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Review article

Review of Raynaud's phenomenon: pathomechanisms, diagnosis and treatment

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Abstract

Introduction: Raynaud's phenomenon (RP) is a quite common but often unrecognised vasospastic condition of the peripheral vessels. This may happen after exposure to the cold, stress, vibrations or a wide range of medical conditions. It causes episodic colour changes of the digits, firstly there is a pallor, followed by cyanosis and/or redness, usually with pain. Raynaud's phenomenon can be primary (i.e. Raynaud's disease) or secondary (i.e. Raynaud's syndrome) to underlying disease.

Aim of the study: The aim of the study was to discuss the complex and incompletely understood pathophysiology of Raynaud's phenomenon and to evaluate treatment approaches of both 'uncomplicated' - mostly primary and 'complicated' - mostly secondary Raynaud's phenomenon.

State of knowledge: Raynaud's phenomenon is a common disorder with an unclear pathophysiology. Although many treatment approaches have been reported, there is still no cure or gold standard therapy. Further investigations into treatment are required.

Conclusions: Future research is needed to understand the complex pathogenesis of RP and to develop optimised approaches to management.

Key words: Raynaud's phenomenon, Raynauld's disease, Raynauld's syndrome, diagnosis, treatment

Abbreviations: RP - Raynauld's phenomenon, PRP - primary Raynauld's phenomenon, SRP - secondary Raynauld's phenomenon, SSc - systemic sclerosis

1. Introduction

In the 19th century, French doctor Maurice Raynaud first described Raynaud's Phenomenon which appeared in one of his female patients. He noticed a symmetrical, vasospastic, episodic disorder of the peripheral arteries, usually best seen in the fingers but can also affect toes, nose, ears and nipples. Typically in response to the cold or stress exposure. The classic triphasic colour change is white - pallor (ischaemia), followed by blue - cyanosis (de-oxygenation) and red (repercussion), sometimes with pain and paraesthesia [1].

RP is indeed a syndrome of symptoms and signs related to many probable ethologies. It is crucial to tell apart RP from other disorders that cause change of digits' colours, including pernio, acrocyanosis, or livedo reticularis, as course and treatment may differ significantly between conditions.

RP can be primary (idiopathic, i.e. Raynaud's disease) or secondary (i.e. Raynaud's syndrome).

Prevalence of primary Raynaud's Phenomenon (PRP) is around 80% to 90% of all patients diagnosed with RP, it is noticeable higher in women than in men. The cause of PRP is unknown. Patients typically do not have autoantibodies and present normal inflammatory markers. A typical digital colour change is symmetric and episodic [1,2]. It does not progress to tissue damage [3] but long-term suffers firstly identified as having Raynaud disease may present features of underlying disorders. Ingegnoli et al. [4] undertook a systematic review and meta-analysis which showed that the mean incidence rate of transition from PRP to SRP was 2.65/100 patient years and to systemic sclerosis (SSc) was 0.93/100 patient years.

Secondary Raynaud's Phenomenon (SRP) known as Raynaud's syndrome is a symptom of underlying conditions, such as connective tissue diseases (e.g. systemic sclerosis, systemic lupus erythematosus, polymyositis, rheumatoid arthritis), certain drugs (e.g. ergotamine, beta-blockers, methylphenidate, cisplatin, nicotine) and vibration exposure (hand-arm vibration syndrome) [2]. The incidence in people with systemic sclerosis is almost 100% [5]. On rare occasions, secondary RP can lead to ulcerations of the fingers and toes and critical digital ischaemia. Attacks of digital colour changes are more frequent, usually asymmetric and painful. One study found that 203 people (17.4%) of 1168 people with systemic sclerosis over

an 18-month period had Raynaud's phenomenon complications such as gangrene, digital ulceration or needed peripheral sympathectomy [5].

2. Epidemiology

Reports of incidence of RP vary widely, it is commonly accepted that 3-5% of the general population have RP but there is an estimate that RP might be present in 4-14% of men and 5-20% of women [6]. The most common age of onset is from 15 to 30 years of age for primary Raynaud's phenomenon and over the age of 40 for secondary Raynaud's phenomenon [5]. PR and particularly PRP is more common in women compared with men. Around 50% of patients with PRM and especially females have a family history of RP. PRM may remit over time [3]. Prevalence also depends on geographic variations, it is more common among subjects who live or used to live in colder regions [2].

3. Pathophysiology

Precise mechanism of PR is still not fully understood. It has been suggested that the key issue is dysregulation between vasoconstriction and vasodilation with predominance of vasoconstriction. Evidence points to microvascular, neural and intravascular abnormalities [1,3].

Vascular abnormalities

It is generally accepted that in PRM the vascular abnormalities are primarily functional but they are more apparent in patients with SRP. Vascular anomalies typical for SRP include endothelial cell apoptosis, interplay of a great number of growth factors or cytokines. Endothelium produces many vasodilator substances, e.g. nitrous oxide (NO) and prostacyclin which increase blood flow. As the endothelium is damaged, there might be a deficiency of these. Moreover, there is also overproduction of vasoconstriction, e.g. endothelin-1 and angiotensin II. In skin biopsies from patients with systemic sclerosis endothelin-binding density is increased and endothelin-1 is overexpressed [1,2,7].

It is suggested that prostacyclin production is reduced on cold exposure. Zamora et al. [8] reported that endothelin-1 levels were higher at baseline and rose more in patients with RPR compared to controls in response to a cold challenge. Leppert et al. [10] alike Smythe et al. [11] described that endothelin-1 levels at baseline were much the same in PRP patients and

healthy controls, after cooling the whole body levels rose in the PRP but not in the healthy group.

Neural abnormalities

The sympathetic nervous system plays a main role in thermoregulation. Autonomic nervous system, both central and peripheral mechanisms contribute to the pathogenesis of PRP and SRP, but peripheral neural mechanisms are the most significant. There are a variety of neurotransmitters and their receptor that are probably involved in RP, one of them is calcitonin gene-related peptide (CGRP). There was shown a reduction in the number of CGRP-immunoreactive nerve fibres in finger skin biopsies from patients with PRP, SSc and hand-arm vibration syndrome. Cold stimuli causes activation of Rho/Rho kinase signalling pathway which induces relocation of alpha 2c- adrenergic receptors from Golgi apparatus to the cell surface and induces increased sensitivity to calcium of contractile protein and consecutive vasoconstriction [1,2].

Intravascular abnormalities

Contributory mechanisms which have been involved in the ethology of both PRP and SRP contain platelet activation. Platelets release thromboxane and B-thromboglobulin. Thromboxane is a vasoconstrictor and platelet aggregator so at least some patients with SSc have impaired fibrinolysis, which can incline vascular obstruction and fibrin deposition. Żuk et al. [11] showed that plasma clots of patients with PRP display smaller pores and are degraded at a slower rate. Fibrin clots are more prothrombotic, denser and more resistant to lysis.

Another factor of RP initiation and progression might be oxidative stress mediated by free radicals. It was found that circulating levels of reactive oxygen species (ROS) correlate with SSc vasculopathy, the production of autoantibodies and the formation of fibrosis [12].

White blood cell activation, reduced red blood cell deformability and increased viscosity also have been implicated in the pathophysiology of RP [7].

Genetic

Genetic factors are supposed to play a significant role in the development of RP as proved that half of patients with PRP have positive family history with first degree relatives having RP [2,7]. Of mechanistic interest, Munir et al. [13] claimed that RP is associated with variation in gene NOS1.

4. Diagnosis

The diagnosis of RP in primary care is based on a history of Raynaud's symptoms and physical examination. Practitioners should ask about age of onset of RP, frequency of attacks and accompanying symptoms, such as paraesthesia, pain or numbness. Important signs to clarify are tightening of the skin, dryness of eyes or mouth, mouth ulcers and photosensitivity. Family history should be taken, as should be drug and occupational history. Episodes of migraine or irritable bowel are more apparent for PRP [14].

On physical examination colour change of digits should be checked, as well as signs of poor tissue nutrition, e.g. ulcers, trophic changes in the nails or digital pitting. There might also be symptoms of related disorders, such as telangiectasia, sclerodactyly, malar rash or patchy alopecia. Blood pressure should be checked in both arms and Allen's test may help with detection of distal arterial disorder of the upper limb.

If the history and physical examination significantly propose RP, the next investigation should contain blood tests, such as full blood count, inflammatory markers, creatinine kinase, fasting lipid profile and autoantibody tests. Autoantibody testing is typically important for those patients who are likely to develop a connective tissue disease as it is helpful in determining the antigenic target of autoantibodies. Antinuclear antibody (ANA) tires should be measured and if the ANA is positive, en ENA may be crucial. The ENA may happen to be a positive anti-DNA titre associated with SLE, anti-topoisomerase antibodies with diffuse systemic sclerosis, anti-centromere antibodies with limited systemic sclerosis and anti-Ro or La with Sjögrens [14,15].

Capillaroscopy is one the most precise examinations to differentiate PRP from early SRP. It provides a non-invasive insight into the structure of capillaries. Capillary size, capillary density, changes in architecture or the presence of haemorrhage can be noticed. Nailfold capillaroscopy is performed at the base of the fingernails. It can be performed with low-

magnification examination (~x10 magnification) using dermatoscope, ophthalmoscope or stereomicroscope which provides a wild-field examination or high-magnification examination (~200-600 magnification) using videocapillaroscopy which can provide a panoramic “mosaic” of the entire nailfold. At the moment, semi-manual or manual image analysis is time-consuming but software for semi-automated or automated analysis is subjected to evaluation [16].

A patient with PRP needs to fulfil the criterion of having a normal capillaroscopy. Normal capillaroscopy consists of a normal range capillary density (>=7 capillaries per linear mm), a normal capillary dimension (width of limbs <20um), a normal capillary morphology (hairpin shape), absence of large confluence bleedings and absence of “non-specific abnormalities". Maricq et al. [17] presented the “scleroderma pattern” which comprised loss of capillaries, a striking widening of all segments of the capillary loop and disorganisation of the nailfold capillary bed. Normal patterns and multiple of “non-specific” capillary anomalies have been noticed to appear in other connective tissue diseases [1,14,18].

Although nailfold capillaroscopy is not often performed in primary care, some physicians who use dermatoscopy for skin lesions as differentiating mole from melanoma, can try to visualise the nail fold vessels. Low-magnification examination can miss early changes so a referral to a secondary care physician and especially a well-trained capillaroscopist is suggested [14].

5. Treatment

The aim of Raynaud Phenomenon treatment is to reduce the frequency and severity of the attacks and to prevent tissue ischemia. The recommended primary therapy is non-pharmacological management. The first step is to avoid exposure to cold and rapid temperature changes. Maintenance of core and especially hands and feet temperature within the appropriate range is significant. Prevention of RP also includes avoiding smoking, emotional stress and vibration tools, such as jackhammers [1,3,15].

Those patients who fail to respond to general measures will require drug therapy. Dihydropyridine calcium channel blockers (CCB) are the first-line therapy drugs. Most analyses included nifedipine, but amlodipine also can be used. The most common administered form is long-acting form, but slow-release, rapid-, short- and long-acting forms also can be prescribed. Amlodipine dosage is from 5mg to 20mg daily, nifedipine dosage is from 30 mg to 180 mg daily [15]. A standard approach is to start with the lowest recommended dose and gradually up-titrate the dose in order to avoid adverse effects, such as

reflex tachycardia, dizziness, headache or nausea [1,3]. The Cohrane review of primary and secondary RP concluded that evidence of moderate quality (downgraded for inconsistency) from 23 trials with 528 participants points out that calcium channel blockers (CCBs) were superior to placebo in reducing the frequency of attacks. CCBs decreased the average number of attacks per week by six in comparison to 13.7 attacks per week with placebo. Higher doses may be more effective than lower doses and CCBs may be more effective in primary RP [19].

Alternative therapy to treatment failure using CCB is phosphodiesterase type 5 (PDE5) inhibitors. They restrain the degradation of cyclic guanosine monophosphate (cGMP) and therefore raise nitric oxide (NO) impact on vessels. It can be used together with CCB or as monotherapy when CCB is not tolerated or gives no result [1,3]. Sildenafil and tadalafil are examples of PDE5. Usual dose of sildenafil is from 20 mg three times daily to 50 mg three times daily and for tadalafil from 20 mg alternate days to 20 mg daily [3]. The Cohrane review included a total of 411 participants. The majority had Raynaud's phenomenon secondary to systemic sclerosis. The frequency of attacks per week was 24 with placebo and PDE5 reduced the frequency of attacks by an average of three attacks per week. The duration of attacks per day was 55 minutes with placebo and an average five minutes with PDE5. Use of PDE5 may result in little to no difference in contrast to placebo in reducing the average pain of Raynaud's attacks [20].

Another option are topical nitrates, e.g. vasodilator nitroglycerin. Its action derives from its metabolic conversion to nitric oxide (NO) in the vascular smooth muscle cell. NO activates guanylate cyclase, which results in an increase of guanosine 3′5′ monophosphate (cyclic GMP) and leads to dephosphorylation of myosin light chains and result in vasodilation [21]. Usually, 2% nitroglycerin ointment is applied to areas where RP appeared. It increases blood flow in digits and has predictable and mild side effects [22]. Nitroglycerin ointment has an onset of action 15-20 min and a duration of action of 60 min. FDA accepted it for prevention and therapy of angina pectoris [5,22]. There are also nitroglycerin transdermal patches, they rely on systemic absorption. Current literature proposes that nitroglycerin patches increase local blood flow and the temperature at the site of application in patients with SSC [23].

Angiotensin II receptor blockers also can be used as they block action of angiotensin II on vascular smooth muscles. Daily dose of losartan is 25 mg to 100mg. A randomised, parallel-

group, controlled trial with 52 patients proved a decrease of severity and frequency of Raynaud's episodes with use of losartan 50 mg/day compared to nifedipine 40 mg/day [2,24].

Other options, if the patient does not react to the above treatment, include: selective serotonin reputable inhibitors, such as fluoxetine and intravenous prostanoids, such as iloprost. Iloprost takes part in a vasodilation and inhibiting activity of blood platelets. It can be prescribed in a severe SSc-related RP as it may prevent or heal digital ulcers even long after intravenous infusion was given [1,3,15,25].

Alpha1-adrenoreceptor antagonists, e.g. prazosin, terazosin and doxazosin are also used for RP therapy. Two randomised controlled crossover studies have shown that prazosin was more efficient in the treatment of RP secondary to SSc [26]. While, double-blind, placebo-controlled, crossover study of 24 patients has shown that a low dose of prazosin decreased the duration and number attacks of both PRP and SRP [27].

Endothelin-1 receptor antagonists, such as bosentan block endothelin-1 on smooth muscle cells and are helpful with treating refractory secondary RP and preventing recurrent digital ulcers in patients with SSc [1,3].

There is increasing interest in botulinum toxin injections into the perineurovascular tissue of the wrist, distal palms, or along digits. The evidence base to confirm this therapy is limited. Botulinum toxin A is thought to block the sympathetic innervations. A placebo-controlled RCT in 40 patients with SSc showed there were positive outcomes for hand function, pain and cold sensitivity but failed to confirm advantages with laser Doppler imaging. The use of botulinum toxin with severe secondary RP is right now an off-licence therapy and further investigation is required before this treatment can be widely recommended [28].

In patients with critical digital ischaemia or resistant ulceration, despite aggressive pharmacological therapy, digital periarterial sympathectomy may be considered. Methods of this procedure widely vary, from stripping a few millimetres of the proper, common or most symptomatic digital vessels to extensive procedure to e.g. the superficial arch, dorsal radial and/or ulnar arteries. A retrospective chart review was performed on 46 patients and 58 periarterial sympathectomies (12 bilateral). 94.8% of patients noticed a permanent decrease in pain. Of the 50 patients diagnosed with fingertip ulcerations, 39 fully healed and 11 needed amputation or stump revision subsequent to sympathectomy [29].

A retrospective analysis of 16 patients who underwent digital artery sympathectomy showed that in all cases postoperative reperfusion was immediately established and mean pain score (0 - no pain, 3 - severe pain) fell from 3.6 before surgery to 2.9 after surgery [30]. Although many positive results have been published, comparing results is difficult due to different surgical techniques and different patients selection [31].

Thoracoscopic sympathectomy is recommended to patients with a severe course of RP. During the surgery the sympathetic chain is visualised behind the parietal pleura, cauterised and destroyed by using electrocautery, harmonic scalpel, endoscopic scissors or other modern techniques [32,33,34]. A retrospective study of 34 patients who were treated by thoracoscopic sympathectomy showed that an immediate effect was seen in 83% of the patients but symptoms occurred again in 60% during the 40 months follow-up period. 40% regretted having this procedure mostly because of lack of long-acting effects and a presence of compensatory sweating. However, in patients with digital ulcerations all the ulcers healed [34]. In a long term observational study of 140 patients who had an open sympathectomy, 66% observed no improvement beyond one year [35]. Major complications after the sympathectomy are uncommon and contain Horner's syndrome, haemo- and pneumothorax [34]. Single-port thoracoscopic sympathectomy is a new and less invasive technique compared to conventional sympathectomy. This surgery was performed in eight patients with RP and there was an improvement of perfusion in all patients, during cooling and recovery procedure. Perfusion at room temperature also increased. It might be a promising therapy option, however long-term effects need to be established [33].

6. Conclusion

RP is a common condition which for the majority of people is not a health threat but can cause a painful and intrusive vasospasm. A key feature is that a secondary RP might lead to digital ulceration and its complications. Careful clinical investigation, such as history taking, laboratory tests, detection of autoantibodies and/or nailfold capillaroscopy are required in all patients with RP. Lifestyle modifications should be indicated in all patients. Primary RP usually does not need pharmacological treatment, while secondary RP often requires vasodilator therapy. Surgical intervention might be needed in severe RP and persistent digital ischeamia. Future analysis is significant to understand pathogenesis and develop complex management including pharmacological therapies.

Disclosure:

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