Review
Raynaud’s phenomenon
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Abstract
Vascular acrosyndromes constitute a common reason for physician visits. They are associated with connective tissue disease; for example, 90% of patients with scleroderma experience Raynaud’s phenomenon. The rheumatologist must strive to establish the diagnosis, to identify a potential underlying cause, and to prescribe effective treatment when the symptoms are incapacitating. Raynaud’s phenomenon is the acrosyndrome most commonly encountered by rheumatologists. The diagnosis of Raynaud’s phenomenon rests on clinical grounds. Nailfold capillaroscopy and immunological tests are useful chiefly for determining the cause. Calcium-channel antagonists are the treatment of reference for Raynaud’s phenomenon. Drugs introduced over the last few years for severe refractory forms include prostacyclin and its derivatives, endothelin receptor antagonists, and phosphodiesterase inhibitors. These drugs were developed as a result of new knowledge on the pathogenesis of Raynaud’s phenomenon. Acrocyanosis, which is extremely common, and erythromelalgia are the other main vascular acrosyndromes.

Keywords: Raynaud’s phenomenon; Scleroderma; Calcium-channel antagonists

1. Definition
In 1862, Maurice Raynaud described a paroxysmal phenomenon that included three phases: ischemia, with pallor of the digits due to vasoconstriction of the digital arteries, precapillary arteries, and cutaneous arteriovenous shunts; hyperemia with redness of the digits; and a return to normal (Fig. 1). Whereas the ischemic phase is required for the diagnosis, the hyperemic phase may be lacking. The abnormalities usually spare the thumb but involve most of the other digits, although they may start in a limited number of digits. The nose, ears, and tongue may be affected. The attack resolves within an hour after the end of cold exposure [2,3]. Raynaud’s phenomenon is associated with migraine and chest pain (usually from the chest wall, an association with spastic angina being controversial) [4].

2. Epidemiology
Raynaud’s phenomenon may be primary or secondary. It may occur as the first manifestation of an underlying disease, most notably scleroderma [1–3]. A 7-year study conducted in Caucasians in the United States showed baseline prevalences of 11% in women and 8% in men and incidences of 2.2% in women and 1.5% of men [5]. The rate of remission during the study period was 64% in both women and men [5]. Variations in prevalence occur across climates [6]. In a study of teenagers, the prevalence was 15% with a predominance in females [7]. The attacks occur when the ambient temperature drops below a cutoff, which is specific of each individual patient. The cutoff temperature may be relatively high, with attacks occurring even during the summer months.

3. Pathogenesis
New insights into the pathogenesis of Raynaud’s phenomenon have led to the development of specific treatment approaches [8] (Fig. 2). Primary Raynaud’s phenomenon is related to functional alterations alone. Secondary Raynaud’s phenomenon, in contrast, also reflects structural microvascular abnormalities, most notably in patients with scleroderma or vibration injury [8,9].

Factors that promote vasoconstriction include z2-adrenoceptor overactivity, increased endothelin-1 production [10]...
and tyrosine kinase overactivity in endothelial cells [11,12]. Furthermore, there is probably a role for angiotensin II and serotonin. The endothelium releases vasodilating substances such as nitric oxide (NO) and prostacyclin. L-arginine, which increases NO production, has been reported to improve Raynaud’s phenomenon [13]. Loss of nerve fibers supplying the capillaries leads to decreased production of vasodilating substances such as neuropeptides (calcitonin gene-related peptide, substance P, neuropeptide Y, and vasointestinal peptide) whose effects are mediated by NO production. The role for intravascular alterations is less clear.

4. Identifying the cause

Primary Raynaud’s phenomenon, also called Raynaud’s disease, is defined as Raynaud’s phenomenon with no identifiable underlying disease. A family history supports a diagnosis of Raynaud’s disease, particularly in younger individuals [14]. Among women with Raynaud’s phenomenon, 85% have the primary form and 15% the secondary form, whereas the distribution is balanced in men. Table 1 lists the diagnostic criteria for primary Raynaud’s phenomenon.

The causes of secondary Raynaud’s phenomenon are listed in Table 2. In a study of 639 patients, 12.6% developed symptoms of an associated disease within 24 months [15]. Of 142 patients followed up for 12.4 years on average, 14.1% experienced progression to connective tissue disease [14]. Capillaroscopy, tests for antinuclear factor, and tests for inflammation should be performed routinely in patients with Raynaud’s phenomenon [9]. Capillaroscopy is crucial [16,17]. It consists in examination of the nailfold capillaries under a light microscope (×10 to ×300 magnification) with cold light illumination. Capillaroscopy is difficult to perform in patients who have pigmented thick skin (manual laborers). Nailfold capillaries are normally horizontal. Capillary enlargement, which is the most specific finding, occurs in three connective tissue diseases: scleroderma, mixed connective tissue disease, and dermatomyositis (Figs. 3, 4). The enlarged intravascular mechanisms are listed in Table 2.
capillaries may be visible to the naked eye (Fig. 5). Digital ulcers may develop, making the diagnosis obvious to inspection (Figs. 6, 7). Joint lesions are common in patients who have digital ulcers.

Table 2

<table>
<thead>
<tr>
<th>Causes of secondary Raynaud’s phenomenon</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>CONNECTIVE TISSUE DISEASE</td>
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<tr>
<td>Systemic sclerosis</td>
<td>90–95%</td>
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<td>CREST syndrome</td>
<td>100%</td>
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<td>Mixed connective tissue disease</td>
<td>70–85%</td>
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<td>SLE</td>
<td>10–30%</td>
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<td>Sjögren’s syndrome</td>
<td>5–15%</td>
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<td>Dermatomyositis</td>
<td>15–35%</td>
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<td>DRUGS AND TOXIC AGENTS</td>
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<td>β-Blockers (including those in ocular solutions)</td>
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<td>Ergot derivatives</td>
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<td>Cancer chemotherapy</td>
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<td>Cyclosporine</td>
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<td>Interferons α and β</td>
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<td>Exposure to vinyl polychloride</td>
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<td>Cocaine</td>
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<td>Smoking (probable)</td>
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<td>ENDOCRINE DISORDERS</td>
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<td>Hypothyroidism</td>
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<td>Pheochromocytoma</td>
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<td>Carcinoid syndrome</td>
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<td>TRAUMA (unilateral Raynaud’s)</td>
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<td>Vibration injury</td>
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<td>Ulnar aneurysm (hypothenar hammer syndrome)</td>
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<td>Repetitive stress injury</td>
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<tr>
<td>(thoracic outlet syndrome)</td>
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<tr>
<td>ARTERIAL DISEASE (often unilateral)</td>
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<td>Thromboangiitis obliterans</td>
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<td>Atheroma</td>
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<td>Peripheral embolism</td>
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<td>Vascularites (giant-cell arteritis, Takayasu)</td>
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<td>HEMATOLOGICAL DISORDERS AND CANCER</td>
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<td>Cryoglobulinemia</td>
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<td>Cold agglutinin disease</td>
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<tr>
<td>Myeloproliferative and lymphoproliferative disorders</td>
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<td>Cancers</td>
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Unilateral Raynaud’s phenomenon suggests an arterial lesion or an occupational injury [3,18,19]. Vibration injury occurs in workers who use jackhammers, chisels, rivet presses, drills, compacters, chain saws, buffers, or sanders. Longer exposure times and vibration frequencies in the 25–250 Hz range are associated with an increased risk of vibration injury [19]. Hypothenar hammer syndrome is related to dysplasia of the ulnar artery anterior to the superficial palmar arch. An aneurysm develops then undergoes thrombosis, and emboli are released. Construction workers, carpenters, metal workers, and mechanics are at highest risk. Hypothenar hammer syndrome has been reported in association with several sports (e.g., karate, mountain biking, hockey, and golf). Vascular Doppler ultrasound and angiography establish the diagnosis [18] (Fig. 8). Workers with hypothenar hammer syndrome are eligible for compensation (in France, Table 69 for salaried workers and number 29 for farmers). Thoracic outlet syndrome, which manifests chiefly as neurological symptoms, is associated with Raynaud’s phenomenon in 45% of cases. The link between vessel and nerve compression in the thoracic outlet and Raynaud’s phenomenon is unclear. When the diagnosis is suspected, a radiograph of the cervical spine and clavicles should be obtained to look for a cervical rib or elongated
transverse process [20]. Arterial lesions due to mechanical factors or inflammatory disease (vasculitis or thromboangiitis obliterans (Fig. 9) manifest chiefly as symptoms of digital ischemia. Fig. 10 summarizes the diagnostic process.

5. Treatment

Pharmacotherapy is usually unnecessary in patients with primary Raynaud’s phenomenon [21].

5.1. Functional factors

Exposure to cold should be avoided. Warm loose clothing with thermal gloves and socks is often sufficient. Appropriate clothing can often be found in mountain sports stores. Hand warmers are useful. Patients should not use medications or other substances that induce vasoconstriction, such as ergot derivatives, β-blockers, caffeine, and nasal vasoconstrictors [2,3,21]. Smoking cessation is essential in patients with thromboangiitis obliterans.

5.2. Medications (Fig. 2)

5.2.1. Calcium-channel antagonists

Calcium-channel antagonists are the most widely used medications in patients with Raynaud’s phenomenon [2,3,21].
In addition to relieving vascular spasm, they decrease superoxide anion production by monocytes and limit the progression of endothelial lesions in patients with scleroderma [22,23]. A meta-analysis of 17 studies showed that calcium-channel antagonist therapy was associated with a 33% reduction in attack severity and with a reduction in the number of attacks from 5 to 2.8/week [24]. In 130 patients given nifedipine 30 mg b.i.d. for 1 year, the number of attacks decreased by 66%, and 15% of patients experienced adverse effects requiring discontinuation of the drug [25]. Similar results were obtained in patients who had Raynaud’s phenomenon associated with scleroderma [26]. Amlodipine is as effective as nifedipine, diltiazem is less effective, and verapamil has no effect [27]. Delayed-release once-daily formulations have been suggested based on their better safety profile. The dosage should be increased gradually until a response is achieved. Raynaud’s phenomenon often requires a higher dosage than hypertension (up to 60 mg of nifedipine or 20 mg of amlodipine).

5.2.2. Nitrate derivatives

Evidence that nitrate derivatives administered transcutaneously may improve Raynaud’s phenomenon comes from only a small number of studies [3,28]. The gel is no longer marketed in France. A preparation containing 2 g of nitroglycerine per 100 g of vaseline and lanolin ointment with 18 g of lactose monohydrate can be used.
5.2.3. \( \alpha \)-Adrenoceptor antagonists

Prazosine, which inhibits the \( \alpha_1 \)-adrenoceptors, has been proved effective [3]. A selective inhibitor of the \( \alpha_2 \)-adrenoceptors, which play a pivotal role in vessel reactivity, was found to improve digital blood flow in patients with scleroderma who were exposed to cold temperatures [29].

5.2.4. Buflomedil and naftidrofuryl

The effectiveness of these agents remains controversial, and the number of studies is small [3,30,31]. However, buflomedil is widely used in everyday practice.

5.2.5. Prostaglandins

Prostaglandins are potent vasodilating agents that also inhibit platelet aggregation, decrease leukocyte margination, and exert fibrinolytic effects [2,3]. Ilomedin, a synthetic analog of prostaglandin \( \mathrm{I_2} \), has been evaluated in Raynaud’s phenomenon secondary to connective tissue disease [32–36]. The drug was given as 6-h infusions in doses of 0.5 to 2 ng/kg/min for 3 to 6 days [32]. In a study of 114 patients with scleroderma, ilomedin therapy decreased attack frequency and severity and improved skin healing, compared to a placebo [32]. The 0.5 ng/kg/min and 2 ng/kg/min dosages were similarly effective, and the lower dosage induced fewer side effects (headache, hot flashes, and gastrointestinal symptoms). Despite the short half-life of ilomedin, the beneficial effects lasted several weeks, suggesting endothelial and cellular effects in addition to the vasodilating effect [33]. In comparisons of ilomedin infusions to nifedipine per os in patients with scleroderma, ilomedin was at least as effective as nifedipine [34,35]. Oral prostaglandins have not been proved effective [36]. A placebo-controlled study of beraprost for 6–12 months in 107 patients with digital ulcers showed no difference in attack frequency or severity but revealed a trend toward decreased ulcer size [37].

5.2.6. Endothelin receptor antagonists

Endothelin, which is released by endothelial cells, induces vasoconstriction. Endothelin receptor antagonists are approved for use in primary arterial hypertension and in arterial hypertension associated with scleroderma functional class III [38,39]. In a placebo-controlled study of bosentan 25 mg b.i.d., there were fewer new ulcers with the drug, and this effect was most noticeable in patients who had primary ulcers at baseline [40]. Hand function improved, but there was no effect on healing of preexisting ulcers [40]. Other studies showed rapid ulcer healing, even in patients who were previously treated with ilomedin [41–44].

5.2.7. Phosphodiesterase inhibitors

The phosphodiesterase-5 inhibitor sildenafil increases guanosine monophosphate levels in vascular smooth muscle cells, inducing vasodilation. Sildenafil, which is used to treat erectile dysfunction, has been evaluated in primary and scleroderma-associated pulmonary arterial hypertension [45]. The results showed that sildenafil improved Raynaud’s phenomenon. Sildenafil (12.5 to 150 mg once to three times a day) has been used in a few patients to treat digital ulcers associated with severe Raynaud’s phenomenon (due to connective tissue disease or cancer) that was unresponsive to calcium-channel antagonists and ilomedin. Improvements were noted within a few days, and tolerance was good [46–48]. Similar results were obtained with tadalafil [49,50].

5.2.8. Selective serotonin reuptake inhibitors

Serotonin has vasoconstricting effects. This mediator is released by nerve terminals and by platelets undergoing activation. The selective serotonin reuptake inhibitor fluoxetine induced improvements in small studies. Fluoxetine (20 mg/day) was significantly more effective than nifedipine (40 mg/day) in decreasing attack frequency and severity, and the difference was particularly marked in the subgroup with primary Raynaud’s phenomenon [51].

5.2.9. Angiotensin II receptor antagonists

Results obtained with angiotensin II receptor antagonists to treat Raynaud’s phenomenon have been inconclusive. Losartan 50 mg/day was better than nifedipine 40 mg/day in decreasing attack frequency and severity and also improved vascular parameters, most notably in patients who had primary Raynaud’s phenomenon [52].

5.2.10. Fibrinolytic agents, anticoagulants, and platelet inhibitors

The evidence is not sufficient to support the use of these medications. Controlled studies are needed to determine their role in Raynaud’s phenomenon.

5.2.11. Medications approved for use in France

Nifedipine and ilomedin are approved for the treatment of Raynaud’s phenomenon. Several vasodilating agents are approved as adjunctive treatments; they include buflomedil, naftidrofuryl, and dihydroergocriptine. Other medications are not approved for Raynaud’s phenomenon and should be used only when the condition is severe and refractory to the above-listed drugs, after a careful review of the literature. Ilomedin is costly and is reimbursed by the French healthcare system when used in hospitalized patients. The 3- to 6-day treatment duration is well-suited to 1-week hospitalization.

5.3. Nonpharmacological treatments

The level of proof is inadequate to support the use of biofeedback, acupuncture, low-frequency laser therapy, cord stimulation, or sympathetic block [2,3,21,53]. Surgery is rarely appropriate, despite the introduction of thoracoscopy. Thoracoscopic sympathectomy induced rapid improvements, with healing of the ulcers within 1 month, but the recurrence rate was high (82%) [54]. Digital sympathectomy with periarterial denervation also carried a high recurrence rate and also induced postoperative complications in 37% of patients with scleroderma [55].
Acknowledgments

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References


