



## Treatment of Raynaud's phenomenon

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### ABSTRACT

Raynaud's phenomenon is an episodic vasospasm of the peripheral arteries, causing pallor followed by cyanosis and redness with pain and sometimes paraesthesia, and, rarely, ulceration of the fingers and toes. Primary or idiopathic Raynaud's phenomenon (Raynaud's disease) occurs without an underlying disease. Secondary Raynaud's phenomenon (Raynaud's syndrome) occurs in association with an underlying disease. Initially conservative, non-pharmacologic approach is important for these patients, although pharmacologic therapy may ultimately be necessary. Advances in vascular physiology have showed the role of the endothelium as well as endothelium-independent mechanisms in the altered vasoregulation of Raynaud's phenomenon. This has opened promising therapeutic avenues, and it is likely that therapies targeted towards specific pathophysiologic steps become available in the near future.

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## 1. Introduction

Raynaud's phenomenon (RP) is an episodic vasospasm of the peripheral arteries due to an exaggerated reaction to cold weather or emotional stimuli. Fingers and toes are typically involved. The classic triad of symptoms and color variation was first described by Maurice Raynaud in 1862. They consist of pallor of the skin (secondary to vasospasm), followed by cyanosis (produced by de-oxygenated blood), and finally blushing (produced by the return of blood flow from the fingers followed by a reactive increase in temperature) [1–2].

Raynaud's phenomenon is classified as primary or secondary. Patients presenting with primary Raynaud's phenomenon (PRP) most likely have a history of recurrent events, with symptoms that vary from mild to severe, but it lacks complications or ischemic damage. [3,4] Approximately, 25% of PRP have also a family history of familiar recurrence in first degree relatives. The average age at PRP appearance is around 14 years old, only 27% of the cases starts after 40 years. Secondary Raynaud's phenomenon (SRP) mainly develops as a consequence of a systemic autoimmune disorder [5–6], particularly systemic sclerosis [7] or mixed connective tissue disease [8].

RP can manifest itself as an isolated, acute or sub acute disorder as well, presenting with cold, pain and numbness of the fingers, secondary to ischemia that can lead to ulcerations and/or gangrene [1]. The main criteria to distinguish PRP and SRP are as follows: characteristic color variations caused by cold or stress, presence or absence of an underlying diseases that causes RP (i.e. a systemic autoimmune disease), digital ulcers or gangrene, elevated erythrocyte sedimentation rate, antinuclear antibodies (ANA), rheumatoid factor, C3 and C4 complement factors, chest X-ray, hand X-ray and nail-fold capillaroscopy. Patients presenting asymmetric attacks, absent pulse, and/or asymmetric blood pressure, need more specialized studies, such as digital pletismography and arterial Doppler ultrasound or angiography to establish the diagnosis and rule out vascular diseases (i.e., thromboangiitis obliterans, embolic disease, Paget-Schoetter syndrome, or atherosclerosis) [9].

## 2. Treatment of Raynaud's phenomenon

Treatment for mild disease is almost exclusively conservative, changing life-style conditions that precipitate the illness [10]. Pharmacologic treatment is used when the manifestations are severe (Table 1). Surgical treatment is reserved for complicated conditions that do not respond to pharmacological treatment [1–3]. A great variety of drugs have been tested for the treatment of RP, questioning their utility, since none of them show efficiency in clinical trials, and most of them have noxious side effects and are difficult to administrate.

Before beginning a pharmacological treatment it is necessary to investigate the existence of extrinsic factors that cause arteriolar vasospasm and try to eliminate them.

Also it should be determined if there is an underlying autoimmune disease that causes RP and treat it accordingly.

Treatment for RP depends on its severity and of the underlying disease. However, patients should know that the treatment will not eliminate the disease, but the severity of the condition can be reduced with different treatment modalities which can be divided in conservative measures, pharmacological treatment and surgery.

## 3. Non-pharmacologic therapy

Mild RP can be treated almost exclusively with conservative measures. The main objective is to try to make the patient able to change his or her life-style [3]. Patients have to learn how to recognize reflex vasospasm as a main thermoregulative mechanism, and to identify circumstances that can cause acute attacks like sudden changes in temperature, digital trauma, or some drugs [2,11].

Drugs with a high potential for vasospasm in peripheral arteries should be avoided, all in patients with PRP and SRP. Sympathomimetic drugs (i.e., ephedrine and serotonin agonists such as sumatriptan), should not be used by patients with RP. Amphetamines as well as certain chemotherapeutic drugs (bleomicine, cisplatin, carboplatin, vinblastine) can cause vascular occlusion and cause RP episodes [2]. The role of estrogens as a RP trigger is controversial. The Framingham's epidemiologic study concluded that women that took estrogens have a higher incidence of presenting RP. However, it is reported that treatment with estrogens in patients with systemic

**Table 1**  
Pharmacologic treatment of Raynaud's phenomenon

Agent	Dose	Side-effects
Nifedipine	10–30 mg TID (PO)	Tachycardia, hypotensión, palpitations, constipation, anxiety
Amlodipine	5–20 mg QD (PO)	
Diltiazem	30–120 mg TID (PO)	
Losartan	25–100 mg QD (PO)	Dizziness, headache, fatigue, diarrhea
Prazosin	1–5 mg 2 times QD (PO)	Orthostatic hypotension, nausea, headache
Fluoxetine	20–40 mg QD (PO)	Insomnia, nausea, diarrhea, tremors
Pentoxifyline	400 mg TID (PO)	Dyspepsia, nausea, vomiting
Epoprostenol	0.5–8 ng/kg of body weight/min endovenously for 6–24 h, for 2–5 days	Diarrhea, headache, rash, hypotension
Iloprost	Infused at a rate of 0.5 to 2.0 ng/kg/min, peripheral intravenous line	Headache, rash, hypotension.
Alprostadil	6 to 10 ng/kg/min through a central intravenous line	Headache, rash, hypotension.
Bosentan	62.5 mg twice daily for 4 weeks; increase to maintenance dose of 125 mg twice daily	Headache, hemoglobin decreased typically in first 6 weeks of therapy, Flushing, edema, hypotension, palpitation, increase in liver enzymes.

sclerosis causes vasodilatation [12]. The impact of smoking on RP has not been completely clarified, there are studies that show nicotine can decrease distal blood flow, but other epidemiologic studies did not find a direct association between smoking and RP [13]. Besides, it is important to avoid smoking because of the important cardiovascular side effects. Recent findings suggest that the use of drugs that contain caffeine and ergotamine (drugs prescribed for migraine), inhibitors of p450cytochrome CYP3A4 fraction, and macrolide antibiotics present a potential vasospastic effect and should be used with caution [2,11].

Dietary supplements of polyunsaturated fatty acids,  $\omega$ 3 eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) have pleiotropic effects including on endothelial vascular cells. These two essential fatty acids which are not synthesized by the body have to be supplemented. Studies have shown benefit in patients with PRP but not SRP with anti-inflammatory, anti-arrhythmic, antithrombotic and vasodilatation properties. They are precursors of a group of eicosanoids that can cause these effects, producing better tolerance to cold, delaying the vasospasm onset, and a better response to ischemia. An intake of 2 g/day of  $\alpha$ -linoleic acid or 200 mg a day of polyunsaturated fatty acid  $\omega$ 3 should be encouraged [14].

Relaxation and acupuncture techniques [15] can be part of the general treatment for RP, especially in those patients where stress has been identified as a triggering factor of RP.

The use of these general measures should be enough for many patients with RP, without the need of drugs which are reserved for more complicated situations.

#### 4. Pharmacological treatment

If non-pharmacologic treatment alone does not succeed, drug therapy may be necessary. The objective of using drugs in RP consists in reducing the frequency and severity of the acute vasospastic episodes, maintaining blood flow and preventing ulcers, ischemia and necrosis [16]. In the more severe cases, where chronic ischemia has caused an alteration in vascular structure, the therapeutic strategy will be to maintain adequate blood flow and to prevent vasoconstriction and avoid necrosis.

A wide variety of drugs have been used to treat RP. Among the drug classes that have been used are calcium channel blockers, other vasodilators, sympatholytic agents, prostaglandins, ACE inhibitors (ACEi), angiotensin receptor blockers (ARB); thromboxane A2 inhibitors; serotonin antagonists and others like griseofulvine [17]. But the use of some of these drugs has been questioned, since none of them have shown efficiency in clinical trials, and most of them have noxious side effects and are difficult to administrate.

##### 4.1. Vasodilators

The use of these drugs benefits more PRP than SRP patients [3], probably because SRP patients have more structural damage than those with PRP. Calcium channel blockers have been widely used in RP treatment, being the drugs of first choice [18]. In particular, those drugs derived from dihydropyridine due to its selectiveness for smooth musculature and their reduced side effects on cardiac function [18–20].

The available calcium channel blockers exert their effects primarily at voltage-gated calcium channels of the plasma membrane, because of vascular tone and contraction are determined largely by the availability of calcium from extracellular sources (influx via calcium channels) or intracellular stores. Drug-induced inhibition of calcium influx via voltage-gated channels results in widespread dilation and a decrease in contractile responses to stimulatory agents. Arteries and arterioles are more sensitive to the relaxing actions of these drugs than are the veins, and some arterial beds (e.g., coronary and cerebral vessels) show greater sensitivity than others [21,22]. Peripheral vasodilation and the consequent fall in blood pressure are commonly accompanied by reflex tachycardia when nifedipine and its analogues are used; this is in contrast to verapamil and diltiazem, whose effects on peripheral vessels are accompanied by cardiodepressant effects. Nifedipine (dihydropyridine derivative) is the most frequently used drug, since it also has the ability to inactivate platelet activation and has antithrombotic effects [23]. Treatment usually starts with low dosage, slowly incrementing it according to clinical response. Dosage usually starts at 10 to 40 mg, with sustained release drugs. You can reach a dose over 60 mg a day in refractory RP. The recommended dose can vary from 30 to 120 mg a day depending on the condition severity [2,18–20]. Patients treated with nifedipine improve their condition, but sometimes cannot tolerate the side effects so they can be treated with the association of low dosage nifedipine plus another vasodilating drug. The use of other calcium antagonists (diltiazem, felodipine, amlodipine, nitrendipine, isradipine, or nicardipine) is controversial, due to the variety of results in clinical trials, most of short term duration, but they can be effective [18,23].

Thompson et al. [20] evaluated the efficacy of calcium channel blockers in patients with PRP, finding a 2.8 to 5.0% reduction of weekly attacks ( $p=0.01$ ) and a 33% reduction in their severity ( $p=0.005$ ). In clinical practice, the effective dosage of calcium channel blockers varies from patient to patient, so the doses used in clinical trials do not mean the adequate dosage to reach the maximum benefits. The recommended dose of nifedipine in patients with RP is 10 to 30 mg TID [17–18]. The most common side effects are orthostatic hypotension, tachycardia, edema, headache and constipation [22].

Different studies have shown the efficacy and the adequate tolerance of long-acting nifedipine [20]. In a randomized clinical trial made by Wigley et al. [24] with 313 patients with RP, treatment with long-acting nifedipine was effective and safe, it also showed a positive response to temperature changes, revealing that patients treated with nifedipine showed a 66% reduction of attacks versus the placebo group ( $p<0.001$ ). Some investigations reported that the beneficial effect of the calcium channel blockers was lost with prolonged treatment [23].

Treatment with nifedipine can also be combined with drugs that inhibit platelet aggregation such as aspirine (150 mg/day), with few side effects [10,16]. It acetylates and irreversibly inhibits cyclooxygenase (primarily cyclooxygenase-1) both in platelets and in endothelial cells, preventing the formation of thromboxane A2 (TxA2), a product of arachidonic acid, a potent vasoconstrictor and platelet aggregator, thus inhibiting the synthesis of prostacyclin (PGI<sub>2</sub>). While endothelial cells can synthesize cyclooxygenase,

platelets cannot. The goal of therapy with aspirin is to selectively inhibit the synthesis of platelet TxA<sub>2</sub> and thereby inhibit platelet aggregation [17].

Pentoxifylline is recommended at a dose of 400 mg BID or TID, only in combination with other vasodilators. It is useful in the treatment of RP [10,17,18] because it improves erythrocyte flexibility by inhibition of erythrocyte phosphodiesterase which causes an increase in erythrocyte cAMP activity. This increase allows the erythrocyte membrane to maintain its integrity and become more resistant to deformity. It also reduces the blood viscosity reducing the fibrinogen concentration and enhancing tissue oxygenation [17]. The side effects can include angina, tachyarrhythmia, difficult breathing, hypotension, edema, dry mouth, anxiety and confusion.

The use of transdermal nitrates is important in RP treatment [1,6]. Nitroglycerine has a potent vasodilating activity of great reach. The mechanism of action of nitroglycerine and other organic nitrates involves an interaction with the nitrate receptors that are present in vascular smooth muscle, which possess a sulfhydryl group that reduces the nitrate to inorganic nitrite and nitric oxide [25]. Nitric oxide, the active intermediate compound common to all agents of this class, activates the enzyme guanylate cyclase, thereby stimulating the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP). This second messenger then activates a series of protein kinase-dependent phosphorylations in the smooth muscle cells, eventually resulting in the dephosphorylation of the myosin light chain of the smooth muscle fiber and the subsequent release, or extrusion, of calcium ions. The contractile state of smooth muscle is normally maintained by a phosphorylated myosin light chain (stimulated by an increase in calcium ions). Thus, the nitrite- or nitrate-induced dephosphorylation of the myosin light chain signals the cell to release calcium, thereby relaxing the smooth muscle cells and producing vasodilation.

The formation of these compounds has been proposed to stimulate the soluble guanylate cyclase enzyme, which increments the formation of intracellular cyclic guanosine monophosphate GMPc, probably inhibiting the access of calcium through the L-type calcium channels, lowering its liberation from the sarcoplasmic reticulum, thus reducing intracellular calcium which instead relaxes the smooth vascular muscle [18,25]. The topic application of nitroglycerine is recommended at a dosage of a quarter and half an inch of a 2% cream a day [7]. Just like other nitrates, it can cause headache, skin rash, pruritus, and allergic dermatitis. In rare occasions orthostatic hypotension, tachycardia, nausea and vomiting.

#### 4.2. Alpha-adrenergic blockers

Considering that the sympathetic nervous system regulates a tonic vasoconstrictor effect over the vascular wall and it has an important role in skin temperature regulation [26,27], it has been proposed the use of postganglionic non-selective blockers of the sympathetic nervous system (reserpine, guanethidine, fenoxibenzamine), although its long-term benefit has not been proven. Reserpine has shown efficacy in the treatment of RP, as well as restoring digital ulcers, but more studies are needed to prove it. Reserpine acts by breaking down the storing vesicles of noradrenaline and desoxifenilnoradrenaline (DOPA) in the nerve endings making these neurotransmitting amines spill in the cytoplasm.

Monoaminooxidase (MAO) then inactivates them and prevents normal sympathetic transmission in the periphery. The periphery decrease of neurotransmitters causes vasodilation, reduces vascular resistance and blood pressure as well as cardiac output. The side effects of this drug include nasal congestion, nausea, dyspepsia, lethargy, and depression which in most cases induces patients to abandon treatment.

Prazosin is a peripheral vasodilator that blocks the  $\alpha$ -1 post synaptic adrenergic receptors without activating norepinephrine liberation; this is why there is a low incidence of reflex tachycardia [18]. The usual recommended dose is 1 to 5 mg TID [2]. According to the meta-analysis by Pope et al. [27] reported a decrease in frequency and severity of attacks DPP –3.50 (CI of 95% –5.85, –1.15). The most common reported side effects are nausea, dizziness, headache, insomnia, weakness, lethargy, palpitations, and occasionally orthostatic hypotension that can be resolved by lowering the dosage.

Wigley et al. [28] showed the effect of OPC-28326, a selective adrenergic antagonist of  $\alpha$ 2C adrenergic receptors on skin temperature and digital blood flow in patients with systemic sclerosis and RP by reducing the recuperation time after an acute attack of RP with a dose between 10 and 40 mg in comparison with a placebo (50% of recuperation in 5.8 min vs 10.0 min ( $p=0.02$ ); 70% of recuperation in 13.8 min vs 19.5 min ( $p=0.01$ ).

#### 4.3. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers

Angiotensin converting enzyme inhibitors (ACEi) are also used in RP, but they have shown no improvement of symptoms [2,3,18]. Many of the pharmacological effects of ACEi are attributed to the inhibition of the synthesis of angiotensin II, however the angiotensin converting enzyme, being not selective, metabolizes a family of kynins into active products; bradycinin is one of the major kyninase that acts as a vasodilator through mechanisms related to the production of nitric oxide and prostacyclin (PGI<sub>2</sub>) by the vascular endothelium. Therefore, administration of ACEi prevents the degradation of bradycinin, which contributes to its therapeutic efficacy, this is important because it is the main cause of the side effects shown by ACEi: cough, which sometimes makes patients stop ACEi treatment [17]. Other symptoms are skin rash and fever. ACEi should be avoided in patients with bilateral or unilateral renal arterial disease, since they can produce renal failure or malignant paroxysmic hypertension. Angiotensin receptor blockers (ARBs) have shown a greater efficacy in reducing attacks in patients with systemic sclerosis and RP against ACEi [29]. Angiotensin II can easily bind with high affinity to two distinct receptors denominated angiotensin II receptor type 1 (AT1) and 2 (AT2), most of the physiological effects are mediated by AT1. The administration of an antagonist of AT1 localized in the vascular smooth muscle results in a diminished peripheral resistance by inhibiting the activation of phospholipase C and the generation of inositol triphosphatase and diacylglycerol kynase, with this, vasoconstriction is avoided. This allows vascular relaxation, at the same time, prolonged treatment with ARBs lowers the secretion of renin and increases the levels of angiotensin II, this increments the stimulation of AT2 receptors [29]. This is important because evidence shows



that activation of AT2 causes vasodilatation and other beneficial effects. The recommended dose of losartan is 25 to 100 mg QD, by mouth [1,17]. The most common side effects are headache, dizziness, fatigue and diarrhea.

Dziedzic et al. [30] in a randomized, parallel-group, controlled trial with 25 PRP and 27 SRP patients associated to systemic sclerosis, compared the efficacy of losartan (50 mg/day) with nifedipine (40 mg/day) confirming a more beneficial short term effect with losartan. There was an improvement of symptoms in the PRP group treated with losartan compared with the group treated with nifedipine ( $p < 0.05$ ) and the frequency of episodes was reduced only in the group treated with losartan ( $p < 0.01$ ).

#### 4.4. Phosphodiesterase inhibitors

A novel therapeutic option in RP is sildenafil which is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The physiologic mechanism involves release of NO from the endothelium that then activates the enzyme guanylate cyclase, which results in increased levels of cGMP, causing vasodilation. Phosphodiesterase type 5 is responsible for cGMP degradation. Sildenafil enhances the effect of NO by inhibiting PDE5 thereby raising concentrations of cGMP at the same time the NO/GMPc pathway resists vasoconstriction mediated by the autonomous nervous system [31]. Fries et al. [32] in a double-blind, placebo controlled, dose–response study in 16 patients with secondary RP that was resistant to therapy showed the efficacy of sildenafil. The recommended dose according to this study was between 50 and 100 mg/day. A dose of 50 mg BID reduced the frequency ( $35 \pm 14$  vs  $52 \pm 18$ ,  $p = 0.0064$ ) and the duration of RP's attacks ( $581 \pm 133$  vs  $1046 \pm 245$  min,  $p = 0.0038$ ) and the capillary blood flow speed in average more than quadrupled with sildenafil ( $0.53 \pm 0.09$  vs  $0.13 \pm 0.02$  mm/s,  $p = 0.0004$ ). Headache is the most common side effect, followed by nasal congestion and rhinitis.

#### 4.5. Nitric oxide

Vascular endothelium derived substances may be a possible target for the treatment of RP, by blocking the mediating vasoconstrictors and supplying it with vasodilators. In the body, nitric oxide is produced via synthesis from L-arginine by nitric oxide synthase (NOS) in various tissues. One of them is endothelial NOS (eNOS). Other substance as acetylcholine, bradykinin, and other agents that increase intracellular calcium levels stimulate the activity of eNOS [18]. In pathologic conditions, the endothelium can develop an altered phenotype favoring vasoconstriction, inflammation and thrombosis. According to the study developed by Tucker et al. [33] in 20 patients with RP with severe manifestations, could be secondary to a deteriorated synthesis, or a diminished sensitivity to NO. They then conducted an experiment with the use of a gel with chemical substances that generate NO and stimulates blood flow in RP patients. The results obtained showed that the use of the active gel causes a significant increase in the microcirculatory volume ( $p < 0.05$ ), which rapidly returned to its basal condition when the gel was withdrawn. The active gel also increased the microcirculatory blood flow ( $p < 0.01$ ) to close to the normal values of the control group.

#### 4.6. Prostaglandins

Prostaglandins are the most potent vasodilators that have been proven worthy in RP. Several studies have examined the efficacy of treatment of severe refractory RP and ischemic digital ulcers with preparations of prostaglandin E1 (PGE1), and iloprost (a PGI2 analogue) [17,18]. Prostacyclin (PGI2) exerts a potent vasodilatory action and an antiproliferative effect on smooth muscular cells, as well as inhibition of platelet aggregation. It also improves the malleability of the red cells and reduces the leucocitary adhesion to endothelial cells. Unfortunately, the oral preparations of the prostacycline analogs like iloprost, misoprostol, cicaprost and beraprost were not shown to be beneficial in the treatment of RP [10].

Iloprost is a stable chemical analog of prostacyclin; acting in a similar way by activating adenylate cyclase which increments the cAMP levels, with marked vasodilatory and platelet antiaggregating action [6]. Iloprost has been administered intravenously during RP crisis, reducing symptoms, as well as healing skin ulcers both in adults and children [34].

Intravenous administration of iloprost as a five day infusion during the first cycle, and posterior cycles of 24 h, with a dosage of 0.5 to 2.0 ng/kg/min improved the attacks and digital ischemic ulcerations in severe RP. It also improved the quality of life [1,6,35]. In a multicenter study by Wigley et al. [35] involving 131 patients with systemic sclerosis, the number of severe RP attacks during the week of the infusion, decreased by 39.1% with iloprost and 22% with placebo ( $p = 0.005$ ); while 14.6% of the patients that received iloprost had a 50% increase in cicatrization compared with the placebo group (95% CI, 0.9% to 30%). Furthermore, according to the RP severity score, those who received iloprost (34.8%) had a greater decrease in the severity of RP in weeks 3, 6 and 9 than those who received placebo (19.7%) ( $p = 0.011$ ).

In practice, in RP patients with severe manifestations (ulcers or digital gangrene), secondary to systemic sclerosis or another connective tissue alteration, iloprost can be used intravenously in short term courses, under constant observation and vigilance of side effects such as diarrhea, headache, skin rash, and hypotension [1,10,35]. Data obtained in a comparative study between iloprost and aprostadil [18] showed the beneficial effects of both were similar, with 45% vs 90% of clinical improvement in patients with RP, respectively. Nonetheless, the simplicity of use and low cost of alprostadil favors its widespread use. Common side effects of this group of drugs are headache, nausea, vomiting, blushing, diarrhea, and ischemia [1]. In some clinical trials no difference in efficacy had been found, when IV iloprost and nifedipine (sustained release presentation) had been compared, although, adverse effects were more common with nifedipine. Iloprost used in long periods (12 months) acts as a disease modifier, compared to nifedipine (iloprost vs nifedipine:  $p = 0.016$ ). In patients in whom the response to the iloprost infusion IV is not the predictable, is practical to use phosphodiesterase inhibitors starting 50 mg TID by mouth [18]. Preparations of oral prostaglandins and analogues are available, like cicaprost, a synthetic prostacyclin analog that reduced the severity of RP. The exact role of oral prostaglandins in the management of severe RP need additional experience and controlled studies to be recommended.

#### 4.7. Antithrombotic drugs

Anticoagulation and thrombolytic therapy can be considered during the acute phase of an ischemic event when embolic or thrombotic complications are suspected. Multiple antithrombotic agents have been utilized in patients with RP in whom ulceration and thrombosis have occurred. These include aspirin, dipyridamole, systemic anticoagulation, and thrombolytic therapy. Aspirin (100 mg/day) therapy can be considered in all patients with secondary RP with a history of ischemic ulcers or thrombotic events, however, caution should be exercised as aspirin can theoretically worsen vasospasm via inhibition of prostacyclin [1,7,10]. It is totally accepted that platelets play a role in the pathogenesis of RP. Activated platelets are the source of various vasoconstrictor agents like serotonin and TxA2. In systemic sclerosis, micro clots are formed and cause vascular obstruction, this can be linked to the pathogenesis of SRP [6]. The use of antithrombotic drugs is common in the treatment of RP, especially in SRP, being both ischemia and thrombosis in fingers especially intense. Some studies evaluated the efficacy of aspirin and dipyridamol, but both were non conclusive. Occasionally, it has been observed a complete healing of digital ulcers after the use of a tissue plasminogen activator followed by long-term anticoagulation therapy. The use of low molecular weight heparin to treat refractory RP had showed improvement of symptoms, but without objective structural changes. However, anticoagulation should not be used as a routine for the treatment of RP; it is usually regarded as a second choice of treatment.

#### 4.8. Selective serotonin reuptake inhibitor

Serotonin is a potent vasoconstrictor released by platelets; in spite of this, its role in the pathogenesis of RP is not well documented [18,36]. Conversely, several reports have shown the efficacy of selective serotonin reuptake inhibitor drugs have over the treatment of RP. One of the studies showed that fluoxetine has a beneficial effect in the treatment of SRP using a dosage of 20–40 mg daily. Possible side effects are lethargy, insomnia, nausea, diarrhea and tremors [1,10,17].

#### 4.9. Endothelin receptor antagonists

New studies have shown that endothelins play a major role in the pathogenesis of vascular disease and systemic sclerosis, as well as RP [18,33]. Several drugs have been used for treatment, including bosentan which is an endothelin receptor antagonist. Two types of endothelin receptors have been identified on vascular smooth muscle cells: A and B; only type B receptors have been found on endothelial cells. Stimulation of type A endothelin receptors mediates vasoconstriction while type B receptors mediate both vasoconstriction and vasodilation. Bosentan is a specific and competitive antagonist to both types A and B endothelin receptors, although has a slightly higher affinity for type A receptors than for type B receptors; as a result it is able to prevent the development of ulcers and to improve digital ulcers and hand functionality [36]. Recently, Garcia de la Pena-Lefebvre et al. [37] in a prospective, observational, non-controlled study evaluated the efficacy and tolerability of bosentan in patients with systemic sclerosis who developed digital ulcers and concluded that bosentan may be a safe long-term alternative for the treatment of skin ulcers in systemic sclerosis.

### 5. Sympathectomy

Surgical treatment is reserved for patients with severe and complicated RP, in which pharmacological treatment was not successful [1,10]. The recommended surgical treatment consists of open decompression with resection of fibrotic layering along with digital sympathectomy, which is helpful in some patients who are unresponsive to medical therapy and patients with secondary RP with critical ischemia or active digital ulcers are likely to have some immediate improvement in blood flow following sympathectomy, but the degree and duration of improvement is variable [38]. As well, temporary chemical sympathectomy can be achieved by infiltration of local and regional anesthetic (lidocaine or bupivacaine), or near the appropriate cervical or lumbar sympathetic ganglia. Surgical sympathectomy may be proximal or distal. Cervical sympathectomy is associated with some risks like temporary or permanent Horner's syndrome, persistent neuralgia, and decreased localized cutaneous sweating, but an endoscopic approach may be safer [1,10,18].

Electric stimulation of the bone marrow alongside therapy with low dosage laser [18,39] is also indicated when pharmacological treatment is not responding or patients in whom their clinical evolution gears towards worsening symptoms or frequent attacks presenting with severe complications like atrophic process and ulcers.

### 6. Vascular reconstruction

On the other hand, in patients with systemic sclerosis, vascular occlusion most commonly occurs in the ulnar artery and the digital arteries; so revascularization of ulnar artery occlusive disease in this setting may improve RP and improve healing of digital ulcers [40].

#### Take home-messages

- Avoid cold exposure. Use warm gloves, hats, and garments during the winter months or before going into cold environments.
- Calcium channel blockers are the most effective treatment for Raynaud's phenomenon.
- Patients who do not tolerate or fail to respond to calcium channel blocker therapy can try other vasodilator drugs alone or in combination.
- Chemical or surgical sympathectomy has been reported to be effective in relief of symptoms for very severe, refractory cases, however, results of this therapy may be short-lived.

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### Predictors of stroke in rheumatoid arthritis

Previous studies have demonstrated a high frequency of stroke in patients with rheumatoid arthritis, however no one of them has assessed the risk factors for the development of cerebrovascular complication. To analyze and to identify these risk factors, Nadareishvili *et al.* (*Arthritis Rheum Car Res* 2008;59:1090–6) have performed a nested, case-control study with a large number of rheumatoid arthritis patients and controls without this disease. The authors found a high odds ratio (1.64) for the risk of all-category strokes in rheumatoid arthritis and also for ischemic strokes (2.66). Predictors for ischemic stroke were hypertension, myocardial infarction, low dose aspirin, co morbidity score, Health Assessment Questionnaire score, and total joint replacement. However, others traditional risk factors such as smoking, diabetes, exercise or body mass index were not associated with stroke. In addition, anti-TNF therapy and rofecoxib use were not predictors for strokes. This study has confirmed that patients with rheumatoid arthritis have an increased risk for stroke. This complication is predicted by rheumatic disease severity, some cardiovascular risk factors, and comorbidity.