

Raynaud's phenomenon and digital ischemia: a practical approach to risk stratification, diagnosis and management

Digital ischemia is a painful and often disfiguring event. Such an ischemic event often leads to tissue loss and can significantly affect the patient's quality of life. Digital ischemia can be secondary to a vasculopathy, vasculitis, embolic disease, trauma or extrinsic vascular compression. It is an especially serious complication in patients with scleroderma. Risk stratification of patients with scleroderma at risk for digital ischemia is now possible with clinical assessment and autoantibody profiles. Because there are a variety of conditions that lead to digital ischemia, it is important to understand the pathophysiology underlying each ischemic presentation in order to target therapy appropriately. Significant progress has been made in the last 20 years in defining the pathophysiological processes leading to digital ischemia in rheumatic diseases. In this article we review the risk stratification, diagnosis and management of patients with digital ischemia and provide a practical approach to therapy, particularly in scleroderma.

KEYWORDS: digital ischemia ■ digital ulcers ■ Raynaud's phenomenon ■ scleroderma

Inadequate blood flow to living tissue is an excruciatingly painful experience and threatens the life of the tissue involved. Death of digital tissue not only results in both disfigurement and functional disability, but it also is the clinical manifestation of an underlying systemic disease process. Although the differential for digital ischemia is broad, in this article we focus on digital ischemia in the setting of rheumatic disease, particularly in scleroderma.

Digital ischemia is an especially serious complication in patients with scleroderma. Morbidity from digital ischemia is remarkably high in patients with this rheumatic disease; 30% of patients with persistent digital ulcers develop irreversible tissue loss and it often requires hospitalization [1]. As a result, when ischemia threatens the livelihood of a digit, rapid aggressive actions must be taken to prevent permanent damage. One study reported that amputation occurs in one or more digits due to ischemia in 20.4% of patients with scleroderma, 9.2% of which have multiple digit loss [2].

Digital tissue vitality can be threatened by many pathological processes that compromise arterial blood supply. Thrombosis, vasculopathy, vasculitis, emboli and trauma can contribute to digital arterial compromise, and each process can be complicated by secondary vasospasm. Because all etiologies of digital ischemia are not alike, it is important to understand the pathophysiology underlying each ischemic presentation in order to target therapy appropriately. Significant progress

has been made in the last 20 years in defining the pathophysiological processes leading to digital ischemia in rheumatic diseases. This knowledge has led to many new treatment options.

Identifying patients at risk

Digital ischemia results from an inadequate supply of oxygenated blood to digital tissue. The presence of digital pain associated with pallor or cyanosis of the skin of the affected digit(s) is the first clinical sign of impending digital tissue loss. When confronted with a painful discolored digit, it is imperative to quickly determine the likely etiology of the ischemia so that appropriate therapy can be promptly initiated to prevent tissue injury. An immediate assessment for predisposing risk factors for vascular disease should be conducted to elucidate the cause of the ischemic event (TABLE 1).

Digital ulcers are representative of vascular involvement in scleroderma and occur in approximately 30–50% of patients with scleroderma [3,4]. Predicting the patients who are at high risk for the development of significant vascular involvement and subsequent digital loss is important. Such high-risk patients can be monitored closely to consider preventive measures, and treated early when ischemia occurs. Autoantibodies and microvascular damage, as seen in nailfold capillary microscopy, are indicators used to predict the onset of scleroderma or another connective tissue disease in patients initially diagnosed with primary Raynaud's phenomenon.

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Table 1. Differential for patients presenting with critical digital ischemia.

Large vessel	Medium vessel	Small vessel
Takayasu's Dissection	Polyarteritis nodosa	Lupus (SLE)
Thoracic outlet	Scleroderma	Buerger's disease
Atherosclerosis	Kawasaki's	Scleroderma
	Endocarditis	Cryoglobulinemia
	Hypercoagulability/APLS	Dermatomyositis and other CTDs
	Postsurgical	Hypercoagulability
	Trauma	Endocarditis
	Atherosclerosis	Paraproteinemia
		Polycythemia
		Dysfibrinogenemia
		Trauma
		Frostbite
		Postsurgical

APLS: Antiphospholipid syndrome; CTD: Connective tissue disease; SLE: Systemic lupus erythematosus.

Nailfold capillaries can be examined in the office using immersion oil placed on the skin and viewing the capillaries with either an ophthalmoscope, hand-held microscopes or dermlites [5,6]. The nailfold capillary changes in scleroderma are characterized by a decrease in the density of capillaries and a reduction in blood flow. Nailfold videocapillaroscopy (NVC) has enhanced our ability to classify the vascular patterns seen in scleroderma patients. The patterns, early, active and late, are described in detail by Cutolo and colleagues [7]. The three patterns correlate with both Raynaud's and scleroderma disease duration [8]. A decreased number of loops is considered by these investigators to be highly specific for secondary Raynaud's. Handheld NVC devices are now available and may eventually play a larger role in bedside nailfold capillary assessment [7].

Houtman and colleagues also determined that there is an inverse relationship between the severity of Raynaud's at first presentation and the capillary density in patients with connective tissue disease [9]. These findings were specifically noted in patients with manifestations of the scleroderma phenotype such as sclerodactyly, digital ulcers, tuft resorption and telangiectasias [9]. Other studies found that the association of the scleroderma specific antibodies, antitopoisomerase I and anticentromere antibody (ACA), with nailfold capillary microscopy increased the sensitivity in predicting that the presence of Raynaud's is associated with a connective tissue disease [10]. Patients presenting with Raynaud's phenomenon alone without a definite diagnosis who have a known scleroderma-related autoantibody (ACA, anti-Th/To, antitopoisomerase I, or anti-RNA polymerase III antibodies) and

nailfold capillary changes are 60-times more likely to develop definite scleroderma [11] than patients with Raynaud's phenomenon and normal capillary and negative serology. Patients with scleroderma who are positive for ACA are at an increased risk for severe digital ischemia and macrovascular events with digital loss [2,12,13]. In addition, among scleroderma patients, anti-Scl70 positivity and early-onset Raynaud's are associated with an increased incidence of digital ulcers [14]. Likewise, scleroderma patients with anti-PM/Scl-75/100 antibodies are also more likely to develop digital ulcers [15].

Therefore, it is now understood that a positive antinuclear antibody, especially with positive scleroderma specific antibodies, and abnormal nailfold capillaries as detected by capillaroscopy, are predictive of secondary connective tissue disease and are not seen in primary Raynaud's phenomenon [16-18]. ACA and anti-Th/To both predict capillary enlargement, and these antibodies in combination with antiribonucleoprotein predict capillary loss. Interestingly, each of these antibodies was associated with a distinct rate of microvascular damage. Koenig and colleagues followed digital vascular changes defined by nailfold capillary microscopy and noted that enlarged capillaries occurred earlier in patients with anti-RNA polymerase III than in patients with anti-Th/Tho antibodies [11]. The nailfold capillary changes occur the latest in the disease course in patients with ACA [11].

A variety of ulcers are often present on the hands of patients with scleroderma. Such ulcers are found at the tips of the fingers, and the dorsal surface of the proximal interphalangeal and metacarpophalangeal joints. The digital tip lesions are typically a consequence of ischemia and can be associated with pain, digital pits and loss of digital pulp. By contrast, the ulcers located on the dorsum of the proximal interphalangeal and metacarpophalangeals are thought to be related to trauma imposed upon the atrophic skin of contracted joints. Recently, Caramaschi and colleagues studied the risk factors for ischemic digital ulcers in patients with scleroderma [19]. They found that scleroderma patients with ischemic digital ulcers are characterized by early disease onset, delay in beginning iloprost (a prostacyclin analog) therapy, a smoking habit, and the presence of joint contractions. They proposed that a score reflecting the sum of these factors could be used to predict the risk of developing ischemic digital ulcers [19]. Alvernini and colleagues also identified major risk factors for digital ulcer development in scleroderma.

They evaluated 34 Italian patients with skin ulcers and studied them prospectively over a 20-month period. They found that the most significant, independent parameters associated with the development of skin ulcers were lupus anticoagulant and the presence of avascular areas on nailfold capillaroscopy. Elevated serum IL-6 levels suggesting underlying inflammation also correlated with the above findings [20]. Both in the Caramaschi study and the study recently conducted in Germany by Sunderkotter and colleagues found that male sex, diffuse scleroderma, anti-Scl 70 positivity, inflammation, and the presence of pulmonary hypertension correlated with a high probability of presenting with digital ulcers [21]. These observations all contribute to defining the clinical phenotype of the highest risk patients.

Another means of identifying patients at risk for the development of scleroderma-related digital ulcers is through genetic studies. Combining gene expression data with clinical phenotypes more clearly defines disease subtypes. Milano and colleagues recently conducted a study using DNA microarrays and gene expression profiling with 61 skin specimens from 24 scleroderma patients [22]. They were able to identify genes that had a high positive correlation with severe Raynaud's and limited scleroderma patients. In addition, they identified genes in the diffuse scleroderma subgroup that correlated highly with the presence of digital ulcers. Interestingly, three of the patients with digital ulcers were negative for antibodies to anticentromere antibody and antitopoisomerase antibody suggesting the genetic profiling is an additional means of characterizing seronegative patients [22].

Bos and colleagues also used gene expression profiling in peripheral blood cells in an attempt to distinguish clinical subtypes in systemic sclerosis [23]. They looked at the peripheral blood cells of 12 scleroderma patients and six controls and found that low expression of type I IFN response genes was associated with the presence of anticentromere antibodies. Increased expression of type I IFN was associated with the appearance of digital ulcers and the absence of anticentromere antibodies. As digital ulcer formation is believed to be at least partially related to imbalanced angiogenesis, and type I interferons are known to display antiangiogenic activity, the investigators speculated that there could be a role for increased type I IFN in the process of digital ulcer formation. This concept leads to another potential target in digital ulcer prevention. It is interesting, however, to note that Bos

reports an inverse relationship in gene expression profiling between anticentromere antibodies and digital ulcers, as they are typically associated together in the clinical setting [23].

Another predictor of digital ulceration is the capillaroscopic skin ulcer risk index (CSURI). The CSURI is a mathematical formula that combines the maximum capillary loop diameter, the number of megacapillaries and the total number of capillaries in the distal row to predict the onset of new digital ulcers in patients with scleroderma. If this tool is validated in a larger study, it could also be helpful in identifying at-risk patients, especially if used in combination with genetic profiles and clinical phenotyping [24]. In such cases, aggressive intervention and preventative measures could be taken to prevent ischemic complications.

Mechanisms of ischemia in scleroderma

■ Vasospasm

Vasospasm is observed in many of the rheumatic diseases and can manifest as benign reversible Raynaud's phenomenon, or can be associated with recurrent digital ischemia and tissue injury. The development of Raynaud's phenomenon ultimately occurs as a result of interactions between nerve endings, smooth muscle cells and the endothelium that is observed in the setting of soluble mediators (e.g., nitric oxide, prostaglandins and neuropeptides) and is influenced by the patient's surrounding environment, including temperature, smoking and stress. [25].

Primary Raynaud's disease (aka Raynaud's phenomenon) is a vasospasm that occurs primarily as a result of sensitivity to cold temperatures or emotional stress. It occurs in 4–20% of women and 4–13% of men in the healthy population and varies by geographic region [26]. It is more common in young women, is entirely reversible, painless, and does not progress to tissue injury [27]. Several studies demonstrated a significant familial aggregation in primary Raynaud's which suggests an inherited defect in thermoregulation [28,29]. Primary Raynaud's is associated with distal digital color changes that progress from white to blue to red, representing the initial ischemia from the vasospasm (white), the subsequent slow circulation leading to increased amount of deoxygenated blood (blue), and the final hyperemic state after vessel dilation (red). All three stages of color change do not need to be present in order to diagnose Raynaud's (Box 1) [30]. Although many patients with rheumatic disease have Raynaud's

Box 1. Making the diagnosis of Raynaud's.

- Ask the following questions:
 - Are your fingers unusually sensitive to the cold?
 - Do your fingers change color when they are exposed to the cold?
 - Do they turn white, blue or both?
- Confirmed if positive response to all three questions
- Excluded if response to second and third questions are negative

phenomenon, without signs of tissue injury the presence of primary Raynaud's is not associated with an underlying connective tissue disease [31].

Secondary Raynaud's also occurs in response to cold temperature or emotional stress; however, it occurs in the setting of underlying acquired vascular disturbance and is often associated with digital pain and ischemic ulcers. It is occasionally associated with gangrene, which can lead to tissue loss or digital amputation. Secondary Raynaud's is observed in 95% of scleroderma patients and is often the initial manifestation of the disease [32,33]. It can lead to critical ischemia in scleroderma because it can be associated with a luminal narrowing greater than 75% of digital arteries due to underlying intimal fibrosis and luminal occlusion by thrombi [34,35]. Endothelial cell injury and activation lead to vascular dysfunction and vasospasm that can quickly obstruct the already marginal blood flow of the vasculopathic digital arteries.

■ Vasculopathy

The microvasculature and macrovasculature are both involved in the development of digital ischemia in patients with scleroderma [36]. In scleroderma microangiopathy, a combination of intimal proliferation, medial hypertrophy, and adventitial fibrosis result in the narrowing of the vessel's lumen and leads to progressive ischemia [37,38]. A complex interaction between activated endothelial cells, unregulated smooth muscle cells and pericytes, along with components of the extracellular matrix and intravascular circulating factors, is thought to contribute to the abnormal vascular reactivity and occlusive scleroderma vascular disease. Digital ischemia is one of the subsequent complications of this process. Macrovascular disease has been studied less than microvascular disease in scleroderma; however, it too plays a significant role in digital ischemia. Darbich and colleagues evaluated patients with scleroderma and found ulnar

involvement in 56% of their 27 studied patients [39]. Hasegawa and colleagues used arteriography to evaluate patients with scleroderma who exhibited digital ulcers or gangrene [40]. They found that macrovascular involvement was present in seven out of eight of these scleroderma patients. In addition, vascular disease was not limited to the digit with ulcerations and gangrene but was also found in the surrounding nonulcerated digits [40].

Interestingly, Caramaschi and colleagues recently noted that all of their scleroderma patients with both micro- and macrovascular disease, incurred digital amputation. Interestingly, in the absence of macrovascular disease, patients did not develop digital necrosis with amputation. They proposed that the combination of both micro- and macrovascular involvement exceeds the compensation capacity of peripheral circulation and thus places the patients at an elevated risk of severe complications [19].

■ Vasculitis

The association of vasculitis and scleroderma is unusual but is reported in the literature. Of these cases, the most commonly reported vasculitis observed in scleroderma is antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [41]. Perinuclear ANCA seropositivity is known to predict vasculitis in patients with scleroderma [42,43]. Cases of ANCA vasculitis typically present in scleroderma as a pulmonary-renal syndrome or more commonly an ANCA-associated glomerulonephritis, although reports exist with vasculitis of the nerves and skin [44–46]. ANCA is associated with digital ischemia in some patients with Wegener's granulomatosis [47–49] and we have witnessed digital ischemia in a patient with scleroderma and ANCA-associated vasculitis.

■ Thrombotic phenomena

Although vein thrombosis and CNS events (e.g., stroke) are more likely, one other cause of digital gangrene in connective tissue disease is an associated hypercoagulable state due to antiphospholipid syndrome (APLS). APLS is believed to not only cause a thrombotic microangiopathy, but there is also some *in vitro* evidence that suggests that certain antiphospholipid antibodies (aPL) may be proatherogenic [50,51]. Interestingly, anti- β 2glycoprotein 1 was recently reported to be independently associated with macrovascular disease in scleroderma. Boin and colleagues found that patients with digital loss in scleroderma were much more likely to be anti- β 2GPI

positive and that these patients also ultimately have higher mortality rates [12]. The vascular events were associated with IgA and IgM isotypes of anti- β 2glycoprotein-1 and not the IgG isotype suggesting that these antibodies were a secondary phenomenon and not a causative factor.

Diagnosis

The approach to the patient with digital ischemia begins with a careful history that should guide the physician towards the etiology of the disease (TABLE 1). The history is followed by a thorough physical examination with particular focus on the patient's vasculature and skin. This examination will often clarify the underlying diagnosis, the size of vessels involved and the presence or absence of critical vascular compromise. On initial evaluation it is important to document the patient's bilateral blood pressures and to look for any asymmetry in pressure or pulses. Asymmetrical blood pressures and asymmetrical or nonpalpable pulses can be an indication of underlying macrovascular disease as can be seen in vasculitis, atherosclerosis, embolic disease or extrinsic vascular obstruction. A positive Allen's test in the wrists is suggestive of medium-vessel involvement and should ideally be performed in all patients with severe Raynaud's and refractory digital ulcers on routine examination [52,53]. It is essential to listen over major arteries for bruits as this can provide insight on luminal narrowing, which is noted most often in atherosclerosis, but is also observed with underlying vasculopathy. Once these parameters are evaluated, it is necessary to look for physical signs that can direct one to the underlying diagnosis. A meticulous examination of the skin should include evaluation for sclerodactyly, telangiectases, hypopigmentation, digital pitting, loss of digital pulp or calcinosis cutis, all of which would suggest scleroderma. Periungual capillary loop dilation is also a key finding and will place the patient in the group of patients with connective tissue diseases and can help differentiate between primary and secondary Raynaud's. The presence of livedo reticularis or livedo rasemosa would be suggestive of a secondary process such as antiphospholipid syndrome, while splinter hemorrhages, petechiae and/or purpura could point the examiner towards an underlying vasculitis.

Once the physical examination is complete, laboratory tests should be sent for further evaluation. However, if critical digital ischemia is present by examination, then it is an emergency and it is important not to wait until for all test results to be returned before initiating treatment.

A listing of recommended laboratory tests is presented in TABLE 2, but it should be recognized that the history and examination will often dictate the priority laboratory testing required.

Imaging

■ Doppler

Noninvasive assessment of the peripheral circulation will supplement the physical examination and may provide clues as to the cause and size of the vessels involved. Doppler ultrasound is a useful tool and a relatively cost-effective way to evaluate patients with digital ischemia. The use of ultrasound is reported to differentiate between vasculopathy and vasculitis. In vasculopathy, the luminal narrowing is evident and the digital arteries can demonstrate decreased digital pulsation and are often chronically occluded. Alternatively, patients with vasculitis will often have an ultrasound image consistent with acute arterial occlusion [53,54]. Stafford and colleagues used ultrasound to evaluate macrovascular disease in scleroderma and described significant arterial narrowing with arterial walls characterized by smooth thickening along their entire length [52]. We recommend using Doppler ultrasound in the initial evaluation of all patients presenting with digital ischemia in order to quickly and accurately diagnose the size of vessels involved and to determine if surgical intervention is a viable option.

Laser Doppler imaging is a useful research tool used to evaluate microcirculatory flow [55]. Because laser Doppler is able to assess more than one area of the hand at any given time and it has been shown to be more effective than a single probe Doppler [55]. Laser Doppler imaging can also be used to differentiate between primary Raynaud's from patients with scleroderma [56]. Murray and colleagues suggested that combining laser Doppler with other imaging modalities such as nailfold capillaroscopy and thermal imaging is more effective than laser Doppler alone, but thermal imaging is not yet widely available [57].

■ Angiogram

Angiography is a well-established imaging modality used to evaluate vascular disease. Digital arteriography was reported as far back as the 1960s when several groups observed patients whose digital vasculature was evaluated with this technique [58-60]. Takaro and colleagues noted the diagnostic utility of arteriography as they demonstrated both micro- and macrovascular involvement in patients with scleroderma, and noted digital hypervascularity in patients

with Raynaud's [60]. Dabich and colleagues later described a 'characteristic pattern' of arterial involvement in the hands of patients with scleroderma. They noted, "The arch is usually of the balanced variety with broad communications between the ulnar and radial components. The radial artery is usually spared and the ulnar artery is frequently involved. The superficial arch and common digital arteries are most often uninvolved, while the proper digital arteries are obstructed in almost all patients in the mid and distal portions of the fingers" [39].

Arteriography is now used in specific cases of digital ischemia when the underlying cause is in question or the option of surgery is considered. Park and colleagues recently studied a cohort of 19 scleroderma patients and recommended that patients with scleroderma and digital ulcers or severe Raynaud's phenomenon should consider angiography with ulnar revascularization because of the increased risk of digital loss with macrovascular disease [53]. Angiography was also used to confirm the site of vascular occlusion prior to peripheral artery bypass grafts in the hands and feet of two patients with severe Raynaud's [61]. The clinical application of angiography continues to grow, and based on the available data we recommend using this application to define the vascular anatomy of patients with severe digital ischemia who are candidates for angioplasty or surgery.

■ Magnetic resonance angiography

Magnetic resonance angiography (MRA) is a newer, imaging modality that is used to evaluate vascular abnormalities of the hand. It is a fast, noninvasive exam that takes less than 5 min to perform and produces high-quality images [62]. Allanore and colleagues used MRA to evaluate both arterial and venous lesions in patients with scleroderma. These investigators not only found substantial arterial and venous damage in the hands of these patients, but they also noted that the vascular lesions were associated with the extent of clinical disease and phenotype suggesting that MRA may be useful in evaluating disease progression [63]. MRA showed some promise in evaluating patients with Raynaud's phenomenon when compared with conventional angiography. Vasodilators are often used with conventional angiography and, as a result, the true degree of vasospasm is often underestimated [62,64]. In addition, diagnosing connective tissue disorders is also possible with MRA as these disorders in general are defined by characteristic findings on imaging such as

tapering of the ulnar, radial and proper digital arteries, superimposed vasospasm and areas of narrowing found between normal segments. The use of contrast-enhanced MRA instead of standard angiography prior to vascular surgery of the hand was favored by some groups because it is a less invasive form of imaging [62]. The use of MRA, however, requires experienced radiologists [65]. To our knowledge, there are no large studies, to date, comparing MRA and conventional angiography use for imaging of the vasculature of the hand. Until such a study is conducted, conventional angiography should still be considered the gold-standard for evaluating the vascular anatomy of the hand, particularly in the preoperative setting.

Therapeutic interventions

The approach to treating digital ischemia can be daunting given that it must be initiated quickly and effectively, and there are many new therapeutic options available. A recent study conducted in Germany by Herrgott and colleagues examined patients with digital ischemia who presented to subspecialists (rheumatologists, dermatologists, pulmonologists and nephrologists). Their study demonstrated that cutaneous vascular complications of scleroderma are often undertreated or treated inappropriately [66]. It will be imperative in the future to standardize care for the management of the ischemic digit. Here we review the data and describe our approach to therapy. It is important to note that many of the treatments discussed later are applicable to the management of Raynaud's, but are not recognized or demonstrated to be effective for healing or the prevention of digital ulcers.

■ Nonmedical therapy

The initial approach to treating a small ischemic digital area that presents as a mild discoloration at the tip of the finger is often aimed at symptom control and improving tissue integrity and viability. Avoiding triggers such as cold temperatures and stress are helpful in reducing vasoconstriction. This includes adjustment of lifestyles to avoid extreme cold, shifting temperatures and wearing appropriate clothing to keep the whole body warm. Studies examining conditioning, biofeedback and relaxation techniques show variable outcomes. One large, controlled trial in primary Raynaud's phenomenon found no benefit in the use of biofeedback and its use is also not recommended for secondary Raynaud's phenomenon [67]. The use of gloves is helpful in protecting the skin from trauma

Table 2. Laboratory evaluation in digital ischemia.

Differential diagnosis	Laboratory testing
Scleroderma	ANA titer and pattern (i.e., centromere), Scl-70 antibodies, RNP polymerase III antibodies (i.e., β -2 glycoprotein, anticardiolipin antibody, lupus anticoagulant)
Vasculitis (e.g., SLE, ANCA-related vasculitis, cryoglobulins and rheumatoid vasculitis)	ANA, pANCA, cANCA, MPO, PR3, cryoglobulins, anti-dsDNA, RNP, Smith, C3, C4, Ro, La, ESR, CRP, RF, CCP, antiphospholipid antibodies
Embolic	Antiphospholipid antibodies
Other	CMP, CBC with diff, TSH, lipid profile, urinalysis with micro, SPEP, UPEP

ANA: Antinuclear antibody; cANCA: Cytoplasmic neutrophil cytoplasmic antibody; CCP: Cyclic citrullinated peptide; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MPO: Myeloperoxidase; pANCA: Perinuclear antineutrophil cytoplasmic antibody; PR3: Proteinase 3; RF: Rheumatoid factor; RNP: Ribonucleoprotein; SLE: Systemic lupus erythematosus; SPEP: Serum protein electrophoresis; TSH: Thyroid-stimulating hormone; UPEP: Urine protein electrophoresis.

and keeping it warm in the cold. Ischemic lesions are painful and appropriate pain control is needed with acetaminophen, a nonsteroidal anti-inflammatory and/or narcotics. Smoking cessation is essential given that smoking can contribute to the underlying vascular disease. In addition, topical creams and lotions can be applied to keep the affected skin moist. For more serious lesions, occlusive dressings serve to protect them from trauma and to promote healing. Hydrocolloid dressing also promotes healing of digital ulcers [68].

Patients who experience a critical ischemic event should be allowed to rest in a warm environment. This may mean hospitalization or taking leave from work for home care. Preventing trauma to the digits by avoiding typing or repetitive hand work can improve blood flow and recovery in conjunction with other measures.

■ Medication

The agents used for the treatment of Raynaud's phenomenon and scleroderma vascular disease can be divided into agents that primarily work as vasodilators, those that have the potential to protect vessels from disease progression, and agents that prevent thrombosis. A given agent may have more than one effect. For example, prostaglandins can be vasodilators and protective of vessel damage. Our discussion will first outline medications in current use and then we will focus on our specific approach to critical ischemia.

Vasodilator therapy

■ α -adrenergic blockers

α -adrenergic blockers were the first agents used with some success in treating Raynaud's phenomenon. α -2 adrenoreceptors are present throughout much of the vascular system and they play a significant role in cutaneous thermoregulation

[38]. Prazosin was studied by several groups of investigators for the treatment of Raynaud's phenomenon [69,70]. A subsequent Cochrane systematic review concluded that Prazosin is modestly effective in treating Raynaud's secondary to scleroderma, but the side effects can limit tolerability [71]. In addition, several other members of this class of medications demonstrated a clinical benefit [69,72]. Interestingly, the α -2c receptor, a subtype of the α -adrenergic receptor, is specifically upregulated during cold exposure [73]. As a result, Wise and colleagues studied the efficacy and tolerability of a selective α -2c-adrenergic receptor blocker in scleroderma patients with vasospasm. They found that the time to rewarm a patient's finger affected by secondary Raynaud's after a cold challenge was decreased after ingestion of the drug, thus suggesting a clinical response. [74]. Although this agent is not currently under study, this is an exciting new area with therapeutic potential. From a practical viewpoint, α -adrenergic blocking agents are not the first-line therapy for critical ischemia but the potential of selective new agents for the prevention of vasospasm in the digital and thermoregulatory circulation is of major interest.

■ Calcium-channel blockers

Calcium-channel blockers are widely used for Raynaud's phenomenon and act on vascular smooth muscle to cause arterial dilation. Thompson and colleagues published a meta-analysis looking at their use in Raynaud's phenomenon and reported moderate efficacy at best [75]. In addition, the magnitude of effect of calcium-channel blockers is much smaller for patients with secondary Raynaud's phenomenon than in patients with primary Raynaud's although numbers may be higher as appropriate dosing is not always reached. Herrgott and

colleagues showed that 92% of the German centers they surveyed did not aim for the recommended 360 mg of diltiazem or for the goal of 10 mg of amlodipine, and 80% did not aim for at least 40 mg of Nifedipine [66]. Longer acting formulations can be used to minimize side effects of the medication and increase tolerability. Calcium-channel blockers are also effective in the treatment of digital ulcers [76].

■ Nitrates

Glyceryl trinitrate (GTN) has been studied in various means of administration. Initially the intravenous form was evaluated only to find that while there was an initial response, the effect was eventually blunted with disease progression [77]. GTN patches (0.2 mg/h) were studied a few years later in patients with primary Raynaud's and in patients with Raynaud's secondary to scleroderma. The treatment was effective in both groups; however, the side effects, and in particular headaches, were intolerable. Finally, Anderson and colleagues used GTN in the topical ointment formulation and found that it was effective with minimal side effects, even in patients with very thick skin [78]. While topical nitrates can improve digital blood flow, the use of these agents is limited by practical issues of difficulty with repeated application and side effects. Newer formulations are being tested and suggest some benefit in reducing Raynaud's condition score [79]. It is our practice to use topical nitrates in conjunction with another vasodilator such as a calcium-channel blocker during periods of critical ischemia of a digit.

■ Phosphodiesterase inhibitors

Phosphodiesterase inhibitors (PDE-Is) work by elevating levels of cGMP, causing intracellular calcium levels to fall, leading to vascular smooth muscle relaxation. Through this mechanism, PDE-Is cause vasodilation and increase perfusion to distal tissues [80]. This class of drugs has demonstrated significant effects in patients with digital ischemia [81–84]. The five drugs available in this class of medications include sildenafil, tadalafil, vardenafil, pentoxifylline, and cilostazol; the first two of these are well-studied. Fries and colleagues conducted a double-blind, placebo controlled, fixed dose, crossover study in 16 patients to evaluate the effects of sildenafil on symptoms of capillary perfusion in patients with Raynaud's. They found that sildenafil was associated with a decreased frequency and duration

of Raynaud's as well as a decreased Raynaud's Condition Score. Capillary blood flow velocity increased in individual patients and the mean capillary blood flow velocity of all patients who received sildenafil more than quadrupled [81]. Interestingly, Shenoy and colleagues reported in a double-blind, randomized placebo controlled trial that tadalafil decreased the severity and duration of Raynaud's attacks, healed digital ulcers and improved endothelial dysfunction in cases of secondary Raynaud's patients who were resistant to other vasodilators [85]. By contrast, a recent randomized placebo controlled trial using tadalafil suggested no benefit over placebo [86]. Unfortunately, the patient numbers were small as only 39 patients with scleroderma were enrolled. Larger randomized controlled trials are still required to validate the use of PDE-Is in secondary Raynaud's. In our uncontrolled experience, we have clinical success using a PDE-I for severe Raynaud's secondary to scleroderma when used in conjunction with a calcium-channel blocker but often see less benefit with the PDE-I alone.

■ Prostacyclins

Prostanoids are beneficial to both the micro- and macro-vasculature as they induce vasodilation, increase intracellular cAMP and prevent smooth muscle proliferation [87]. Prostacyclins in particular are found to be an effective therapy for Raynaud's and digital ischemia. Intravenous iloprost is now a popular intervention outside the USA for the treatment of severe Raynaud's secondary to scleroderma. Intravenous iloprost is known to decrease the frequency and severity of attacks and prevents and heals digital ulcers [88,89]. Cyclic iloprost is now used for severe Raynaud's and digital ulcers using various protocols [19,88,90–93]. These reports suggest that intermittent use of prostacyclin by intravenous delivery can prevent digital ischemic events. Low dose (0.5 ng/kg compared with 2 ng/kg bodyweight per min) iloprost was shown to be equally effective [94]. Several authors reported that subcutaneous treprostanil is also effective in the treatment of severe digital ulcerations [87,95]. Of note, the efficacy of oral prostacyclins was also studied in the last decade for treatment of severe Raynaud's and digital ulceration. However, several trials using oral iloprost, beraprost and cicaprost showed no significant benefit over placebo [96–98]. A trial testing a new formulation of oral treprostinil is underway for the treatment of digital ulcers in patients with

scleroderma. Inhaled preparations of treprostinil and iloprost are available but not studied in the treatment of Raynaud's or digital ischemia.

■ Intravenous & transdermal prostaglandin E1

Transdermal prostaglandin E1 ethyl ester was also reported to be effective in improving blood flow in capillaries in the skin in systemic scleroderma patients and in healing acral skin lesions in patients with scleroderma [99,100], however, this agent is not readily available. Intravenous prostaglandin E1 is used in the treatment of Raynaud's and is an alternative to prostacyclin therapy [101].

■ Angiotensin converting enzyme inhibitors & angiotensin receptor blockers

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers were also studied in scleroderma in relation to digital ischemia. Initial studies showed promise as captopril produced a significant improvement in cutaneous blood flow; however, it was not shown to alter the frequency or severity of Raynaud's attacks [102]. A subsequent study also showed promise as enalapril demonstrated a reduction in the frequency of primary Raynaud's attacks [103]. However, in a further study and investigation with clinical trials, there were ultimately mixed results [104]. Most recently, Gliddon and colleagues organized a multicenter, randomized, double-blind, placebo-controlled study evaluating quinapril 80 mg/day, or the maximum tolerated dosage, in over 200 patients with limited scleroderma or with Raynaud's phenomenon and the presence of scleroderma specific anti-nuclear antibodies [105]. They treated the cohort for 2–3 years and were unable to demonstrate any benefit in limiting the occurrence of digital ulcers or influencing the frequency or severity of the Raynaud's episodes [105]. As a result, this class of medications is not recommended for treatment of Raynaud's or digital ulcers as a first-line or monotherapy.

■ SSRIs

The selective serotonin reuptake inhibitors have the potential of increasing regional blood flow by blocking the uptake of the vasoconstrictor serotonin. A small study using fluoxetine has demonstrated some benefit compared with low-dose nifedipine in Raynaud's, although it has not been studied for the treatment of digital ulcers [106]. We have used this agent in

conjunction with a calcium-channel blocker or when low blood pressure limits our ability to use more potent vasodilators.

Vasoprotective agents

■ Antiplatelet agents

Several groups have reported elevated platelet activity in patients with scleroderma [107–110]. In one such study, scleroderma platelet activation markers correlated with disease activity and severity [111]. In addition, through the use of combination therapy with aspirin and dipyridole, significant reductions in circulating platelet aggregates and β -thromboglobulin levels were achieved [107]. Although one double blind placebo-controlled trial reported no benefit with combination therapy with aspirin and dipyridole versus placebo; it was a short trial over only a 2-year period in a group of 28 patients. Therefore, no meaningful conclusions can be drawn regarding the long-term benefits [112]. We regularly use low-dose aspirin (81 mg) therapy in our scleroderma patients with significant vascular disease because, we feel, it makes biological sense to do so.

■ Endothelin receptor antagonists

The endothelin receptor antagonists has also been demonstrated promise in preventing digital ulcers and has been shown to have vasoprotective effects. Korn and colleagues conducted a small preliminary study with 122 patients evaluating the effect on preventing digital ulcers [113]. They found that patients receiving bosentan had a 48% reduction in the mean number of new ulcers during the treatment period, suggesting that it could be a promising agent [113]. A second study, RAPIDS 2, found similar benefit in the prevention of new ulcers, particularly in patients with a high number of digital ulcers at baseline. On the other hand, in RAPIDS 2, a trial of 24-week duration with 198 subjects, higher rates of healing of ulcers were seen with placebo than active drug. At the end of 24 weeks of drug therapy, there were no differences between active treatment and placebo in net digital ulcer burden, pain, measures of activities of daily living by Health Assessment Questionnaire or UK Functional Score (UKFS) or in hospitalization rates [114]. Larger studies will be required to determine the efficacy and long-term outcomes, but these findings are encouraging.

■ Statins

More recently, statins have become a focus of scleroderma research. Statins demonstrate vasoprotective effects by decreasing low-density

Box 2. Critical digital ischemia.

- Start short-acting calcium-channel blocker
- Titrate aggressively to maximum dose tolerated
- Once this dose is reached, switch to a long-acting calcium-channel blocker
- Local injection of lidocaine or bupivacaine at the base of the finger; repeat if required
- Rapidly advancing ischemia?
 - Consider heparin drip for 24–72 h
 - Start intravenous iloprost, alprostadil or epoprostenol if available
- No response?
 - Surgical consultation for angioplasty or sympathectomy

lipoprotein, increasing high-density lipoprotein, decreasing free radicals, coagulation, and blood viscosity, decreasing matrix metalloproteinases, and increasing platelet function [38,115,116]. Abou-Raya and colleagues recently examined 84 patients with scleroderma and matched them with 75 control subjects to evaluate the effects of statins on patients with Raynaud's and digital ulcers. They found that the overall number of digital ulcers was significantly reduced in the statin group and that endothelial markers of activation were improved when comparing the statin and control groups [117]. Other studies have noted similar findings [118]. Although these results are promising, larger trials are still needed.

■ Thrombolytics

The role of thrombolytics in the treatment of digital ischemia and its complications have been studied on several occasions. The rationale for this is that in scleroderma, it is thought that the patients have an underlying balance towards clotting with elevated fibrinogen levels and defective tissue plasminogen activator release [38,119,120], although not all groups agreed [121,122].

At this time, there is limited evidence supporting the use of fibrinolytic therapy in patients with digital ischemia, and the complications with the use of these medications can be severe. As a result, they cannot be recommended for day-to-day use in the treatment of digital ischemia.

■ Other

Other medications that offer vascular modulating effects and that are currently still under evaluation include the tyrosine kinase inhibitors and the rho kinase inhibitors [123,124]. Antioxidants such as allopurinol and vitamin E have surprisingly shown little benefit [125–127]. Notably, probucol,

a synthetic antioxidant, did demonstrate a significant reduction in the frequency and severity of Raynaud's attacks when compared with controls [128]. *N*-acetylcysteine was recently studied prospectively in a cohort of 50 patients and was reported to decrease the number of digital ulcers per year and decrease Raynaud's attacks. It was well-tolerated in the long term with only flushing and minor headaches as side effects [129]. Other studies of antioxidants do not demonstrate a clear benefit for these agents, and thus we will need to wait for further data in order to develop clear guidelines for the use of antioxidants.

The role of hyperbaric oxygen therapy (HBOT) in digital ulcers in patients with scleroderma is not well studied. It was recently reported that HBOT was used successfully in two scleroderma patients with intractable bilateral extremity ulcers. Wound healing occurred in both patients after 30 treatments with HBOT [130]. However, in the authors' opinion, data are lacking and HBOT has no benefit in the absence of anaerobic infections.

Botulinum toxin is another reported therapeutic option for Raynaud's and digital ischemia. Fregene and colleagues found that Botulinum toxin type A improves pain and healing in patients with Raynaud's and scleroderma. They concluded that it is an effective treatment of vasospastic digital ischemia. Their study was limited by a small group of only 26 patients and a retrospective design [131]. Other small case series have also demonstrated success with botulinum toxin in pain and healing for patients with Raynaud's phenomenon and digital ulcers [132]. Although promising, we await controlled trials to evaluate the therapeutic efficacy of botulinum toxin in scleroderma patients with digital ischemia.

■ Sympathectomies

Sympathetic nerve mediated vasospasm is implicated as a major mechanism leading to digital ischemia. As a result, sympathectomies are aimed at blocking this mechanism. Uncontrolled series of case reports suggest benefit for both Raynaud's and for the treatment of refractory digital ulcers. Local 'digital sympathectomy' performed by surgical periarterial sympathectomies have also demonstrated long-term benefits in patients with digital ischemia secondary to autoimmune disease [133,134]. Hartzell and colleagues followed patients for 7.5 years and found that this intervention resulted in complete ulcer healing and decreases in the total number of ulcers in 75% of the

patients in this subgroup [135]. Although the study group was small, consisting of only 20 patients, these results are promising for patients with refractory disease. Arterial revascularization is sometimes performed simultaneously and has also demonstrated success [53].

Summary on treatment: a practical approach

The availability of many different therapeutic agents to treat Raynaud's can lead to confusion when initiating therapy in the clinical setting. Accordingly, an outline of a practical approach to treatment is given based on our experience. Although specific studies are required, we find this approach to therapy to be reasonable and effective (FIGURE 1).

■ Raynaud's alone

In scleroderma patients with Raynaud's without digital ulcers we first begin with supportive therapy, including keeping the fingers warm with gloves and avoiding of triggers such as stress, smoking and cold temperatures. Next we begin

low-dose aspirin at 81 mg daily. At the same time, we begin a long-acting calcium-channel blocker, such as amlodipine, for preventative therapy and titrate it up to the highest dose tolerated. Toleration is limited by the possible side effects of this class of medication, including fluid retention, symptomatic hypotension, constipation and aggravation of gastroesophageal reflux disease. Most patients benefit from low doses (e.g., amlodipine 5-mg daily) but we will titrate up the dose as required (e.g., amlodipine 20-mg daily). Our goal is not to eliminate every Raynaud's event but rather to improve the quality of life and prevent severe attacks and any progression to ischemic lesions. Thus, if a patient is not having digital lesions and reports an improvement and reasonable tolerance, then we continue on a calcium-channel blocker alone with low-dose aspirin. If the patient is still experiencing severe symptoms once the calcium-channel blocker is titrated to the maximal tolerated dose, then we will add a second agent, while recognizing there are few studies documenting the risks and benefits of additive therapy. Agents used include topical nitrates, a

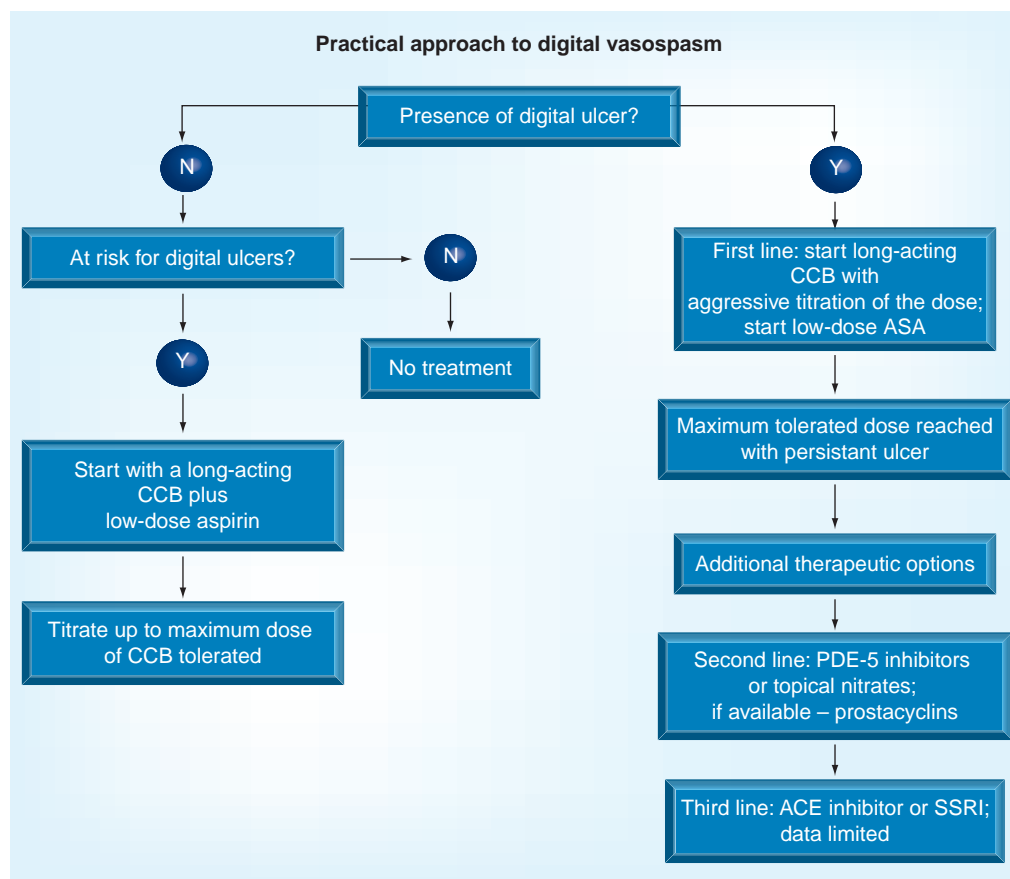


Figure 1. This chart is based upon our experience with the cohort of patients at the Johns Hopkins Scleroderma Center.

ASA: Aspirin; ACE: Angiotensin converting enzyme; CCB: Calcium channel blocker; PDE: Phosphodiesterase; SSRI: Selective serotonin reuptake inhibitor.

phosphodiesterase inhibitor or an SSRI based on availability and tolerance. We do use antioxidants but have no preference to a particular agent.

■ Raynaud's with digital ulcers & severe Raynaud's phenomenon

In patients with digital ulcers and severe Raynaud's, we again stress supportive therapy, initiation of low-dose aspirin, and titration of a long acting calcium channel to the highest dose tolerated. If the patient is still experiencing recurrent ulcers or moderate-to-severe Raynaud's once the calcium-channel blocker is at the highest dose tolerated, we then add a second agent. Usually our second agent is a topical nitrate or a PDE-I such as sildenafil; however, both should not be used together as there is a risk of severe hypotension. Intermittent infusion of prostacyclins (e.g., iloprost or epoprostenol) is considered appropriate in conjunction with the calcium channel blocker. The exact interval for therapy is not well defined but previous studies suggest that benefits last approximately 10 weeks after a 5 day (6 h each day) infusion of iloprost is a period of continued benefit. If a combination of medications is not effective, and we have a nonhealing ulcer or chronic digital ischemia then we pursue a digital sympathectomy.

■ Critical ischemic event

In the setting of a critical ischemic crisis, treatment must be initiated quickly and aggressively to prevent permanent tissue damage and digital loss (Box 2). During an ischemic crisis, irreversible vasospasm and severe pain are present. At initial presentation, a local injection of lidocaine or bupivacaine at the base of the finger can relieve pain and vasodilate rapidly. This can be

repeated again if necessary. Systemic pain medication is often required. If the patient is not on a vasodilator at the time of the crisis, then we initiate a short-acting calcium-channel blocker and rapidly titrate it up to the maximal dose tolerated. Once that dose is reached, we change to a long-acting calcium-channel blocker at an equivalent dose if the crisis is improved. If the signs of digital ischemia continue to progress, we add a heparin drip for 24–72 h and initiate therapy with intravenous prostacyclin (epoprostenol or iloprost) continuously at low dose for approximately 5 days. If stable, then we attempt to prevent relapse with continued calcium-channel blocker alone or in combination with either a PDE-I or topical nitrate. If this is still ineffective, we then recommend surgical consultation for digital sympathectomy. Doppler studies are performed to investigate larger vessel disease and an MRA or angiogram is done in selected cases to localize potentially correctable arterial disease. If no larger vessel disease is found that can be corrected and the patient is not improving, then surgical sympathectomy is performed. In critical ischemia with the presence of digital gangrene, it is always important to evaluate for underlying infection and add appropriate antibiotics if necessary. Surgical consultation may also be needed in this setting.

Future perspective

We anticipate great progress in the diagnosis and management of scleroderma over the next 10 years. From a diagnostic perspective, antibody profiling of patients at high risk for digital ischemia will continue to guide prevention. Genetic profiling will likely take on a larger role in diagnosis and targeting treatment. As our understanding

Executive summary

Risk stratification for digital ischemia

- Positive antinuclear antibody, especially with positive scleroderma specific antibodies and abnormal nailfold capillaries as detected by capillaroscopy predict pathologic Raynaud's.

Risk for developing digital ulcers

- Male sex, diffuse scleroderma, anti-Scl 70 positivity, inflammation, and the presence of pulmonary hypertension correlated with a high probability of presenting with digital ulcers.
- Gene expression profiling is an area that is under investigation to better identify the patients at risk for digital ischemia.

Mechanisms behind digital ischemia

- Vasospasm, vasculopathy, vasculitis and thrombosis all contribute to the development of digital ischemia.
- Identifying the underlying etiology of the digital ischemia is critical in the rapid initiation of appropriate therapy.

Approach to diagnosis

- Available modalities that are currently available for the diagnosis of the underlying etiology of digital ischemia include Doppler ultrasound, conventional angiogram and magnetic resonance angiography.
- Future diagnostic modalities may include thermography and other modalities currently only available for research.

Treatment

- Both nonmedical and medical therapies are currently used in combination for patients with digital ischemia.

of the molecular mechanisms underlying the disease continues to evolve, more specific targeted therapies will emerge allowing for more effective interventions and eliminating much of the morbidity associated with digital ischemia.

Acknowledgements

The authors thank the Scleroderma Research Foundation for their support and Pam Hill for her assistance in the preparation of the manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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