic Receptor. II. Agonist and Antagonist Properties at Subtypes of Dopamine D2-Like Receptor and α1/α2-Adrenoceptor. J Pharmacol Exp Ther. 2002; 303: 805-14.
52. de Leeuw van Weenen JE, Parlevliet ET, Maechler P, Havekes LM, Romijn JA, Ouwens DM, Pijl H, Guigas B. The dopamine receptor D2 agonist bromocriptine inhibits glucose-stimulated insulin secretion by direct activation of the alpha2-adrenergic receptors in beta cells. Biochem Pharmacol. 2010; 79: 1827-36.
53. Cohen JS. Erythromelalgia: New theories and new therapies. J Am Acad Dermatol. 2000; 43: 841-7.
54. Skeik N, Rooke TW, Davis MDP, Davis DMR, Kalsi H, Kurth I, Richardson RC. Severe case and literature review of primary erythromelalgia: Novel SCN9A gene mutation. Vasc Med. 2012; 17: 44-49.
55. De Broucker T, Lhote F. Severe Raynaud's phenomenon associated with interferon-beta 1a and fluoxetine. Ann Medecine Interne 2000; 151: 424-5.
56. Rudnick A, Modai I, Zelikovski A. Fluoxetine-induced Raynaud's phenomenon. Biol Psychiatry. 1997; 41: 1218-21.
57. Bell C, Coupland N, Creamer P. Digital infarction in a patient with Raynaud's phenomenon associated with treatment with a specific serotonin reuptake inhibitor. A case report. Angiology. 1996; 47: 901-3.
58. Peiro AM, Margarit C, Torra M. Citalopram-induced Raynaud's phenomenon. Rheumatol Int. 2006; 27: 599-601.
59. Bourgade B, Jonville-Bera AP, Le Gare C, Ferquel D, Autret-Leca E. Raynaud's syndrome in a patient treated

with milnacipran. Ann Pharmacother. 1999; 33: 1009-10.
60. Rudikoff D, Jaffe IA. Erythromelalgia: response to serotonin reuptake inhibitors. J Am Acad Dermatol. 1997; 37 (2 Pt 1): 281-3.
61. Bertoli R, Girardin F, Russmann S, Lauterburg BH. Raynaud's phenomenon induced by drugs acting on neurotransmission: two cases under reboxetine and one under tegaserod. Eur J Clin Pharmacol. 2003; 58: 717.
62. Garcia-Porrua C, Margarinos CC, Gonzalez-Gay MA. Raynaud's phenomenon and serotonin reuptake inhibitors. J Rheumatol. 2004; 31: 2090-1.
63. Syed RH, Moore TL. Methylphenidate and dextroamphetamineinduced peripheral vasculopathy. J Clin RheumatolPract Rep Rheum Musculoskelet Dis. 2008; 14: 30-3.
64. Jefferson HJ, Jayne DR. Peripheral vasculopathy and nephropathy in association with phentermine. Nephrol Dial Transplant. 1999; 14: 1761-3.
65. Osman EA, Barrett JJ, Bewick M, Parsons V. Does cyclosporin affect renal blood vessels? Lancet. 1984; 1: 1470.
66. Arinsoy T, Derici U, Yuksel A, Reis KA, Sindel S. Cyclosporine–a treatment and a rare complication: Raynaud's phenomenon. Int J Clin Pract. 2005; 59: 863-4.
67. Ravindran V, Rajendran S. Digital gangrene in a patient with primary Raynaud's phenomenon. J R Coll Physicians Edinb. 2012; 42: 24-6.
68. Frances C, Allanore Y, Cabane J, Carpentier P, Dumontier C, HachullaE, Hatron PY, Lipsker D, Meaume S, Mouthon L, Senet P, Sibilia Jand the French Scleroderma Research Group. Management of digital ulcers in systemic sclerosis: Recommendations from a multidisciplinary group of experts. Presse Med. 2008; 37 (2, Part 2): 271-85.
69. Berger CC, Bokemeyer C, Schneider M, Kuczyk MA, Schmoll HJ. Secondary Raynaud's phenomenon and other late vascular complications following chemotherapy for testicular cancer. Eur J Cancer. 1995; 31A (13-14): 2229-38.
70. McGrath SE, Webb A, Walker-Bone K. Bleomycin-induced Raynaud's phenomenon after single-dose exposure: risk factors and treatment with intravenous iloprost infusion. J Clin Oncol. 2013; 31: e51-52.
71. Batteux F, Kavian N, Servettaz A. New insights on chemically induced animal models of systemic sclerosis. Curr Opin Rheumatol. 2011; 23: 511-8.
72. Fraenkel L. Raynaud's phenomenon: epidemiology and risk factors. Curr Rheumatol Rep. 2002; 4:123-8.
73. Fraenkel L, Zhang Y, Chaisson CE, Evans SR, Wilson PW, Felson DT. The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women. Ann Intern Med. 1998;129:208-11.
74. Lafferty K, De Trafford JC, Potter C, Roberts VC, Cotton LT. Reflex vascular responses in the finger to contralateral thermal stimuli during the normal menstrual cycle: a hormonal basis to Raynaud's phenomenon? Clin Sci (Colch). 1985;68:639-45.
75. Momoi H, Ikomi F, Ohhashi T.Estrogen-induced augmentation of endothelium-dependent nitric oxide-mediated vasodilation in isolated rat cerebral small arteries. Jpn J Physiol. 2003; 53:193-203.
76. Huang A, Sun D, Wu Z, Yan C, Carroll MA, Jiang H,Falck JR, Kaley G. Estrogen elicits cytochrome P450-mediated flow-induced dilation of arterioles in NO deficiency: role of PI3K-Akt phosphorylation in genomic regulation. Circ Res. 2004;94: 245-52.
77. Susol E, MacGregor AJ, Barrett JH, Wilson H, Black C, Welsh K,Silman A, Ollier B,Worthington J. A two-stage, genome-wide screen for susceptibility loci in primary Raynaud's phenomenon. Arthritis Rheum. 2000; 43: 1641-6.
78. Smyth AE, Hughes AE, Bruce IN, Bell AL. A case-control study of candidate vasoactive mediator genes in primary Raynaud's phenomenon. Rheumatology 1999; 38:1094-8.
79. Zhou X, Tan FK, Wang N, Xiong M, Maghidman S, Reveille JD, Milewicz DM, Chakraborty R, Arnett FC. Genome-wide association study for regions of systemic sclerosis susceptibility in a Choctaw Indian population with high disease prevalence. Arthritis Rheum. 2003;48: 2585-392.
80. Cherniack M, Clive J, Seidner A. Vibration exposure, smoking, and vascular dysfunction. Occup Environ Med. 2000;57: 341-7.
81. Palesch YY, Valter I, Carpentier PH, Maricq HR. Association between cigarette and alcohol consumption and Raynaud's phenomenon. J Clin Epidemiol. 1999; 52: 321-8.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not applicable.