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Review

Raynaud's phenomenon: From molecular pathogenesis to therapy

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ABSTRACT

Raynaud's phenomenon (RP) is a well defined clinical syndrome characterized by recurrent episodes of digital vasospasm triggered by exposure to physical/chemical or emotional stress. RP has been classified as primary or secondary, depending on whether it occurs as an isolated condition (pRP) or is associated to an underlying disease, mainly a connective tissue disease (CTD-RP). In both cases, it manifests with unique "triple" (pallor, cyanosis and erythema), or "double" color changes. pRP is usually a benign condition, while sRP can evolve and be complicated by acral digital ulcers and gangrene, which may require surgical treatment. The pathogenesis of RP has not yet been entirely clarified, nor is it known whether autoantibodies have a role in RP. Even so, recent advances in our understanding of the pathophysiology have highlighted novel potential therapeutic targets. The aim of this review is to discuss the etiology, epidemiology, risk factors, clinical manifestations, recently disclosed pathogenic mechanisms underlying RP and their correlation with the available therapeutic options, focusing primarily on pRP and CTD-RP.

Contents

Abbreviations: α2C-R, α2-adrenergic C receptor; ACA, anti-centromeric antibodies; ANA, antinuclear antibodies; ATII, angiotensin II; CCB, calcium channel blockers; CGRP, calcitonin gene-related peptide; CTD, connective tissue disease(s); DUs, digital ulcers; ET1, endothelin-1; ET1-R, endothelin-1 receptor; MCTD, mixed connective tissue disease; NFVC, nailfold videocapillaroscopy; pRP, primary Raynaud's phenomenon; RP, Raynaud's phenomenon; SLE, systemic lupus erythematosus; sRP, secondary Raynaud's phenomenon; SMC, smooth muscle cells; SSc, systemic sclerosis; PGI2, prostaglandin I2, prostacyclin; PTK, protein tyrosine kinase; RAMP-1, receptor activity modifying protein-1; ROS, reactive oxigen species; VIP, vasoactive intestinal peptide.

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1. Introduction

Raynaud's phenomenon (RP) is a vascular acro-syndrome characterized by recurrent, reversible episodes of vasospasm, involving peripheral small vessels (arteries, arterioles, pre-capillary and post-capillary venules). They are triggered by exposure to physical [1], chemical [2] and/or emotional stress [3,4]. RP is classified as primary RP (pRP) when it occurs as an isolated condition, accounting for 80% of cases [5], and secondary RP (sRP) if it is associated to other diseases, mainly connective tissue diseases (CTD) (CTD-RP). RP may also occur in other non CTD (Table 1). While in pRP no structural changes, or only minimal alterations of the vessel walls occur [5], in sRP (especially in CTD-RP) the vasospasm is more sustained, long-lasting and highly recurrent, and is associated with structural alterations of the vessel walls mainly due to the underlying CTD [6]. The clinical severity of RP varies greatly, ranging from a simple but uncomfortable condition to severe symptoms that seriously affect the patient's quality of life [6].

Although 150 years have passed since the identification of RP as a clinical entity, its etiology and pathogenesis still has not been fully clarified.

The first part of this review summarizes the etiology, epidemiology, risk factors and the clinical manifestations of pRP and sRP, highlighting the relationship with CTD. Then, a critical evaluation of recent insights into the pathogenic mechanisms underlying RP is discussed, laying a particular emphasis on vascular, neuronal and intravascular abnormalities to highlight the crucial key points and potential targets for therapeutic intervention. Finally, the results of the most salient clinical trials are illustrated, highlighting the drugs that have been successfully employed in this clinical condition.

2. Methods

We conducted a literature search in the MEDLINE database through the PubMed interface, using the following terms: Raynaud's phenomena (primary Raynaud's phenomenon or secondary Raynaud's phenomenon) and/or systemic sclerosis, in combination with epidemiology, risk factors, clinical features, pathogenesis, connective tissue diseases, vasculitis, atherosclerosis, hand arm vibration syndrome, digitals ulcers (DUs), nailfold videocapillaroscopy (NFVC), autoantibodies, and therapy. Additional associated terms were: mediators, alpha2-adrenergic C receptor (α2C-R), nitric oxide, Rho kinase, vasoconstrictors, vasodilators, oxidative stress, clinical trials, calcium channel blockers, phosphodiesterase inhibitors, endothelin receptor antagonists, and prostaglandin analogs. All relevant English-language articles published up to and including November 2013 were reviewed and further relevant papers were selected from the reference lists of retrieved articles.

3. Epidemiology and risk factors

RP has a prevalence of 3–5% in the general population [6], and the mean age of affected patients ranges from 47.2 years in Europe [7] to 53.5 years in the US [8]. In Italy, the prevalence rate ranges from 3.4% in women to 0.5% in men [9], while in the US it ranges from 9.6% in women to 5.8% in men [10]. In a recent randomized clinical trial performed in California in 162 RP patients of various ethnic origins, RP was more frequent in non-Hispanic white people (80.2%) than in American Indian/Alaska natives (0.6%) or in Asian/Pacific islander natives (1.2%) [11].

Table 1
Raynaud's phenomenon (RP) and associated diseases.

Clinical setting	Subset		Disease/drug class
CTD	Connectivitis		SSc, MCTD, SLE, UCTD, rheumatoid arthritis, Sjögren syndrome, dermatomyositis/polymyositis
	Vasculitis	Small vessels	Granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg–Strauss), hypersensitivity vasculitis, cryoglobulinemic vasculitis, hypocomplementemic urticarial vasculitis
		Medium vessels	Polyarteritis nodosa
		Large vessels	Takayasu's arteritis
		Miscellaneous	Buerger's disease
Occupational factors, repetitive trauma			Hand arm vibration syndrome, hypothenar hammer syndrome, freezing fingers syndrome, exposure to polyvinylchloride, nitrates
Intrinsic vascular obstruction			Atherosclerosis
Malignancies	Hematological		Cryoagglutininemia, cryofibrinogenemia, light chain amyloidosis, multiple myeloma, polycythemia, POEMS syndrome
	Solid		Lung, gastro-intestinal tract, female genital tract, prostate
Clotting diseases			aPLs syndrome, DIC
Neurovegetative causes			Reflex sympathetic dystrophy, Dressler post infarct syndrome
Nervous system diseases			Idiopathic peripheral neuropathy
Endocrine diseases			Hypothyroidism
Surgical diseases			Carpal tunnel syndrome, thoracic outlet syndrome, compression by extrinsic, artero-venous fistulae, arterial embolism
Iatrogenic	Drugs		Chemotherapy drugs (vinblastine, bleomycin), interferon-α, cyclosporin, estrogens, sympathetic mimetic agents, non selective beta blockers, clonidine, serotonin receptor agonists, ergotamine bromocriptine, imipramine
	Drugs addiction		Nicotine, narcotics, amphetamines, cocaine

aPLs: anti-phospholipid antibodies; CTD: connective tissue diseases; DIC: disseminated intravascular coagulation; MCTD: mixed connective tissue disease; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; SLE: systemic lupus erythematosus; UCTD: undifferentiated connective tissue disease.