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Review

Raynaud phenomenon

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ABSTRACT

Raynaud's phenomenon is a common clinical disorder characterized by recurrent vasospasm episodes of digital arteries, arterioles, pre-capillary and post-capillary venules triggered by exposure to cold or emotional stress. RP can be classified as primary (idiopathic), or secondary to several diseases or conditions. The pathogenesis of RP is still not entirely clear or understood, but recent insights into the pathogenic mechanisms underlying Raynaud's phenomenon include vascular, neuronal and intravascular abnormalities which may identify crucial key points and potential targets for therapeutic intervention.

In this review we summarize the epidemiology, pathogenesis, clinical manifestations and assessments as well as the recent advances in therapeutic approaches.

An extensive review of recent literature was conducted, according to the guidelines proposed at the PRISMA statement. MEDLINE database (PubMed) and Thomson Reuters Web of Knowledge platform were searched for articles published in peer-reviewed journals and published in English language. The keyword search terms included: Raynaud phenomenon, epidemiology, pathogenesis, thermoregulation, endothelium dysfunction, risk factors, clinical features, nailfold videocapillaroscopy and treatment.

Inclusion criteria were: (1) Randomized controlled trials (2) Reviews, systematic reviews and meta-analysis of randomized controlled trials (3) English language. Studies lacking clinical end points of relief, case reports and open label trials were excluded.

Contents

Abbreviations: ACE, Angiotensin-Converting Enzyme; ADMA, Asymmetric dimethylarginine; AR, Adrenoreceptors; ARB, Angiotensin II Receptor Blockers; AVA, Arteriovenous anastomoses; cAMP, Cyclic adenosine monophosphate; CCB, Calcium Channel Blockers; CGRP, Calcitonin gene-related peptide; CTD, Connective Tissue Diseases; CTA, Computed Tomography Angiogram; cGMP, Cyclic guanosine monophosphate; CVD, Cardiovascular disease; DSA, Digital Substraction Angiography;; DU, Digital Ulcers; ERS, Erythrocyte sedimentation rate; ET-1, Endothelin^{-1}; GPCR, G Protein-coupled receptor; HANAC syndrome, Hereditary angiopathy, nephropathy, aneurysms and cramps syndrome; MRA, Magnetic Ressonance Angiogram; NCV, Nailfold videocapillaroscopy; NO, Nitric oxide; PDE, Phosphodiesterase;; PRP, Primary Raynaud's Phenomenon; RAMP^{-1}, Receptor Activity Modifying Protein-1; RCT, Randomized Controlled Trial; RP, Raynaud's Phenomenon; ROCK, RhoA/Rho kinase pathway; ROS, Reactive Oxigen Species; SMC, Smooth Muscle Cells; SRP, Secondary Raynaud's Phenomenon; SSRI, Selective Serotonin Re-uptake Inhibitors; SSc, Systemic Sclerosis; VIP, Vasoactive intestinal peptide; VSM, Vascular Smooth Muscle Cell

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1. Introduction

Raynaud's Phenomenon (RP) was first described by Maurice Raynaud in 1862. By definition RP are bouts of reversible vasospastic ischemia of the extremities, which most frequently involve hands and toes, less frequently nose and earlobes, and rarely tongue [1,2]. Episodic color changes of the fingers classically turn into white (ischemia), blue (cyanosis) and red (reperfusion), but the three color stages are not needed to be present RP diagnosis [3,4]. When a patient presents with RP, the clinician must diagnose whether RP is primary or secondary, due to different clinical significance, treatment and prognosis.

Primary RP (PRP), also known as Raynaud's disease, is a functional vascular disorder that occurs as a sporadic exaggerated response to cold or emotional stress. PRP does not progress to irreversible tissue injury [5,6] and has usually a benign clinical course [3]. Secondary RP (SRP), also known as Raynaud's Syndrome, appears in response to the same triggers, however it occurs in the setting of an underlying structural vascular disease and is often associated with digital ulceration, scarring or gangrene [3].

2. Epidemiology

The real prevalence of RP varies between studies mostly due to different geographic conditions such as climate. PRP is a common condition, with a prevalence of 3–5% in the general population [2]. In a systematic review and meta-analysis based on six studies assessing the general population, the lowest prevalence of PRP was found in Japan, with an overall prevalence of 1,6 (2,1% in women *vs.* 1,1% in men) and the highest overall prevalence was in the USA with a median prevalence of 7,5% (7,8% in women *vs.* 5,8% in men) [7]. Onset age is usually below 40 years and a family history of RP may be present [3].

Secondary RP has a high prevalence among patients with connective tissue diseases such as Systemic Sclerosis (SSc) (90%), systemic lupus erythematous (30%), rheumatoid arthritis (20%), Sjögren's syndrome and polymiositis [8,9]. SRP is an important red flag that raises suspicion for very early SSc [10,11].

Recent reports alert that RP can be considered a sign or precursor of undiagnosed vascular disease. The presence of RP among whites was associated with 1,6 fold increase in the hazard cardiovascular disease (CDV)-related death [12]. Risk factors of RP are complex and not consensual. Some studies suggested that smoking increased risk of RP in male, but heavy alcohol consumption and hormonal factors increased risk only in women [2,13]. The contribution of genetic factors is not clear, however familiar aggregation and some rare syndromes such as Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps HANAC syndrome suggest a polygenic etiology [2].

3. Raynaud pathogenesis

Pathogenesis of RP is undoubtedly complex, once both central and 'local' mechanisms are involved. Vascular, neural and intravascular abnormalities can impair blood flow and/or cause endothelial injury. The blood vessel wall (endothelium), the neural control of the vascular tone (deficiency of the vasodilator calcitonin gene-related peptide, α_2-adrenoreceptors activation) and many circulating factors (activated platelets, impaired fibrinolysis, increased viscosity, oxidant stress) all together play a role in the pathogenesis of RP [14].

During body or local cooling, blood flow falls to markedly low levels in patients with RP and in SRP individuals it can fall to absolute zero [15]. Comparing PRP with SRP, in response to local finger cooling patients with SRP demonstrated increased sensitivity to cold with a more severe and prolonged blood flow reduction. Additionally with local warming blood flow recovery was higher in PRP [15] probably due to structural alterations in SRP.

3.1. Vascular mechanisms

Finger blood flow compromises both nutritional blood flow and through arteriovenous anastomoses (AVA). In control subjects, when exposed to cold, total and AVA blood flow are reduced but no changes in nutritional blood flow are observed. In contrast, nutritional and AVA blood flow is markedly reduced in RP subjects, affecting severely nutritional blood flow in SRP SSc-associated patients [15].

The pallor phase of RP is due to cold induced vasoconstriction (arterial and venous vasospasm). Sympathetic neurotransmission is more effective in cutaneous veins than in arteries, due to better penetration of nerve fibers in the low-pressure cutaneous veins. Smooth muscle cells in veins wall that have an extremely high activation of α_2-adrenoreceptors (α_2 AR), making them highly responsible for to the local cold-induce amplification of sympathetic constriction [15].

The cyanotic phase is often attributed to local hypoxia. However, it is likely mediated by early vasodilation of venous cutaneous system with deoxygenated blood flow, while AVA remain constricted [15].

Hyperemic phase might be a consequence of delayed dilation of AVA allowing a large influx of fully oxygenated flow into the dilated venous system.

3.2. Functional abnormalities

RP occurs when the balance of vascular tone is disturbed, favoring vasoconstriction. Endothelial activation and/or damage leads to underproduction and efficacy of vasodilators and/or overproduction of vasoconstrictors. A complex and still not fully understood response to whole body and local cooling add a challenge to the unraveling pathogenesis of RP [5].