Recent advances in the workup and management of Raynaud’s phenomenon

Authors: Anna Lis-Święty

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Recent advances in the workup and management of Raynaud's phenomenon

Anna Lis-Święty

School of Medicine in Katowice, Medical University of Silesia, Chair and Department of Dermatology, Katowice, Poland

Short title: Workup and management of Raynaud's phenomenon

Corresponding author:

Anna Lis-Święty, MD, PhD
Chair and Department of Dermatology
Francuska Str. 20/24, 40-027 Katowice, Poland
Tel/fax: +48322561182
E-mail: alis-swiety@sum.edu.pl

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Abstract

Raynaud’s phenomenon (RP) is defined as recurrent, reversible episodes of vasospasm involving peripheral small vessels, typically in the fingers and toes. Primary RP (idiopathic RP) is common, occurring in circa 5% of the general population, and is usually benign. Secondary RP accounts for 10–20% of all RP cases and may be associated with complications such as tissue loss, ulcers, and gangrene. Systemic sclerosis (SSc) or more rarely other connective tissue diseases are the main underlying conditions. A careful clinical history and physical examination may be helpful in identifying the cause. The routine investigations comprises a full blood count, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, biochemical profile, thyroid function tests, protein electrophoresis, chest x-ray, and nailfold capillaroscopy. Capillaroscopy can facilitate very early diagnosis of SSc. Doppler ultrasound is recommended to evaluate the potential of large to medium artery pathology. Lifestyle modifications may be sufficient to control the primary RP, but some patients, and most with secondary RP, require pharmacologic treatment. Several medications are proposed to manage RP and its complications, such as calcium channel blockers, phosphodiesterase type V inhibitors, intravenous prostanoids, and topical nitrates. However, scientific evidences for use of these drugs are still weak to moderate. Despite lack of efficacy of bosentan in RP treatment, this medication is approved for the secondary prevention of digital ulcers in SSc patients. In conclusion, management of RP still represents a challenge. Collaboration between healthcare professionals, patient organisations and the public could encourage earlier medical assessment of people at risk of SSc.

Keywords: capillaroscopy; Raynaud's phenomenon; thermography; ultrasonography; therapy
Introduction

Raynaud’s phenomenon (RP) is defined as recurrent, reversible episodes of vasospasm involving peripheral small vessels of the fingers and/or toes, at times also of the other acral sites (nose, ears, oral mucosa, lips or nipples), when exposed to a cold environment or stressful situation [1]. This is characterized by a series of color changes in the affected area: first white (lack of blood flow), then bluish (deoxygenation of remaining blood), and red (reperfusion). Attacks can cause distal pain, burning, numbness and paresthesia [2]. Regarding its etiology, RP is classified as primary (idiopathic) or secondary. Primary RP that is an isolated finding without underlying pathology is common, occurring in circa 5% of the general population with a higher prevalence in women (female to male ratio is 9 to 1) living in areas with cold climates [3]. There is an associated genetic predisposition; one polymorphic variant was identified within the nitric-oxide synthase 1 gene as significantly associated with RP in the general population [4]. Major risk factors/associations of primary RP include, in addition to the female gender and family history, a previous sensation of cold hands, migraine, cardiovascular diseases, decreased body mass index, manual occupation (not including vibration tool use), and estrogen replacement therapy [3-6]. Cigarette smoking and alcohol consumption are still of unclear significance where primary RP prevalence is concerned [7]. Secondary RP associated with a known disease, mainly with systemic sclerosis (SSc) (>80% of patients) or other connective tissue diseases (CTD), is rare accounting for 10–20% of all RP cases [8]. Other common causes of secondary RP include: diseases of arteries in the upper limbs (60% of RP occurring in individuals older than 60 years), malignancies, endocrine diseases, occupational syndromes, haematological disorders and infections (Table 1) [8,9]. Besides, several medications, such as antimigraine medications (ergot alkaloids), nonselective beta blockers, clonidine, psychostimulants (cocaine, amphetamine, methylphenidate), atomoxetine, risperidone, and aripiprazole are known to induce secondary RP
Interferons, ribavirin, cyclosporine, and chemotherapies (bleomycin, vinca alkaloids, gemcitabine, cisplatin) as well as selective serotonin reuptake inhibitors (insufficient scientific evidence to recommend in treatment of RP), were also reported to be related with RP [12]. Furthermore, recent analysis in the WHO pharmacovigilance database VigiBase® revealed possible risk of RP with proton pump inhibitors [13]. Additionally, unexpected RP was associated with exposure to drugs for which RP are not published (hepatitis B vaccine, isotretinoin, leflunomide, hydroxycarbamide, rofecoxib, telmisartan, zolmitriptan) [14].

The pathophysiology of RP is complex and only partially known. Mechanisms for RP include augmented activity of postsynaptic α2-adrenergic receptors and closing of both arteriovenous anastomoses and finger arterioles [15]. Secondary RP in SSc underlies a microvasculopathy and an abnormal function of the endothelium leading to an imbalance of vasoactive factors including i.a. overproduction of the vasoconstrictor endothelin-1 (ET-1) and underproduction of the vasodilator nitric oxide and prostacyclin [16].

Primary RP has an earlier onset (median age at onset is around 14 years) and is characterized by milder symptoms [17]. Secondary RP often has a later onset (usually after age 40, rare in children) with more severe symptoms, leading to complications, such as digital ulcers (DU), finger necrosis and amputation or associated infection and osteomyelitis [17]. Early detection of SSc or any other cause of secondary RP could allow commencement of early treatment and better outcomes for patients.

The aim of this paper is to clarify and update workup as well as management of RP based on the published data from the past 4 years. Medline searches of primary and secondary sources related to the topic were conducted using the term “Raynaud's phenomenon”.

Clinical aspects of differential diagnosis

The triphasic or biphasic color changes are required to make the diagnosis of RP [18].
White/pallor and blue/cyanosis are the two most important colors (Figure 1 a, b) [18]. Patients must report cold temperatures as one of the triggers for their RP attacks [18]. In contrast, blue or purple finger syndromes present with no changes in colour when subject to temperature changes [19]. Triggers other than cold (e.g. emotional stress), standardized questionnaires, photographs of episodes provided by patients, bilateral hand involvement even if asynchronous and asymmetrical, history of attacks at sites other than the hands, well demarcated color changes, numbness and paresthesia are deemed helpful but not required to make a diagnosis of RP [18]. Clinical recognition of the functional vascular acrosyndromes, such as erythromelalgia, acrocyanosis and chilblains, avoids unnecessary investigation, although these disorders may coexist with RP [20]. To evaluate for large-vessel occlusive arterial disease, peripheral pulse examination (palpation of subclavian, brachial, radial, and ulnar arteries), Allen test and segmental blood pressure measurements in the upper extremity can be performed.

Laboratory examinations
All patients presenting with RP should undergo blood tests including full blood count, erythrocyte sedimentation rate or serum C-reactive protein level, and antinuclear antibodies (ANA) testing [21]. It is known that the presence of SSc-associated antibodies (anticentromere, anti-topo I, or anti-RNA polymerase III) and abnormal nailfold capillaries at baseline increase the likelihood of developing definite SSc, whereas their absence at baseline practically rule out this outcome [22]. ANA positivity is also an important predictive factor for the evolution to CTD other than SSc [22]. In particular, most of the transitions to CTD were toward undifferentiated CTD and systemic lupus erythematosus [22]. The routine investigations should also comprise a biochemical profile, thyroid function tests, protein electrophoresis, chest x-ray [23].

Evaluation of the microcirculation
Capillaroscopy
Capillaroscopy is used to analyze in vivo images of skin microcirculation in the nailfold bed of the second to fifth fingers of each hand. This method detects and quantifies the microvascular changes that characterize secondary RP associated with SSc or scleroderma spectrum diseases [24]. The main parameters that are assessed at capillaroscopic examination are as follows: shape of capillaries, distribution, mean diameter of the arterial limb, mean diameter of the venous limb, mean capillary length, mean capillary density (normal range, 7-12 capillaries/mm), visibility of the subpapillary plexus, and presence of abnormalities such as capillary tortuosity, dilated (capillary limb>20 μm) or giant capillaries (capillary limb>50 μm), elongated or short capillaries, haemorrhages, avascular areas, neoangiogenic capillaries [24]. Multicentre, international studies demonstrated that the reliability of the simple capillaroscopic definition of normal and abnormal morphologies of capillaries was excellent, even when used by clinicians with varying levels of expertise in capillaroscopy (Figure 2 a, b) [25,26]. The presence of giant capillaries and microhemorrhages and the number of capillaries has significant prognostic value for predicting the development of SSc or a scleroderma spectrum disorder [24]. Furthermore, capillaroscopy identifies morphological patterns specific to various SSc microangiopathy stages and is now included in diagnostic criteria for primary RP, in the criteria for very early diagnosis of SSc (VEDOSS), and in the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria for SSc [24]. The early pattern is characterized by the presence of few enlarged and giant capillaries and no evident loss of capillaries, with a well-preserved capillary distribution (Figure 3 a) [24]. In the active pattern there are frequent giant capillaries and microhemorrhages, and moderate loss of capillaries with mild disorganization of the capillary architecture (Figure 3 b) [24]. Typical characteristics at the late pattern is a severe loss of capillaries with extensive avascular areas and disorganization of the normal capillary array, associated with no giant capillaries and microhemorrhages, and the
presence of abnormal capillaries (Figure 3c) [24]. The presence of active and late patterns on capillaroscopy, were associated with 30-fold increased risk of developing definite SSc over a 3-year follow-up [27].

Primary RP patients with non-specific nailfold capillary alterations (dilations of capillary diameter 20-50 micrometers at the level of arterial branch, microhaemorrhages, reduction of capillaries number <7) at first capillaroscopic evaluation should be closely monitored at least every six months, as they run a higher risk of transition to secondary RP [28]. SSc pattern on capillaroscopy can facilitate very early diagnosis of SSc and scleroderma spectrum diseases as well as their sequelae in patients with RP [29]. Correlation between capillaroscopic findings (capillary deletion and severe deformity) and presence of interstitial lung disease in SSc patients was observed [29]. Pulmonary, cardiac and digestive involvements may be present at the stage of very early SSc and must be screened [29]. A higher prevalence of abnormal pulmonary function tests was also revealed in patients with primary Sjögren syndrome, systemic lupus erythematosus and mixed connective tissue disease [30-33]. Therefore, it is proposed to screen for pulmonary arterial hypertension and interstitial lung disease in all RP patients with CTD.

The high intra and inter-reliabilities suggest that overall image grade, capillary density (vessels/mm) and mean vessel apical width have potential as outcome measures in longitudinal studies [34]. Few papers reported a semiautomated or fully automated methods for the quantitative assessment of absolute nailfold capillary number on capillaroscopy images [35]. Capillary density is the most reliable capillaroscopic parameter for prediction of SSc progression and detection of effects of therapies [35]. This parameter was used for the construction of several scoring systems, such as the capillaroscopic skin ulcers risk index (CSURI), the microangiopathy evolution score, and the simple day-to-day risk [36,37].

Capillaroscopy should only be carried out using equipment of good optical quality and by an
experienced operator, usually in secondary or tertiary care [21]. Digital videocapillaroscopy is now a gold standard; it provides a significantly higher magnification from 50x to 1000x and it allows capillaroscopic parameters to be measured precisely [21]. Magnification 200x is one of the most suitable options for everyday clinical practice as well as for research purposes, providing both opportunities for assessment of capillary distribution as well as certain details in the structure of the capillary loops [21]. Excellent inter and intra-observer agreement was also obtained in experienced vascular physicians for the diagnosis of SSc pattern with magnification 100x [38]. According to the authors, using wide-field capillaroscopy (100x) is easier to assess the global architecture of the capillary bed than by using narrow-field capillaroscopy (200x) [38]. Comparative evaluation of dermoscopy and capillaroscopy in RP showed that 80% of patients had the same status, normal or abnormal, for both capillaroscopy and dermoscopy, which resulted in the same clinical management [39]. Nonetheless, the reference method continues to be capillaroscopy [39].

Infrared thermography
Thermography assesses vascular function (blood flow) providing a colour image of the surface temperature (Figure 4). Dynamic testing of patients’ response to cold challenge is mainly used to diagnose RP [40]. The assessed parameters are basal temperature prior to cold provocation, temperature immediate after the cold challenge, the maximum temperature recovery rate the time between the end of the cold challenge to the onset of rewarming, recovery index (the ratio between temperature increase and initial temperature decrease x 100%) [40]. The thermal gradient (fingertips and the dorsum of the hand difference) may be applied to differentiate healthy and RP subjects [40]. While in healthy subjects the thermal gradient is typically positive, in RP it is typically negative due to a lower digital temperature (~26–28 °C) in comparison with the dorsum of the hand (~31 °C) in resting state or in response to cold provocation [41]. The RP
patients reheat their hands slower than controls [41]. After ice water immersion test, the digital temperature of healthy persons returns to normal in 10 min or less, whereas in patients with RP, it takes much longer (about 35 min) [41]. Campos et al. [42] suggested that the ring finger (fourth finger) could become a reference in studies to determine cutting points and to facilitate the clinical diagnoses of RP. Lower recovery rate and thermal gradient as well as higher disparity in the nail fold temperature between the fingers at baseline and also after cold challenge were found in SSc patients and may be useful for differentiating secondary RP from primary RP [43]. As baseline images were more helpful, a mobile phone thermography seems to be a feasible additional tool in the assessment of the patient with RP [44]. The first multicenter study that was undertaken to determine the reliability and validity of a hand cold challenge protocol mobile phone thermography in patients with SSc-related RP confirmed that small variations in room temperature are acceptable during the imaging [44]. Further investigation is needed to establish ranges of normality and abnormality and to validate the use of this method [44].

Laser-Doppler and other techniques

Laser-Doppler techniques are tools for microcirculatory research, evaluating peripheral blood flow and were used to monitor effects in vasoactive therapy trials in SSc [45]. Flow can be measured over a point (Laser Doppler flowmetry-LDF) and over an area (laser Doppler imaging LDI, laser speckle contrast analysis –LASCA, laser speckle contrast imaging -LCSI) [45]. Some authors believe that measuring the baseline microvascular blood flow and then time to peak flow following occlusion using LDF may be a highly accurate test for differentiating patients with primary RP from healthy controls [45]. The post-occlusive time peak flow had a superior specificity of 90% as compared to 66% for baseline microvascular flow [45]. LDI, LASCA and LSCI are characterized by a higher reliability, but are more expensive and are not yet accessible for many clinicians [46].
Assessment of blood perfusion in RP may be also performed by hand perfusion scintigraphy [47]. This method was reported to play role in diagnosis of RP and evaluating the response to therapy [47]. Gamma camera dynamic first-pass study (blood flow) during the first 60 s differentiated the healthy subjects from patients with RP (primary and secondary), while static study (blood pool) after 5 min distinguished primary from secondary RP [47]. The main disadvantage of scintigraphy is the use of radioactivity [47].

It seems that the novel multisite photoplethysmography (PPG) might be a practical and low cost cardiovascular assessment tool for differentiating SSc from control and primary RP subjects by measuring endothelial function [48]. Endothelial and autonomic function as well as arterial disease measures were obtained using pulse wave analysis [48].

Identifying of patients with RP and evaluating their response to a cold stimulus over time by using photoacoustic imaging with a center frequency of 18 MHz and optical wavelength range of 680–970 nm, which allowed to quantify tissue oxygenation levels, were also reported [49].

However, all these techniques are currently mainly available only in specialist centers and need further validation studies prior to their implementation in clinical practice [50].

Evaluation of the potential large to medium artery pathology

Ultrasonography with Doppler is commonly used for evaluation of peripheral blood flow in RP patients [51]. Some researchers prefer color Doppler ultrasound (CDUS) and only use power Doppler ultrasound (PDUS) if the flow is very low [52]. Baseline flow volume measurement can be recommended to patients who refuse the examination with cold provocation [52]. Vessel diameter and flow rate on baseline and cold provocation were found to be lower in the primary RP and secondary RP groups than in the control group [52]. Flow volume normalizing time was found to be different from that in the healthy group in both RP groups, even after treatment [52]. Vessel patency and wall damage of the digital arteries could be visualized in cases of secondary
RP [53]. As structural changes are very common in SSc patients a significant co-occurrence of vasculopathy (number of narrowed or occluded digital arteries) and concomitant digital ulcers/pitting scars in the same finger was found [53]. Examination of digits II–V selectively might be prognostic tool for the development of DU in patients with SSc in future studies [53]. Lescoat et al.[54] and Schioppo et al.[55] suggested that the ulnar artery occlusion and finger pulp blood flow were associated with capillary loss assessed by nailfold videocapillaroscopy, but longitudinal studies to explore the predictive value of these parameters are required.

The differentiation between a vasospastic and obstructive mechanism may be also made using of finger systolic pressures, pulse-volume recording or pulse contour analysis by strain gauge plethysmography or photoplethysmography [48]. A difference of more than 15 mm Hg between fingers, or an absolute finger systolic blood pressure of less than 70 mm Hg may indicate occlusive disease [48]. The normal finger-brachial index may range from 0.8-1.3 [48]. Sphygmic wave amplitude is markedly lower in RP patients than in healthy controls [48]. Conventional angiography and magnetic resonance angiography provide anatomic information about the location and extension of the occlusive lesions and are used to quantify peripheral circulation in RP, but these techniques require an injection of contrast dye and extensive workup, which may limit their applicability for screening [48].

Monitoring of patients with primary RP for the development of CTD SSc diagnosis may be delayed for several years after the onset of RP and even after the onset of the first non-RP symptom [56]. Patient organization-led initiatives can play an important role in raising awareness about RP [56]. Carefully designed tools can provide reassurance to people interested to learn about RP and encourage earlier medical assessment of people at risk of potentially life-threatening disease such as SSc [56].

No findings suggestive of secondary causes, (e.g. ulcerations, tissue necrosis or gangrene,
sclerodactyly, calcinosis, or skin fibrosis), no history of existing CTD, negative or low titer ANA (e.g. 1:40 by indirect immunofluorescence), normal capillaroscopy are included in the diagnostic criteria for primary RP [18]. However, because some patients with characteristics of primary RP can later transit to secondary RP (Figure 5), any patient developing RP in adulthood, especially after the age of 35, should be regularly screened for the development of CTD, including SSc, with evaluation of proximal nailfold capillaries and serologies [57]. A high index of CTD suspicion should also be applied in children under the age of 12, as primary RP may be less common in the younger age groups [21]. Secondary RP is associated with juvenile systemic lupus erythematosus, mixed connective tissue disease, and rarely SSc and Sjögren syndrome [21]. The European expert panel recommends testing ANA, more specific antibodies associated with CTD, and nailfold capillaroscopy in all children presenting with RP [58].

Biomarkers

Several studies suggest that in CTD microcirculatory changes develop before morphological abnormalities are seen with nailfold capillaroscopy [59]. Markers of endothelial damage (plasma levels of tissue-type plasminogen activator, von Willebrand factor and interleukin-6) were elevated in RP patients who subsequently develop SSc or other CTD, even in the absence of capillaroscopic abnormalities [60]. Biomarkers were also emerging as predictors of digital ulceration in SSc (raised ET-1 levels, and low vascular endothelial growth factor – VEGF levels) and were proposed as novel markers for anti-ischemic therapy (hypoxia-inducible factor-1 and heme oxygenase-1) in RP [61,62].

Lifestyle and psychotherapeutic interventions

Very important component of RP patients management is lifestyle modification. Because RP is a vasospastic event, it is important that patients are educated to avoid vasoconstrictive stimuli, including cold, stress, repeated trauma to the fingertips, vibrating tools, caffeine-containing
drinks, nicotine, or any vasoconstrictive medications [63]. Patients should wear gloves in cold environments, be counseled on the importance of smoking cessation, and be given a list of commonly used vasoconstrictive drugs to avoid [63]. Difficulties resulting from RP are usually present and disabling all year round, which underscore the importance of non-pharmacological strategies throughout the year [63].

Activity and severity of RP can be measured by the Raynaud's Condition Score (RCS) that looks at the quality of life (QoL), frequency and severity of attacks, and the effect of RP on an individual [64]. Of note is that a number of factors such as pain, catastrophisation, and coping strategies, may influence RCS [65]. No correlations were observed between severity of vasoconstriction and pain intensity, pressure pain sensitivity, pain magnitude and threshold [2]. Significantly more patients with secondary RP had anxiety and depressive symptoms than patients with primary RP, 43.9% versus 23.3% and 31.7% versus 11.7%, respectively [66]. Patients with secondary RP have a lower physical health condition and RP specific QoL than patients with primary RP [66]. Severity of RP had one of the largest associations with reduced hand function in SSc [67]. Therefore, anxiety, depression and QoL impairments should be taken into account when managing all patients with RP [64]. Patients who are high in anxiety and depression and low in QoL should be referred for psychological care [64]. Increasing exercise, reducing stress levels, treatments targeting SSc-RP pain and the development of behavioral interventions enhancing coping strategies may reduce the burden of SSc-RP [65]. Unfortunately, in systematic review on this topic, only 7 studies reporting biofeedback and one testing a „behavioural treatment” were identified as randomized controlled trials [68]. Five studies reported significant effects in primary outcomes of interest, however, due to missing data, relative efficacy of interventions could not be reliably assessed [68].

Pharmacological treatment
The European Society for Vascular Medicine (ESVM) guidelines and an update of the EULAR recommendations were recently published regarding the management of RP, but the evidence base for treatment of both primary and secondary RP is weak to moderate [21,69]. Although the course of secondary RP is thought to be directly related to the progression of the underlying disorder, treat or not to treat SSc patients in the earliest phases still remain a dilemma [70]. It is rather believed, that pharmacologic therapies should be added only if attacks remain poorly controlled with disabling symptoms, or if the patient has DU [71].

First-line pharmacotherapy

The recommended first-line pharmacotherapy treatments for primary and secondary RP are vasodilators such as dihydropyridine calcium channel blockers (CCBs) [21,69]. A recent systematic review of 38 randomized controlled trials with an average duration of 7.4 weeks and 982 participant revealed that CCBs probably reduce slightly the frequency, severity, and overall patient assessment of Raynaud’s attacks (moderate-quality evidence) [72]. In addition, CCBs produced a potentially clinically important mean improvement in pain associated with RP [72]. Nifedipine was the most extensively studied, but the newer second-generation CCBs (amlodipine, isradipine, nicardipine, felodipine) were also effective in reducing RP attacks [72]. The most common side effects are headache, dizziness, nausea, palpitations, and ankle edema [72]. Serious adverse events (death or hospitalization) were not reported [72]. Use of CCBs may also be limited by hypotension [21,69]. When starting these medications, the lowest dose should be prescribed and gradually titrated every 4 weeks depending on the patient's response [21,69].

Second-line pharmacotherapy

The use of phosphodiesterase type 5 inhibitors (PDE5i) is recommended as second-line therapy [21,69]. Tadalafil, sildenafil, udenafil and vardenafil appeared to have significant but moderate efficacy in secondary RP [73]. Adverse effects of these medications include flushing, headache,
dizziness, and less commonly, hypotension, arrhythmias, cerebral vascular accident, and vision changes [73]. PDE5i should be started at a low dose, and then titrated depending on response over a period of 4 to 6 weeks [21,69]. If the patients with RP are not willing to take a long-term treatment “as required”, then single doses of sildenafil before/during exposure to cold may be a good alternative [74]. Due to highly heterogeneous response, there is the need for personalized approach to the treatment of RP [74].

Third-line pharmacotherapy

Intravenous prostaglandins are indicated for severe SSc-RP, when oral therapy (including CCBs and PDE5i) has failed [21,69]. Prostaglandins function as a strong vasodilator and also prevents platelet aggregation. According to PROSIT experts, iloprost was used earlier across tertiary Italian centers, namely in combination or immediately after CCBs and represented the first line choice for the management of severe RP and DU in SSc [75]. PDE5i were more rarely prescribed and were generally employed as late treatment for RP [75]. The standard treatment protocol consists of intravenous infusion of iloprost at a rate of 0.5–2 ng/kg/min for 3–5 consecutive days, through a peripheral venous access [75]. Due to common side effects (hypotension, flushing, nausea and headaches) patients used to be admitted into hospital for treatment administration [75]. According to Bellando-Randone et al.[76], in the fibrotic/atrophic phase of SSc, iloprost was well tolerated and side effects were managed by reducing/modulating the infusion rate. In edematous patients, side effects were more frequent and led to drug withdrawal, mostly because of painful digital swelling and diarrhea [76]. CCBs should be transitorily stopped while using iloprost and that a pre-treatment approach might reduce or control adverse events [76]. It should be noted that portable devices for iloprost infusion were recently designed, allowing outpatient treatment [77,78]. The devices demonstrated to be safe, feasible and effective, with higher patients’ satisfaction and consequently greater treatment adherence [77,78]. Other intravenous
Prostaglandins include epoprostenol, treprostinil, and alprostadil. There is limited evidence for the benefit of oral prostacyclin analogs in patients with RP [79].

Intravenous prostaglandins infusions combined with anticoagulation (heparin, 5,000 UI twice daily) is preferable in secondary RP with acute digital or limb ischaemia [51]. A digital or regional block with lidocaine or bupivacaine may be also performed to temporarily relieve vasospasm in such situations [7].

Topical vasodilators

The meta-analysis, which included 7 placebo-controlled trials and a total of 347 treated patients, demonstrated a significant treatment benefit for topical nitrates for RP without serious side effects [80]. However, the dose must be carefully selected: sufficient to cause local vasodilation, but not large enough to result in systemic absorption and the risk of adverse systemic effects, such as hypotension, dizziness, and headache [81,82]. There is limited evidence regarding the effectiveness of other topical vasodilators for the management of RP. One study suggests that topical sildenafil can significantly improve digital arterial blood flow in patients with secondary RP, while after topical nifedipine, there was no significant improvement [83]. A case where rosemary essential oil, as compared to olive oil, produced replicable warming of the hand in a patient with SSc and RP was reported [84].

Other options

There is insufficient scientific evidence to recommend selective serotonin reuptake inhibitors (fluoxetine), angiotensin-converting enzyme inhibitors (captopril, enalapril, quinapril), angiotensin receptor blockers (losartan), alpha-blockers (prazosin), and PDE-4 inhibitor (pentoxifylline) as a treatment in RP [21,69,85].

Trials of ET-1 receptor antagonists such as bosentan and macitentan showed no evidence of improvement in RP attack frequency [86]. Nonetheless, bosentan is currently approved for the
secondary prevention of DU in SSc patients [86]. Hepatotoxicity, headache, flushing, edema, fatigue, and hypotension may occur due to this medication [86]. Typically, bosentan is prescribed 62.5 mg twice daily for 4 weeks, with the dose escalation to 125 mg twice daily if needed [86]. In patients with history of DU, low dose aspirin should also be used [86]. It was signalized that clopidogrel treatment may associate with development of new DU in patients with SSc [87]. Riociguat and aminaphtone seem to be a promising new treatment options for RP [88,89]. In a pilot study, a single dose of riociguat was well tolerated and resulted in rapid improvement in digital blood flow in some patient subsets with primary and secondary RP [88]. Aminaphtone is used in some European countries in the treatment of chronic venous insufficiency of the lower limbs, leg ulcers, and diabetic microangiopathy [89]. Six-month open feasibility study demonstrated that aminaphtone treatment increases skin blood perfusion and improves RP clinical symptoms, with sustained efficacy up to 6 months, even in patients with SSc [89]. Some positive effects of botulinum toxin –A (BTX-A) were reported, but its clinical meaning is still questionable [90]. A randomized controlled trial conducted on 40 patients with SSc showed that BTX-A did not significantly improve blood flow to the hands of patients with SSc associated RP, although there was a statistically significant clinical improvement of RP in hands treated using BTX-A [90]. A 3-year retrospective study on 15 patients revealed that BTX-A was generally well tolerated [91]. Similarly, BTX-B injections significantly suppressed the activity of RP and digital ulcers in patients with SSc without serious adverse events [92]. Weum and de Weerd [93] postulated that a single ultrasound-guided BTX injection around the radial artery provided precise administration and distribution of BTX in the perivascular space. The single injection technique was much less painful with minimal risk of temporary intrinsic muscle weakness compared with the multiple injections in the palm of the hand [93]. BTX-A can inhibit arteriole vasoconstriction in a dose-dependent manner by cleaving SNAP-25 in sympathetic
neurons, thus providing a theoretical basis for the treatment of RP [94].

In systematic review and meta-analysis of 14 randomized controlled trials, herbal medicine was found to be potentially safe and effective treatment for cold hypersensitivity in the hands and feet as well as for RP [95]. The most common herbal medicines were Cinnamomi ramulus or Cinnamomi cortex and Zingiberis rhizome [95]. However, according to the authors, the high risk of bias in all studies prevents definitive conclusions [95]. Ginkgo Biloba, acupuncture and other alternative therapies (laser and nutritional supplements) did not prove to impact the frequency, duration and severity of RP [7,51].

Sympathectomy

In patients with RP refractory to medical treatment digital periarterial sympathectomy can be the good treatment option, especially in cases of arteritis associated with very severe spasms [96]. Endoscopic thoracic sympathectomy should be considered an ultimate choice for patients with RP who have treatment-resistant severe symptoms and serious complications, disturbed social and daily lives, and impaired quality of life [97]. All patients should be properly informed before the surgery about the possibility of a high rate of recurrence (66,6%) [97].

In summary, current pharmacologic treatments fail to completely control RP and prevent digital ulcers, and they are not tolerated by many patients. Therefore, the treatment of patients with RP should not only focus on the vascular response, but also on the lifestyle interventions and contemplate pain education, cognitive behavioral therapy, and exercise therapy. Collaboration between healthcare professionals, patient organizations and the public can positively influence health utilization by encouraging involvement of people in their own healthcare. Such partnership is necessary for the very early diagnosis of SSc.

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References


97: 843-850.


Table 1: Non-autoimmune causes of secondary Raynaud’s phenomenon

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive vascular diseases</td>
<td>Atherosclerosis, microemboli, diabetic angiopathy, thromboangiitis obliterans (Buerger’s disease)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Adenocarcinomas (lung, breast, ovarian), hematological malignancies</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>Hypothyroidism and hyperthyroidism, carcinoid syndrome, pheochromocytoma</td>
</tr>
<tr>
<td>Haematological disorders</td>
<td>Cryofibrinogenemia, cold agglutinin disease, paraproteinemia, multiple myeloma, polycythemia, microthromboembolism</td>
</tr>
<tr>
<td>Infections</td>
<td>Parvovirus B19, Cytomegalovirus, Hepatitis B and C, Helicobacter pylori, Mycoplasma</td>
</tr>
<tr>
<td>Mechanical factors</td>
<td>Crutch pressure, thoracic outlet syndrome, scalenus anticus syndrome, cervical rib, carpal tunnel syndrome</td>
</tr>
<tr>
<td>Occupational and/or environmental exposure</td>
<td>Vibration (white hand vibration syndrome), trauma to the upper extremities (hypothenar or thenar hammer syndrome), frostbite, vinyl chloride monomer, chlorinated and non-chlorinated solvents (acetone, toluene, xylene, etc.)</td>
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</table>
Figure 1: Raynaud’s phenomenon. Episodes of vasospasm in the fingers characterized by color changes: (a) white/pallor; (b) blue/cyanosis
Figure 2: Nailfold capillary morphology: (a) normal capillaries; (b) abnormal morphology: marked tortuosity with varied appearance, dilated and giant capillaries. Magnification: ×200.
Figure 3: Morphological patterns specific to various SSc microangiopathy stages: (a) early pattern; (b) active pattern, (c) late pattern. Magnification: ×200.
Figure 4: Thermogram under standard baseline conditions of the dorsum of the hand of a patient with Raynaud’s phenomenon, showing reduced temperatures of the fingers compared with the dorsum of the hand. FLIR T420 thermography camera (FLIR Systems AB, Taby, Sweden).
Figure 5: Monitoring of patients with the primary Raynaud’s phenomenon and at risk of systemic sclerosis and other connective tissue diseases.