Raynaud’s Phenomenon: Etiology and Management

Beatriz E. Joven and Patricia E. Carreira
Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Spain

Introduction
In 1862 Maurice Raynaud described a group of patients who presented transitory ischemic attacks, localized in the distal parts of the body, regularly caused by cold or stress. Since then the term “Raynaud’s phenomenon” (RP) has been used to define these vasospastic episodes, which are manifested through cyanosis or blanching of the fingers of the hands and feet, followed by hyperemia due to reperfusion. Raynaud’s phenomenon is frequently accompanied by paresthesias, dysesthesias and depending on the severity of the case, can lead to ulcers and even necrosis.1

Epidemiology
RP has a universal distribution and approximately affects 3%–5% of the population,2 although with geographical variations which can be explained by differences in climate.3 It affects women more frequently than men,4 and can appear in 20%–30% of young women.5 Although genetic factors can probably be implicated in the development of RP, these have not been adequately studied. In this sense, a familiar association with the appearance of RP, and a greater concordance between homozygous twins (38%) compared to heterozygous twins (18%)6 has been observed. The risk factors for developing RP have not been clearly defined. For example, in the Framingham cohort, the appearance of RP in women is related to alcohol consumption and the marital status, and in men, with advanced age and tobacco consumption.6 However, other studies have not shown any relationship between the appearance of RP and the consumption of tobacco or alcohol.7

Classification
RP is classified as primary (Raynaud’s disease) when it is present by itself and not associated to an underlying disease, or secondary (Raynaud’s syndrome) when it is manifestation of another disease. It is frequently associated to rheumatic diseases and appears in more than 90% of the patients with systemic sclerosis (SSc). In addition, it can appear in patients with systemic lupus erythematosus (10%–45%), Sjogren’s syndrome (30%), dermatomyositis or polymyositis (20%), and rheumatoid arthritis (20%).9 However, most of the cases of RP who come to the clinic for this motive are primary. The risk of developing an autoimmune disease associated to RP is between 6% and 12%, and the diagnosis is usually done in the 2 years after its onset.10,11 There is a series of characteristics that can orient the clinician both to the diagnosis as well as to the conduct that must be followed when approaching a patient with RP: age at onset, the severity of symptoms, the presence of autoantibodies, and the capillaroscopy pattern (Table).

Physiopathology
Although Maurice Raynaud considered PR as the result of a hyperactive sympathetic nervous system (SNS), ever since Lewis12 observed that RP persisted after the interruption of the SNS activity, it is thought that the

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Correspondence: Dra. B.E. Joven. Servicio de Reumatología, Hospital 12 de Octubre. Avda. de Córdoba, s/n. 28045 Madrid, España. E-mail: beatrizjoven@hotmail.com

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Factors Independent to Endothelium

Cold or stress leads to an activation of the SNS that acts on $\alpha_2$-adrenergic receptors, causing vasoconstriction. The activity of these $\alpha_2$-adrenergic receptors is increased in patients with RP, without any need for an endothelial dysfunction.\textsuperscript{13} It is believed that this is the main mechanism in primary RP.\textsuperscript{14}

Endothelium Dependent Factors

The endothelium participates in the regulation of the vascular tone through vasodilating mediators (prostacyclin, nitric oxide) or vasoconstriction (endothelin 1). In addition, the endothelium liberates neurotransmitters such as acetylcholine, calcitonin-gene related peptide (CGRP) or substance P, with a vasodilating action.\textsuperscript{15} An endothelial disfunction caused by episodes of ischemia-reperfusion or direct or indirect immune damage\textsuperscript{16,17} can result in an overproduction of endothelin 1 and a reduction in vasodilating agents.\textsuperscript{18-20} This mechanism is probably no the initial defect of RP associated to SSc, but endothelial damage favors a series of processes, which determine a structural vascular lesion in SSc. In fact, endothelial damage is capable of activating vascular smooth cells, migrating to the intima, and differentiating into myofibroblasts. The myofibroblasts secrete an increased amount of collagen and extracellular matrix,\textsuperscript{19,20} producing intima proliferation and then the fibrosis of the digital arteries in patients with SSc.\textsuperscript{21} Also, the endothelial damage favors the production of proangiogenic mediators (VEGF),\textsuperscript{22,23} which is added to the reduction in angiogenesis inhibiting agents (TSP-1),\textsuperscript{24} which finally contributes to the distorted capillary architecture of SSc. On the other hand, the endothelial damage increases platelet adhesion, which originates the production of vasoconstrictors such as serotonin and thromboxane A2, and activates the coagulation process, hand in hand with a reduction in fibrinolysis, favoring the formation of microthrombi, which can also be observed in sclerodermatous vessels.\textsuperscript{14}

Clinical Findings

RP is generally produced in 2 phases. The first phase is ischemic and produced by a reduction or occlusion of the capillary flow, manifesting as cyanosis or pallor respectively. This reduction in flow is secondary to an excessive vasoconstriction of the afferent digital arterioles. In many occasions, the reduction in flow is milder at the beginning of the episode, leading to cyanosis, and turns more intense later, reaching complete vascular obstruction, producing the subsequent pallor. The ischemic zone of the fingers is usually well limited and initially appears only in 1 or 2 fingers. Ischemia can extend in a symmetric manner to all of the fingers and sometimes to other distal areas. Clinical findings can be milder in cases of primary RP, in which there is no structural alteration of the vessels, and is generally more important in RP associated to SSc that, in addition to functional vasoconstriction, there are obstructive lesions of the arterioles, such as intimal proliferation or media hypertrophy. The ischemic episodes can be painless, but in more severe cases can present with intense acute pain, especially when there is a complete occlusion of the blood flow. It is in these situations in which there is a more frequent formation of ulcers and necrosis.\textsuperscript{15} The second phase of RP is reperfusion, manifesting itself when arteriolar vasoconstriction disappears. It is clinically characterized by erythema secondary to reactive hyperemia. It can be accompanied by paresthesias and dysesthesias of the fingers and toes. They tend to be generally mild, although they can be more intense and produce a certain functional limitation.

Diagnosis

In order to diagnose RP it is enough to carry out an adequate interrogation and examination of the patient, with a positive response to 3 questions:\textsuperscript{1}

- Are your fingers especially sensitive to cold?
- Do they change color when they are exposed to cold?
- Do they turn pale or blue?

No stimulation tests or complicated techniques are necessary for its diagnosis. However, new diagnostic and evaluation tools are continuously being developed, which allow for greater objectivity in the approach to the patient with RP, such as thermography, plethysmography, digital arterial pressure, laser Doppler flow measurements, etc. These are generally of little use in the daily practice due to their technical complexity, variability, and poor reproducibility. Because of this, the evaluation of RP still relies on the clinical signs regarding the number and duration of the attacks, their intensity, which can be measured with a
visual analog scale, and the quantification of the ulcers and zones of digital necrosis. In clinical trials, the evaluation of limitation can be performed through the HAQ, and the global functional evaluation analyzed through the usual means (AIMS2, SF-36). Once the RP has been diagnosed, it is important to carry out a full history and examination, with the objective of determining the presence or not of manifestations of systemic disease. In order to complete the study of the patient, it is important to perform a capillaroscopy and an antibody determination. If both tests, along with the clinical history and examination, are negative, the most probable cause is a primary RP. If, on the contrary, capillaroscopy is pathologic and/or antibodies are positive, it is very likely that the patient has a systemic disease and must undergo an adequate study and follow-up protocol, even if other clinical signs are absent.

**Treatment**

There is no established and universally accepted management protocol for the treatment of Raynaud’s. Although numerous studies regarding this have been done, most of them do not have an adequate level of evidence on the efficacy of the treatments attempted. This is due to the fact that most of the trials have been carried out in a reduced number of cases and they include patients with both primary and secondary RP, who generally have very different progression and prognosis. Also, many of the trials do not consider the placebo effect that, upon result analysis, can reach 20%-40%. General Measures

In many patients with mild or moderate symptoms, general measures can be sufficient and no pharmacologic treatment is necessary. The main aspect is not only avoiding cold in the affected zones, but also maintaining an adequate body temperature with adequate clothing, gloves, boots, etc. In patients in whom RP has an emotional trigger, relaxation techniques can help to manage stressful situations. However, a multicentric study in which double blinded treatment with nifedipine and biofeedback techniques was administered, did not show any benefit from the latter one, but did show it arising from nifedipine, which resulted both efficacious and safe. On the other hand, it is essential to avoid the use of substances or drugs that can produce vasoconstriction, such as beta-blockers, interferon, serotonin agonists (sumatriptan), alkaloids, cocaine, caffeine, or nicotine. Although there has not been any clear demonstrations of RP association with tobacco, there has been an increased incidence of complications in smokers. The use of estrogen is controversial because hormone replacement therapy has been associated to RP. However, estrogens have also been seen to mediate endothelium dependent vasodilation in patients with SSc, which could lead to a beneficial effect.

**Vasodilators**

*Calcium antagonists.* Currently they are considered the treatment of first choice. They act as vasodilators, inhibiting the entry of calcium into smooth muscle on the valves and cardiac muscle cells. According to the binding site, there are 4 different calcium antagonists, but the dihydropyridines, which have a larger selectivity for vascular smooth muscle cells and a lesser inotropic and chronotropic effect, are the most adequate for the treatment of patients with RP. These however, have important side effects such as edema (24%), headaches (17%), flushing (8%), and dizziness (7%), which are the consequence of excessive vasodilation, producing also reflex tachycardia (3%), secondary to the lack of a chronotropic and inotropic effect. The efficacy of calcium antagonists has been demonstrated in different studies. A meta-analysis reviewing 8 trials with calcium antagonists for the treatment of RP, with a total of 109 patients with SSc demonstrated a significant reduction in the number of attacks (mean reduction of 8.3) and intensity (35%) after 2 weeks of treatment. In a comparative study between iloprost and nifedipine, the latter also proved effectiveness in reducing the number of digital ulcers. Another recent metaanalysis that included 17 double blind trials between calcium antagonists and placebo, including a total of 348 patients with RP (125 with SSc), showed similar results, although patients with SSc had a worse response. Nifedipine is the best studied calcium antagonist and is generally employed at a dose of 10-30 mg 3 times a day, but studies done with other dihydropyridines (amlodipine, felodipine, isradipine) seem to point to the usefulness of the latter 2. Among these, amlodipine, a dihydropiridine with a long half-life, taken at doses between 5 and 20 mg once a day, present a very attractive tolerance profile for its clinical use. The use of nicardipine is more controversial, or the use of other, non-dihydropyridines such as diltiazem and verapamil, showing irregular results in the published studies.

*Prostaglandins.* They are widely employed as a second line of treatment for RP, mainly in severe cases that do not respond to standard vasodilator treatment with calcium antagonists. Its mechanism of action is not completely clear: they are potent vasodilators, platelet anti-aggregants, and they also have a less known immunomodulating and cytoprotective effect which is
prolonged beyond the moment of its administration. Since the beginning of the 1980’s, different prostaglandins have been studied as therapy for RP. In an open study, performed on selected patients, prostaglandin E1 (alprostadil) reduced the number and intensity of RP attacks and improved healing of digital ulcers. Although this data was not confirmed in a multicentric, placebo controlled trial, done on 50 patients with RP, later open studies, performed on small numbers of patients with RP seem to demonstrate that alprostadil has an efficacy similar to other prostaclysins, at a lesser cost. Prostacyclin I2 (epoprostenol) has also demonstrated its efficacy in reducing the frequency and intensity of attacks of RP in different studies. But the most frequently used prostacyclin is iloprost, a stable analog of prostacyclin PGII2, the use of which is the most cited in the literature. One multicentric, placebo controlled, double blind trial stands out, having included 131 patients with SSc associated RP, and demonstrating a significant reduction in the frequency and intensity of attacks, as well as a significant increase in the healing of ischemic ulcers. A metaanalysis of 7 trials, 5 with intravenous (iv) iloprost and 2 with orally administered prostacyclin, which included a total of 337 patients (220 with iv iloprost), demonstrates the efficacy of iv iloprost both in reducing the frequency and intensity of RP as in healing ulcers. On the contrary, none of the orally administered prostacyclins, iloprost, and cicaprost, show a statistically significant benefit. Later studies with oral iloprost, performed in a larger number of patients, have failed to demonstrate their efficacy and other oral prostanoids such as misoprostol or beraprost, have not shown a clear vasodilator effect. The secondary effects of prostacyclins are very frequent, but in general are mild and well tolerated by the patients. In addition, in the case of iv prostacyclins, the side effects are limited to the period of infusion and disappear shortly after. The most frequent ones are headache, facial flushing, jaw pain, nausea, vomiting, diarrhea, and hypotension. All of them are dependent on vasodilation and are dose-dependently related to the infusion of the prostanooids. In order to minimize these adverse events, a very slow and progressive increase of the rate on infusion must be performed, personalized in each case, until an optimal dose is achieved with which the vasodilating effect is sufficient, without it being uncomfortable for the patient. The most accepted current form of iloprost administration is intermittently every 3 to 5 days, every 4-6 weeks during the winter months, because clinical trials with this drug have demonstrated a certain advantage vs. nifedipine regarding the number and intensity of attacks.

Angiostein converting enzyme inhibitors. They are potent vasodilators and act on the vascular endothelium. Since their appearance in the 1970’s they have changed the course of the sceroderma-related renal crisis and it is currently thought that they could prevent vascular damage in SSc. However, the experience with these drugs in the treatment of RP is scarce and only 1 study has shown tendency toward improvement and another has proven an increased digital flow. A double blind trial lasting 12 weeks which compared parallel losartan (50 mg/day) with nifedipine (40 mg/day), showed a significant reduction in the frequency and intensity of attacks with primary RP patients receiving losartan, which was less important in those with SSc. Currently, they are not commonly employed as a first choice in the treatment of SSc associated RP.

Alpha-adrenergic inhibitors. The effect of prazosin, an α1-adrenergic blocker, has been analyzed in 2 trials, in which a modest improvement was seen, but with a high incidence of adverse events, making it of little use in the daily practice. A recent double blind, placebo controlled trial carried out in 13 patients with SSc associated RP has shown the benefit of α2-adrenergic selective block, leading to a more prompt reperfusion after exposure to cold in patients who received it, contributing to a reduced appearance of ischemic lesions.

Nitric oxide (NO) is a potent vasodilator implicated in the pathogenesis of RP, indicating that treatment with NO donors could result effective in these patients. For this motive, topic nitroglycerine has been employed for years in the treatment of SSc associated RP, but with little evidence to back it.

L-arginine supplements. L-arginine, the endothelial substrate of NO has not shown efficacy in the treatment of RP when administered orally. However, the results obtained in isolated patients have indicated that the administration of L-arginine and intraarterial nitroprusside could be useful in the acute management of ischemic lesions secondary to RP.

5 phosfodiesterase inhibitors. 5 phosfodiesterases produce vasoconstriction by inhibiting c-AMP and c-GMP, vasodilation mediators produced by prostacyclin and NO respectively. Their inhibitors are, therefore, potent vasodilators both in the lungs as systemically. Although their primary use is for erectile dysfunction, a randomized, double blind, placebo controlled clinical trial carried out in 22 patients with pulmonary hypertension demonstrated that sildenafl is effective in the treatment of this disease. A later study, carried out in 278 patients of whom 84 had an associated rheumatic disease, demonstrated its efficacy in these patients pulmonary hypertension. Although not specifically designed to evaluate their effect on RP, both sildenafl and taladafilo seem to improve it and have successfully been employed in open studies with a small number of patients. This data has been confirmed in
the only double blind, placebo controlled, cross-referenced trial designed to evaluate the efficacy of sildenafil in RP and ischemic ulcers.\textsuperscript{73}

Endothelin inhibitors. Endothelin (ET) is another potent vasoconstrictor very implicated in the pathogenesis of SSc.\textsuperscript{80} Bosentan, a ETA and ETB receptor antagonist, used in patients with pulmonary hypertension, could also be useful in the treatment of RP to prevent the appearance of new lesions,\textsuperscript{81} as was demonstrated in a multicentric, double blind, placebo controlled trial performed in 122 patients with SSc associated RP.\textsuperscript{82} Other ETA receptor selective inhibitors, such as sitaxsentan or ambrisentan, are currently being studied to evaluate their efficacy in pulmonary hypertension and could be potentially effective in the treatment of RP, although evidence is still lacking.

Serotonin inhibitors. Serotonin is a potent vasoconstrictor, making a serotonin inhibitor potentially useful for the treatment of RP. A randomized, open study performed on 53 patients with primary and secondary RP, treated with fluoxetine versus nifedipine found a statistically significant benefit in patients treated with fluoxetine, both in the reduction of the number of attacks as in their intensity.\textsuperscript{83} However, a metaanalysis on the use of ketanserin, another serotonin receptor antagonist, failed to find a clinical benefit with its use for RP.\textsuperscript{84}

Calcitonin gene related peptide (CGRP). It is a vasodilating peptide whose concentration seems to be reduced in patients with RP. Its use is not extensive and its efficacy doubtful, with little evidence for its use.\textsuperscript{85}

Antiaggregation/Anticoagulant Treatment

Based on alterations observed in fibrinolysis and platelet activation, different antiaggregant therapies (aspirin and dipyridamole) have been used with contradictory results.\textsuperscript{86,87} but anticoagulants (such as fractioned heparin) are associated with some improvement.\textsuperscript{88} Although there are no current formal recommendations for their use, the use of low dose aspirin is extensive. More studies are needed in order to recommend long-term anticoagulation in these patients.

Treatments such as pentoxyphiline, used for venous insufficiency, have benefited selected patients.\textsuperscript{89} Cilostazole, an inhibitor of phosphodiesterase III, led to brachial artery vasodilation, but did not influence RP symptoms.\textsuperscript{90}

Antioxidant Therapy

Every day more studies support the fact that oxidative stress is implicated in the pathogenesis of RP,\textsuperscript{91,92} leading to the use of different antioxidant treatments with differing results. In an analysis comparing the antioxidant probucol with nifedipine, both reduced the frequency and intensity of the attacks,\textsuperscript{93} but a later double blind study which combined a series of antioxidant micronutrients (selenium, carotenes, vitamins C and E, and methionine), found no beneficial effect.\textsuperscript{94} and another performed with ascorbic acid did not find any effect on the endothelium either.\textsuperscript{95} It is speculated that these treatments could be of more use in early stages of disease but, once again, even if the evidence is not in their favor, the possible benefits and scarce side effects could lead to many clinicians recommending some form of antioxidant therapy empirically.

Surgery

Sympathectomy is indicated in patients with severe, refractory RP. It is a surgical technique with its own risks, in spite of being approachable through thoracoscopy.\textsuperscript{96} The main inconvenient is that its long-term effectiveness leaves something to be desired.\textsuperscript{97} In the past few years, there has been an increased interest in digital sympathectomy,\textsuperscript{98} less aggressive and with better published results in selected patients.\textsuperscript{99}

Treatment of Acute Digital Ischemia

It should be considered as a medical emergency and merits hospitalization. General measures such as rest, an adequate room temperature and pain control, even with local anesthetic infiltration, is justified. In addition it is important to avoid superinfection through antiseptic occlusive bandages and consider general antibiotics with surgical debridement when necessary. Vasodilating therapy generally is performed with iv prostacyclin (iloprost 0.5-2 ng/kg/min for 1-3 days). Although, as commented above, this is not entirely clear, some patients might benefit with sodium heparin or fractioned heparin anticoagulation for 24-72 h. Finally, if these measures are not useful, surgical proximal or digital sympathectomy can be employed according to each case.\textsuperscript{95}

In summary, the management of RP merits an adequate evaluation to rule out an underlying connective tissue disease and whose treatment might improve the symptoms. General measures such as avoiding cold temperature must be used in every case. Vasodilator treatment must be evaluated in cases that do not improve with these measures. The most commonly used vasodilators are calcium antagonists, especially nifedipine in a delayed-liberation presentation at a dose of 30-60 mg/day or amlodipine at a dose of 5-10 mg/day. These doses can be increased according to the patients' necessities and tolerance. Severe, refractory cases can undergo
intermittent treatment every 4–8 weeks with iv prostacyclins (iloprost 0.5–2 ng/kg/min for 3–5 days). Although evidence is lacking, antiaggregation therapy with low-dose aspirin is usually recommended.

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