

Importance of identification and treatment of Raynaud's phenomenon

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Raynaud's phenomenon (RP) is a stress- or cold-temperature-induced, recurrent, but transient digital ischemia, which is characterized by a demarcated pallor and followed by a re-flow of blood to the digits, that appears as erythema, cyanosis or both. RP is differentiated into primary and secondary forms. Identification of the form secondary to autoimmune phenomenon is essential, because of the potential for complicated outcomes, internal organ involvement and more frequent need for pharmacological treatment. When a secondary form of RP is identified, especially in the case of systemic sclerosis (SSc), internal organ involvement from the disease process directs therapy. It is thought that this internal organ involvement is a manifestation of the same vasospastic propensity that RP represents. Thus, it is possible that a heightened understanding of the pathogenesis of RP demands a more aggressive intervention for secondary RP associated with SSc. This becomes especially important as therapy, in addition to the traditional therapies that improve vasodilatation and inhibit vasoconstriction, are developed. This is possibly best illustrated through the role of statins. These agents impair abnormal vascular remodeling, possibly through effects on apoptosis of the pericyte; a cell that has the potential to develop into a vascular smooth muscle cell and fibroblast and could be important for the development of SSc.

Digital pallor, which must be present to diagnose Raynaud's phenomenon (RP), is the clinical manifestation of an episodic vasoconstriction of digital arteries and arterioles. RP has a prevalence of 3–5% in the general population and has a hereditary component [1]. In most patients with RP who are seen by a general practitioner, the condition is simply an exaggeration of the physiologic response to cold temperatures [2]. Importantly, however, it can also portend a serious underlying disease. Thus, from a prognostic standpoint, it is helpful to distinguish between primary (idiopathic) and secondary forms.

The primary form (Raynaud's disease) is often symmetrical and lacks tissue necrosis, ulcerations, gangrene and nailfold capillary abnormalities. By contrast, an episode of RP secondary to an associated connective tissue disease (Raynaud's syndrome) is often more severe, asymmetric and may have evidence of microvascular disease on microscopy of nailfold capillaries. Clinicians can perform this microscopic examination of a patient's cutaneous capillaries by placing a drop of immersion oil on the patient's skin at the base of the fingernail and viewing the area with a hand-held ophthalmoscope set at 10–40 diopters [1]. The abnormal capillaries of patients with an underlying rheumatic disease appear indistinct, in contrast to normal well-demarcated vascular loops. The dilated capillaries occur from the dropout of

blood vessels with secondary hyperplasia of remaining capillaries. Secondary forms of RP caused by medications, extrinsic vascular obstruction and paraproteinemias do not result in these nailbed changes. In addition to these microscopic changes, laboratory evidence of a positive antinuclear antibody, connective tissue selective autoantibodies and elevated erythrocyte sedimentation can be helpful for distinguishing RP in association with a connective tissue disease, such as systemic sclerosis (SSc), from other causes such as vibration trauma [3].

The importance of making this distinction between primary and secondary forms of RP is highlighted by proposed early SSc criteria, in which RP associated with both capillary and serology abnormalities was sufficient for diagnosis of SSc [4]. Early diagnosis of secondary RP due to SSc is essential for associated disease monitoring and intervention. Additionally, the theory that secondary RP may simultaneously affect the terminal arterial supply of internal organs and that vasospastic activity progresses to a vasculopathy, or structural derangement of the microcirculation, underscores the importance of understanding and treating secondary RP due to SSc [5,6]. The current approach to treatment of SSc is organ-specific; however, a more aggressive approach to RP in this heterogeneous disorder, characterized by immune activation, vascular

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dysfunction and intravascular and extravascular fibrosis, is unproven but logical and may improve overall outcome.

Pathogenesis of Raynaud's phenomenon secondary to autoimmune disease

In contrast to the functional abnormality observed in primary RP, vasculature function and structure is compromised in patients with secondary RP. Although not completely understood, endothelial cell apoptosis, upregulation of cytokine, growth factors and adhesion molecules, and pericyte activation contribute to endothelial dysfunction in secondary RP [7]. Small arteries and arterioles develop a concentric, fibrotic intimal lesion, oftentimes with associated intravascular thrombi [8]. It is the interaction between endothelium, platelets and vasoactive substances that results in this dysfunction, with supportive laboratory evidence to suggest that impaired endothelial-dependent vasodilatation in response to vessel injury is important to the pathogenesis of RP in SSc patients [3].

Normal endothelium appropriately balances the production of vasodilator substances, such as nitric oxide and prostacyclin, with vasoconstrictors, such as endothelin-1. It has been shown that cold temperature can diminish production of prostacyclin [9]. Although a causative role of these substances in secondary RP is unclear, the higher serum levels of an endogenous inhibitor of endothelial NO synthetase and endothelin-1 in a small group of patients with secondary RP is intriguing [10]. Additionally, anti-endothelial cell antibodies are significantly elevated in SSc patients, particularly in those with pulmonary hypertension [11].

Three vasoconstrictors, an α 2-adrenergic agonist, serotonin (a platelet release product) and angiotensin II, have also been shown to increase digital cooling [12]. Increased peripheral expression of α 2-adrenoreceptors in the vascular smooth muscle with cold-temperature exposure or vascular stress may also play a key role in the pathogenesis of autoimmune RP. Dermal arterioles from uninvolved SSc skin have demonstrated this increase in α 2-adrenoreceptors [13]. It is noteworthy that, in addition to vasoconstriction, endothelin-1 and angiotensin can also have profibrotic effects, which is important in the pathogenesis of SSc.

Although vascular endothelium and platelet release factors play a major role in controlling vascular tone, thermoregulation is mediated by

sympathetic neural control of skin blood flow through the noradrenergic vasoconstrictor system and a sympathetic active vasodilator system [14]. Thus, the vasospastic tendency in secondary RP may be influenced by dysregulated noradrenergic and noncholinergic neuropeptides. Soluble neuromediators, such as substance P, neuropeptide Y, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide, epinephrine and norepinephrine, interact with the vascular wall and may be thermally stimulated. Importantly, the peripheral endings of the primary afferent sensory neurons not only influence vascular tone, but also effect vascular permeability and the mitogenesis of smooth muscle cells, fibroblasts, and lymphocytes [15]. The autonomic and peripheral neuropathy seen in SSc highlights the importance of understanding the role of these mediators in disease pathogenesis [16].

Pericytes, which surround endothelial cells in precapillary arterioles, capillaries and post-capillary venules, are important for the development, maturation and maintenance of the vascular system, and may play a role in the pathogenesis of secondary RP. They are normally relatively undifferentiated cells and serve to support the vasculature, however, under stress they can differentiate into fibroblasts, smooth muscle cells or macrophages. It has been demonstrated that PDGF receptors (PDGFRs) are expressed by activated microvascular pericytes in patients with secondary RP and in early SSc patients, but not in those with primary RP or late-stage scleroderma [5]. Additionally, in a study of 46 patients with SSc, all had anti-PDGFR-stimulating antibodies [17]. The upregulation of PDGFR in scleroderma fibroblasts and the involvement of PDGF in the progression of pulmonary arterial hypertension in animal models have been demonstrated [18,19]. It is unclear whether the PDGFR–autoantibody interaction induces the vasculature stress that causes the transformation of pericytes into pathogenic fibroblasts and vascular smooth muscle cells, or if the vasculature dysregulation of endothelium through its interaction with neuropeptides results in transformation of pathogenic pericytes, which subsequently interact with the PDGF autoantibody. In both models, aggressive modulation of vascular stress may improve SSc outcomes. It is also unclear if imatinib mesylate, a small molecule inhibitor that exerts selective inhibition of the PDGF pathway and is being studied in SSc, affects the pericyte [20].

Treatment of Raynaud's phenomenon

The current approach to RP is based on severity. Primary RP may be well controlled with non-pharmacologic therapy, including avoidance of cold temperature, smoking and vasoconstrictive drugs, as well as active warming measures (such as wearing hat and gloves). Although there are no randomized control trials on smoking cessation, there are vasoconstrictive substances in cigarettes [1].

Drug therapy is often required if nonpharmacologic therapy fails. Historically, dihydropyridine calcium channel antagonists are often considered for their vasodilatory effects, and they may be effective for patients with RP secondary to systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis or polymyositis [21]. The usual benefit is an approximately 30% reduction in frequency of RP attack [1]. However, use of these agents often demonstrates a lack of efficacy secondary to the low dose used or the occurrence of adverse effects, including peripheral edema, headache and hypotension [22]. Unfortunately, these agents are often insufficient treatment for the severe RP associated with SSc.

RP associated with SSc can be complicated by digital pits, digital ulcerations or infection. Digital ulceration secondary to trauma often will not improve with vasodilator therapy alone, and requires protection of the digits from further trauma [1]. However, there are two separate randomized control trials, one with intravenous iloprost (prostacyclin) and the other with sildenafil, which are suggestive of improved ulceration healing [23,24]. If infection is not present, sympathetic blocks with guanethidine or other surgical options, such as regional sympathectomy or radical distal microarteriolytic, can prevent the need for amputation [25]. However, concurrent infection all too often results in digital amputation [1].

Other pharmacologic treatment options, including angiotensin II inhibitors, selective serotonin reuptake inhibitors, phosphodiesterase-5 inhibitors and nitrates (topical and oral), have been studied in randomized, controlled trials and have proven to be both safe and effective in decreasing the severity and frequency of attacks. Additionally, low-molecular-weight heparin therapy was studied in a prospective parallel group trial and was found to be well tolerated and potentially beneficial in patients with severe RP [26]. The use of α -blockers is limited by significant hypotension. For severe cases of autoimmune RP, prostacyclin agonists and

endothelin receptor blockade have been used [21]. Endothelin receptor blockers decrease the development of new ulcerations, but do not help the resolution of existing ones [1]. In a small study, intravenous CGRP has been reported to improve severe secondary RP [27].

HMG-CoA reductase inhibitors (statins) have a dose-dependent effect on apoptosis in pericytes [28]. Pilot study data suggest that their use may improve autoimmune RP [29]. This is of particular interest, since statins display numerous effects that may be of potential benefit in preventing vascular remodeling and endothelial dysfunction in SSc patients [30]. Another agent probucol, which also reduces LDL oxidation susceptibility, may be useful for the symptomatic treatment of RP [31].

Alternative medicines, such as evening primrose oil, fish oils and ginkgo biloba, and supplementary treatment, such as acupuncture, low-level laser therapy and ceramic-impregnated gloves, have been investigated for use in RP in single trials. However, the mechanisms of action are not fully understood, division between primary and secondary RP in the treatment group is not always clear and the data have not been reproduced, thus these possible treatments will not be further reviewed.

Conclusion

Secondary RP, particularly when secondary to SSc, frequently fails conventional nonpharmacologic intervention, thus it is important to distinguish this form from primary RP. Currently, the early identification of SSc translates into aggressive internal organ monitoring, and treatment of specific pulmonary, renal and gastrointestinal involvement. It is likely that internal organ involvement is in part a manifestation of the same vasospastic propensity. Thus, in addition to early identification, early and aggressive intervention for RP may be warranted.

Future perspective

Pharmacologic therapy for RP currently focuses on inhibition of vasoconstriction and improving vasodilation. The search for better tolerated treatment of secondary RP needs to be expanded in order to address the components of the disease that make it different from primary RP. Vascular remodeling, evidenced by abnormal microscopic capillaroscopy, is an important target for disease intervention. The interruption of this vascular remodeling through the use of statin drugs may become an

important adjuvant treatment. Additionally, neuropeptide manipulation may also have an important role in the management of secondary RP. In addition to treating autoimmune RP, the efficacy of these treatments in retarding the progression of SSc could help further an understanding of the pathogenesis of SSc, particularly with regards to the interaction of the pericyte and PDGFR.

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Executive summary

It is essential to discriminate between primary and secondary forms of Raynaud's phenomenon

- Raynaud's phenomenon (RP) secondary to autoimmune disease has more severe outcomes and more frequently requires pharmaceutical interventions.

The pathogenesis of RP involves dysfunction of endothelium and platelets, and results in abnormal vasoactive neuropeptides

- It is possible that the microvascular pericyte, which can differentiate into fibroblasts and vascular smooth muscle cells and express PDGF receptors (PDGFRs), significantly contributes to autoimmune RP and early systemic sclerosis (SSc).
- Pharmaceutical interventions currently target enhancement of vasodilatation and inhibition of vasoconstriction.

Future perspective

- Inhibition of vascular remodeling, possibly through statin-induced apoptosis of pericytes, and neuropeptide manipulation may have a role in secondary RP management.
- Modification of PDGFR will likely have a role in both secondary RP and early SSc management.
- Aggressive early management of secondary RP is likely warranted; holding treatment until internal organ damage is evident is likely less efficacious.

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