Raynaud's Phenomenon

A Guide to Pathogenesis and Treatment

Fredrick M. Wigley
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Foreword: United Kingdom

This is a most welcome publication, which fully illustrates every aspect of Raynaud's phenomenon, from epidemiology and pathophysiology to tests, treatments and clinical trials. It is an excellent resource for anyone who is interested in learning more about Raynaud's and associated conditions. I have had Raynaud's for almost 40 years and scleroderma for most of that time. During this period I have personally experienced the devastating effects, which these conditions can cause, including digital ulcers and amputation, in addition to internal organ involvement. I founded a national charity that provided me with the opportunity to understand the suffering of others, and I became a patient advocate, supporting people with these conditions. Literally millions of people worldwide have to cope with Raynaud's on a daily basis, not just in the cold but when faced with changes of temperature or stress. The pain can be excruciating and almost impossible to control. When I was first diagnosed, very little was known about the condition or how to treat it, and I faced a long journey of discovery, searching every possible pathway in pursuit of finding ways to help others and myself with similar problems. Being in touch with other sufferers gave me the incentive to continue my search for information. I formed sound relationships with consultants and researchers, and this bond enabled me to understand just how hard they were working and that research takes a long time and requires substantial financial support. Research and treatments have developed considerably over recent years, thanks to everyone who has devoted time and effort into trying to find a cure and to those who have helped to raise funds in order to finance the research.

I am delighted to be able to recommend this book, which not only gives valuable information but also clearly indicates how research has advanced and offers hope for the future.

Anne H. Mawdsley, M.B.E.
Founder Raynaud's &
Scleroderma Association (UK)

Post-script. Anne Mawdsley: May 1942 to October 2014. She made enormous contributions to the care of people with Raynaud's and Scleroderma, and to Raynaud's and Scleroderma research. She will be very much missed.

Foreword: United States of America

The orderly and regulated movement of blood through blood vessels has been recognized for centuries. In addition to its obvious physiological relevance, blood flow through vessels has been ascribed an almost spiritual significance. The color changes in the digits of the extremities, easily observed by patients and physicians, report on the function of small blood vessels and provide unique insights into age-old diseases. This extraordinary book focuses on the physiology and pathology of blood vessels, seen through the lens of the characteristic reversible changes in perfusion observed as Raynaud's phenomenon. The editors are leaders in the field, and they bring entire careers of knowledge about blood vessels and how they may be affected in disease. They have fashioned a resource which is as outstanding as it is timely.

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Preface

The remarkable clinical and observational skills of Maurice Raynaud defined a previously unappreciated cause of digital gangrene. He recognized that digital and cutaneous blood vessels have the capacity to react to provocation and that compromise to tissue blood flow can occur in the absence of vessel obstruction or vessel wall disease. He described reversible vasoconstriction of digital blood flow triggered by cold that resulted in a "deadly white" pallor or "cyanotic color" of the skin. It is now known that this phenomenon occurs because the skin has specialized thermoregulatory vessels that play a major role in normal physiological responses to the environment in order to maintain stable core body temperature. Raynaud's phenomenon (RP) is an inappropriate and exaggerated response of the digital and cutaneous circulation to cold environmental temperatures. Figure 1 depicts a dramatic clinical picture of the pallor phase of Raynaud's (a); while the adjacent figure demonstrates how low blood flow alters the temperature as measured by thermography (b). Soon after Raynaud's thesis was presented, it was recognized that the phenomenon was not caused by one process but could occur secondary to a variety of disorders that affect the peripheral circulation. We now appreciate that RP is a common disorder that is encountered both in otherwise healthy individuals and as part of a disease process altering the regulation of cutaneous blood flow.

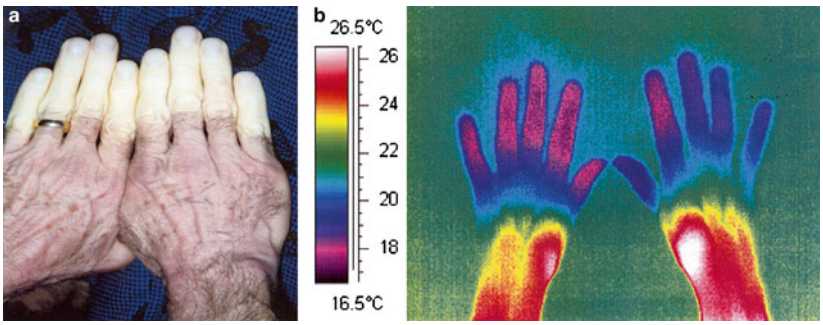

Fig. 1 (**a**) Clinical picture of the pallor phase of Raynaud's. (**b**) Altered temperature resulting from low blood flow, as measured by thermography

A comprehensive review of Raynaud's is now timely because of the incredible progress in understanding the molecular mechanisms of the normal regulation of cutaneous blood flow and how disease can disrupt the function of these specialized vessels. Likewise, the clinical implications of RP are better appreciated with studies defining its prevalence, the associated diseases, and new treatment approaches for patients suffering from it. We have structured the book to cover every aspect of RP from the history to the current treatment approach. The nomenclature use to classify cases has changed over the years and is important to understand these terms both for clinical care and research. Epidemiological studies have shown that RP is common, is influenced by environmental factors, is seen in both men and women, and is seen around the world in both as primary and secondary forms. A review of our current understanding of normal physiology and regulation of cutaneous blood flow sets the scene for an update of the pathology of primary and secondary RP. While primary RP is likely the most common clinical presentation, we wanted to comprehensively discuss various causes of RP including childhood RP, RP secondary to connective tissue disease, occupational causes, and a variety of other associated disorders. The many diseases with vascular perturbation that mimic RP and others that associate with RP are also reviewed.

We know that one of the main challenges facing a clinician who encounters a patient with RP is to define the underlying cause. We therefore included discussions of the pathogenesis as well as the methods and rationale for evaluating a patient with RP. Chapters are included that review the state of the art of nailfold capillary examination, noninvasive imaging, angiography, and appropriate serological testing. The concept that an RP is associated with systemic disease or the manifestation of a systemic vasospastic disorder is also presented.

Another challenge is to document the severity of RP for both clinical care and research toward developing effective treatment. Both outcome measures and the proper approach to study design for clinical trials in RP is reviewed. The final chapters of the book approach both nondrug and drug therapy for RP. We felt it essential to review evidence for and against current approaches to the treatment of RP. The management of the consequences of severe secondary RP is covered in chapters on how to care for digital ulcerations and surgical treatment options. We decided to provide our practical approach in specific clinical situations by presenting problematic cases and our expert opinion on therapy.

In an effort to have each chapter stand-alone, we recognize that some information in one chapter may be repeated in another chapter. We also note that much of the research and clinical trials in RP focuses on primary RP or RP associated with systemic sclerosis. However, we included comments to clearly define the design and population involved in investigations. We made a special effort to include photos of clinical situations and graphics to illustrate points. Each chapter is preceded by a list "key points" to highlight the major message of the chapter. Each author also provided an "expert opinion" to complement his or her review of published evidence.

It is clear that there are many challenges for the future. More studies are needed to better understand the molecular mechanisms of both primary and secondary RP. Appreciation of the full spectrum of diseases that associate or cause RP opens the opportunity to develop specific approaches for prevention and treatment. New diagnostic tools that could provide ambulatory monitoring would enhance our ability to test new treatment in a real-life situation. Better and safer medications are needed. Progress will come about only by applying novel thinking about the phenomenon; much like Maurice Raynaud's did years ago when he debated the usual concepts about digital gangrene of his time.

Baltimore, MD, USA — Fredrick M. Wigley
Manchester, UK — Ariane L. Herrick
Baltimore, MD, USA — Nicholas A. Flavahan

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Fredrick M. Wigley: I am forever indebted for the love, support, and patience of my wife Carol and daughters Joy, Julie and family; I am grateful to the entire staff of the Johns Hopkins Scleroderma Center, my colleagues who helped make this book possible, to Pam Hill for her help in preparing the book, and to the late Dr. Mary Betty Stevens for her inspiration.

Ariane L. Herrick: I am grateful to all the colleagues and patients who over the years have taught me about Raynaud's phenomenon, collaborated in research projects, and been a huge source of inspiration. I hope I do not let them down. Also I am grateful to Pam Hill for her work on this book, and to George, my husband.

Nicholas A. Flavahan: I am grateful for the constant love and support of my family especially my wife, partner, and best friend Sheila; to Fred and Ariane for inviting me to join them in this wonderful endeavor; to Paul Vanhoutte and the Great State of Minnesota for getting me interested in the effects of cold exposure; and for the challenges and inspiration provided by numerous colleagues… and my frequently cold white fingers.

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Historical Perspective of Raynaud's Phenomenon

1

Andrea Fava and Francesco Boin

Abbreviations

RP Raynaud's phenomenon
αAR Alpha-adrenoreceptor

Key Points

1. Maurice Raynaud characterizes cold-induced color changes of the fingers due to vasospasm.
2. Clinical observations concluded Raynaud's phenomenon were due to a "local fault" at the level of the digital vessels.
3. Raynaud's phenomenon is common and exists as both uncomplicated primary RP and RP secondary to underlying disease.
4. Both non-drug and drug therapies have evolved into effective treatment.

Milestones

In the eighteenth and nineteenth century debate over the mechanism of gangrene, there was a group of cases that could not be explained by "ossification of the arteries" nor by direct obstacles in the "vascular cavities." In 1862, the young Maurice Raynaud meticulously described in his medical school thesis 25 patients with spontaneous symmetric gangrene of the extremities. He noticed that some of them were reporting a history of "dead fingers." This phenomenon was characterized by attacks triggered by cold or emotional stress in which the fingers became indolent and turned "deadly white" or, sometimes, "yellow." In more pronounced cases, the pallor was replaced by a "cyanotic color." These episodes could last from a few minutes to many hours and could be followed by a reaction associated with heat and redness, and sometimes pain (Fig. 1.1) [1]. In 1888, Raynaud's thesis was translated into English and a year later Sir Jonathan Hutchinson gave Raynaud's eponym to the digital vasospastic phenomenon previously described in 1862. In 1892, a chapter entitled "Raynaud's disease" was included in William Osler's famous "Principles and practice of medicine" textbook [2]. By the turn of the century, Hutchinson observed that these vasospastic attacks could be associated with systemic diseases such as scleroderma and syphilis. Subsequently, he suggested that the term *Raynaud's phenomenon* (RP) was more appropriate than *Raynaud's disease* to underline the possible secondary nature of the vasospasm [3]. Landmark studies investigating the pathophysiology of RP conducted by Sir Thomas Lewis provided solid evidence that RP was caused by a digital artery "local fault" in contrast with

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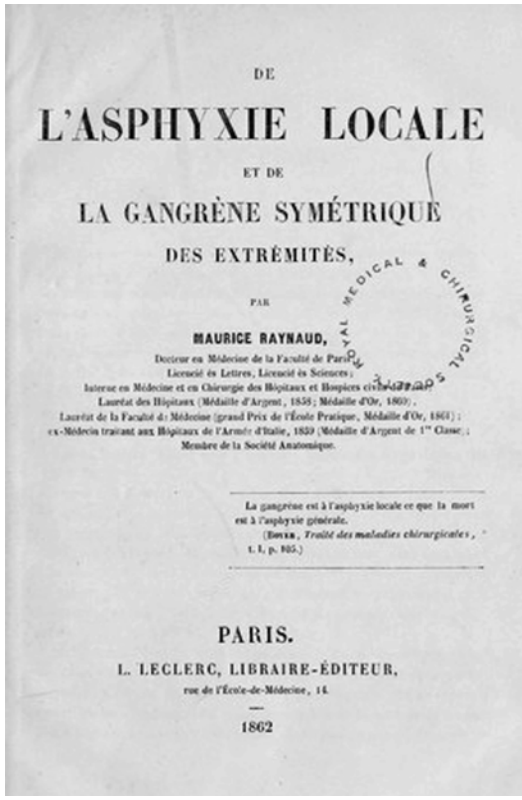

DE

L'ASPHYXIE LOCALE

ET DE

LA GANGRÈNE SYMÉTRIQUE

DES EXTRÉMITÉS,

PAR

MAURICE RAYNAUD,

Docteur en Médecine de la Faculté de Paris,
Licencié ès Lettres, Licencié ès Sciences;
Interne en Médecine et en Chirurgie des Hôpitaux et Hospices civils de Paris;
Lauréat des Hôpitaux (Médaille d'Argent, 1858; Médaille d'Or, 1860);
Lauréat de la Faculté de Médecine (grand Prix de l'École Pratique, Médaille d'Or, 1861);
ex-Médecin traitant aux Hôpitaux de l'Armée d'Italie, 1859 (Médaille d'Argent de 1re Classe);
Membre de la Société Anatomique.

La gangrène est à l'asphyxie locale ce que la mort est à l'asphyxie générale.
(Bouvier, *Traité des maladies chirurgicales*, t. I, p. 805.)

PARIS.

L. LECLERC, LIBRAIRE-ÉDITEUR,
rue de l'École-de-Médecine, 14.

1862

Fig. 1.1 The cover page of Raynaud's 1862 original medical thesis

Raynaud's hypothesis of sympathetic overreactivity (1929) [4, 5]. Three years later, Allen and Brown published the first diagnostic criteria for primary RP [6, 7], which remained widely used until two decades ago, when LeRoy and Medsger incorporated the use of nailfold capillaroscopy, antinuclear antibodies, and erythrocyte sedimentation rate to the defining criteria of primary versus secondary RP [8]. Several studies addressing RP pathophysiology have been published during the early-mid twentieth century favoring alternatively Raynaud's or Lewis' theory, but no substantial advances were made with regard to RP treatment. The introduction of calcium channel blockers and prostacyclin in the 1980s marked the beginning of modern RP pharmacological therapy [9–13]. The subsequent discovery of the vasodilatory role of nitric oxide led to the effective use of phosphodiesterase inhibitors in RP [14]. Recently, the molecular basis of cold-induced cutaneous arterial vasoconstriction partly reconciling Raynaud's and Lewis' theories has been described by Flavahan and colleagues [15].

Pathogenetic Mechanisms

Investigations into the pathogenesis of RP have been a long path lasting more than 150 years. Just two decades ago, Coffman wrote an editorial entitled "The enigma of primary Raynaud's Disease" underlining the challenge of explaining digital vasospastic occlusion in the apparent absence of organic or structural causes [16]. The first contribution came from Claude Bernard's studies in 1852 when he showed that the resection of the cervical sympathetic trunk in a rabbit is followed by a striking circulatory hyperreactivity on the side of the cut, together with increased warmth [17]. On this basis, Raynaud hypothesized that an "overactivity of the grey matter at the level of the spinal cord" was responsible for the distal vascular spasm and showed that the application of an ascending current through the spine was partially beneficial in treating his patients [1]. This observation provided the foundation for the "sympathetic theory" of RP. The first challenge to Raynaud's hypothesis came in 1929 by Sir Thomas Lewis who observed that when reflex vasodilatation was induced through body warming, digital vasospasm could still be triggered by placing the hands in cold water (Fig. 1.2). Conversely, vasospasm could not be elicited by cooling the body when the hands were kept warm. He also showed that RP attacks could be induced in sympathetically denervated fingers and that vasospasm of the fifth digit could not be relieved by anesthetization of the ulnar nerve. This evidence led Lewis to conclude that RP was due to a "local fault" at the level of the digital arteries and not to a defect of the central nervous system [4, 5]. Thereafter, the study on RP pathophysiology focused mainly on these two theories: the Lewis' "local fault" and the Raynaud's "sympathetic theory." In the late 1950s, Peacock showed that the hand blood flow can be restored by sympathetic blockade and that the digital blood collected from the dorsal vein of patients with primary RP had higher levels of catecholamines after cooling in comparison to healthy individuals [18, 19]. These data and the beneficial effects observed on RP symptoms after oral or intra-arterial reserpine, an inhibitor of synaptic

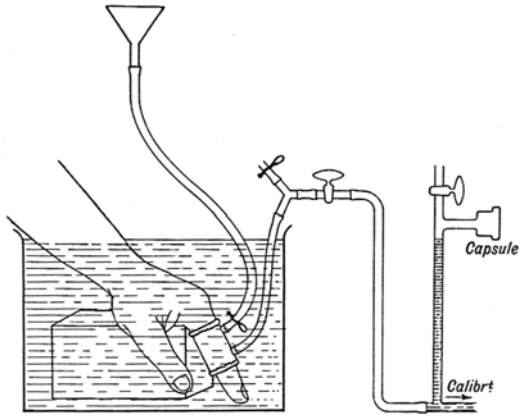

Fig. 1.2 The "local fault" theory experiment (1929). The finger of the patient was inserted in a brass capsule sealed with thin rubber sheeting. Cold water (10 °C) was then circulated in the capsule while the rest of the hand (or the body) was submerged with hot water (30 to 40 °C). The tip of the finger was then observed to turn white and then cyanotic [5]

catecholamine release, provided further support to Raynaud's explanation [20–22]. Conversely, studies by Halpern (1960) and later Freedman (1989) showed that vasospastic attacks could be induced in denervated fingers substantiating Lewis' observation [23, 24]. Jamieson hypothesized in 1971 that patients with RP likely have an increased "local" sensitivity to some aspect of the adrenergic transmission [25]. He showed that an ice cube applied for 10 s to the neck of an individual can reduce the distal digital blood flow and that this preconditioning was associated with more pronounced vasoconstriction in patients with primary or secondary RP (scleroderma) when their hands are immersed in cold water. This prompted him to conclude that the cold applied to the extremities sensitizes alpha-adrenoreceptor (αAR)-mediated mechanisms of vascular smooth muscle contraction, providing a view unifying the "local fault" with the "sympathetic" theories [25]. Further insight about the role of central versus peripheral sympathetic activity in RP was provided by studies conducted by Olsen and colleagues. They showed that a change in body posture from the supine to the sitting position (central reflex) can induce in primary patients with primary RP but not in healthy controls a drop of the digital blood flow and digital systolic pressure as a consequence of vasoconstriction and that this effect could be abolished by digital nerve blocking with lidocaine (peripheral reflex) [26]. The role of αARs was further explored in patients with primary RP using intra-arterial infusion of nonselective α_2-AR inhibitors (α_{2A}-, α_{2B}-, and α_{2C}-AR). This was followed by resolution of cold-induced vasospastic attacks, while α_1 blockade was ineffective [27]. Of note, the intra-arterial infusion of direct α_2-AR agonist did not induce significant vasospasm, failing to demonstrate a definitive role for this mechanism in RP [28–31]. The final entente between the sympathetic and the local fault theory was set in 2000 by Flavahan. He discovered that during cold exposure the normally "silent" α_{2C}-ARs relocate from the Golgi complex to the cell surface, driving a specific cold-induced vasoconstrictive response [15]. His studies confirmed that although the sympathetic stimulation is a major player driving vasoconstriction via the secretion of adrenergic agonists, a "local" sensitivity of the arterioles is crucial to mediate the exaggerated vascular response to cold in RP.

Epidemiology

Raynaud's disease had been initially reported as a rare disease. Sir William Osler described 19 cases out of 23,000 medical patients seen at the Johns Hopkins Hospital in Baltimore Maryland during a period of 20 years [32]. Monro analyzed the England and Scotland general hospital records reporting only 8 cases of diagnosed Raynaud's disease among the 54,793 patients admitted in the decade after the translation of Raynaud's thesis into English (1888–1897) [33]. Likely at that time RP was still largely underrecognized as well as underreported. Moreover, the lack of uniformed criteria to define RP represented another major problem. In fact, only later in 1932 Allen and Brown proposed the first set of criteria to define primary RP (they called it "Raynaud's disease") (see *Diagnosis* section). These criteria have been subsequently validated in a sample of 756 women diagnosed with RP at the Mayo Clinic between 1920 and 1945. Of the 629 cases with available complete information

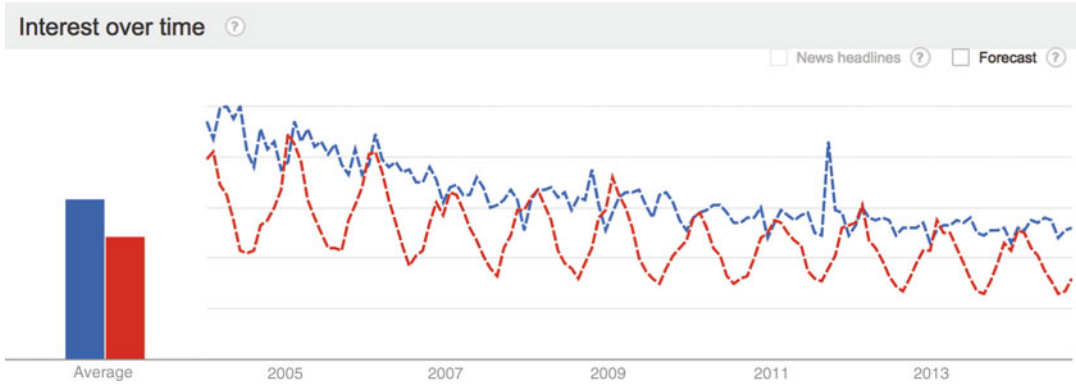

Fig. 1.3 Google searching trends for "Raynaud's phenomenon." Multiple search queries in several languages have been continued by the Google Trends algorithm for the term "Raynaud's phenomenon" (RP) as a disease. The figure shows the relative comparison of the worldwide search interest from Jan 2004 to Jan 2014 for RP (*red*) and for "scleroderma" (*blue*). A cyclical pattern peaking in the month of January is observed for RP. Trends data are normalized by total searches and are represented in relative units. Data source: Google Trends (www.google.com/trends) (color figure online)

eral worldwide geographic areas [36–45]. While for some of these studies a physician assessment of RP was required, a patient-reported history of cold-induced white or blue digital color changes sufficed for others. These surveys showed that RP is more prevalent in young women, younger age groups, and family members of patients with RP [36–45]. Interestingly, the advent of the worldwide web and the diffuse Internet use among the general population have dramatically increased the availability of medical information and boosted the ability to search information for a specific medical condition. "Raynaud's phenomenon" (including all languages) is nowadays frequently queried through the most popular search engines. Intriguingly, data obtained from Google website shows a cyclical pattern for such searches, with a peak during winter months (January) every year (Fig. 1.3).

Diagnosis

Historically, the diagnosis of RP has been eminently clinical, as suggested by Raynaud's own words: "the phenomenon of dead finger was too well known by everybody for it to be necessary for me to delay in discussing it" [1]. He provided the first detailed description of the typical paroxysmal vasospasm to grant him the honor of the Brown in 1932 to define the criteria for a clear and rigorous diagnosis of a primary disorder that could be appropriately called "Raynaud's disease" [6, 7]. They collected 150 patients with suspected RP and carefully documented for each of them a complete neurologic exam, patency of the peripheral arteries, and available long-term follow-up. They concluded that the minimal requirements for diagnosis of primary RP were (1) intermittent attacks of discoloration of extremities excited by cold or emotions; (2) symmetric or bilateral distribution (Fig. 1.4); (3) presence of normal pulsation in the palpable arteries; (4) trophic changes, when present, limited to the skin and never consisting of gross gangrene; (5) absence of evidence of organic arterial occlusion such as cervical rib; and (6) symptoms of 2 years or of longer duration; secondary criteria included (1) female gender and (2) absence of pain [6, 7]. Allen and Brown's criteria remained the main classification system for primary RP until 1992 when LeRoy and Medsger suggested introducing normal nailfold capillaries, negative test for antinuclear antibody, and normal erythrocyte sedimentation rate in addition to presence of symmetric attacks, absence of tissue necrosis, ulceration, or gangrene, and absence of obvious secondary causes (based on patient's history and general physical examination) to discriminate between primary and secondary RP [8].

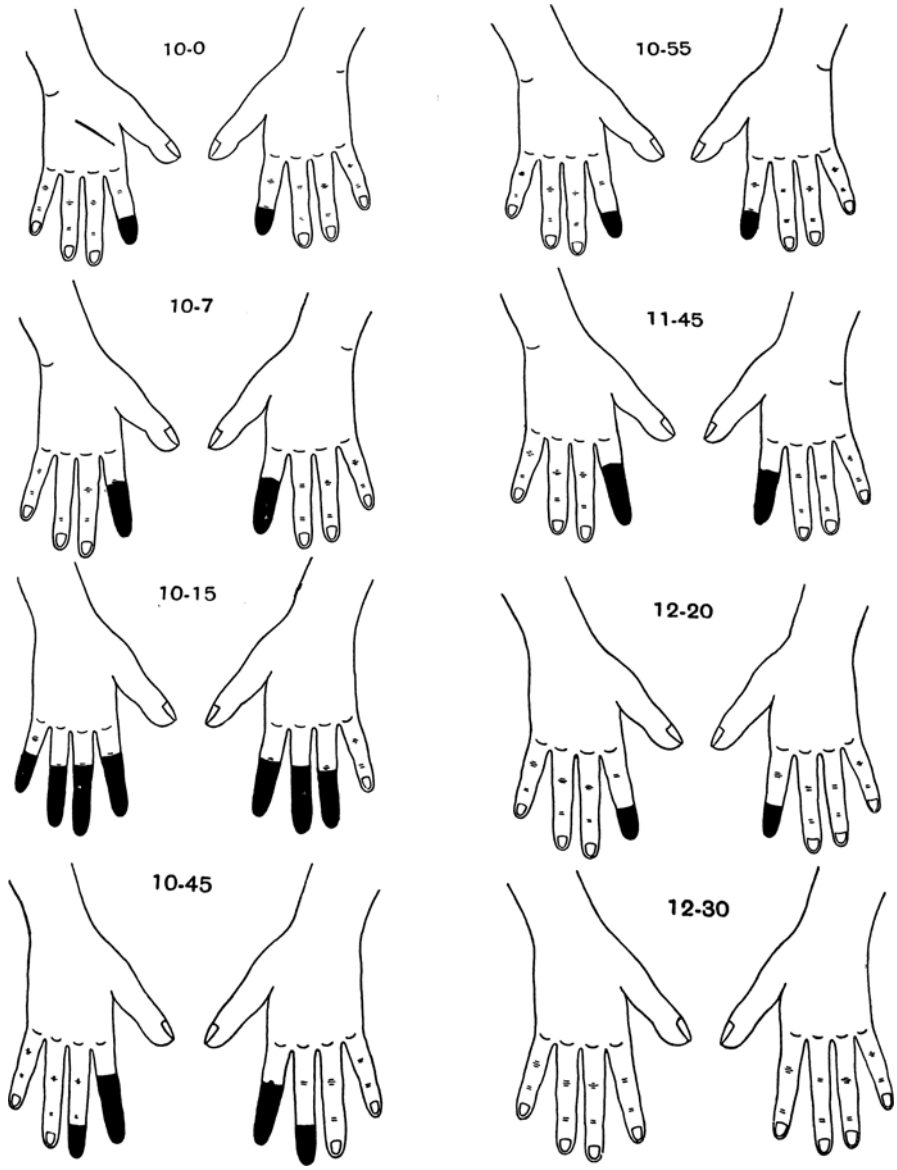

Fig. 1.4 Temporal sequence of a symmetric attack of Raynaud's phenomenon. The "cyanosis of the fingers" developed in this representative patient with probable primary RP at 10 am on 3 March 1929 and resolved a little before 12:30 p.m. (Lewis 1929) [5]

Several instrumental methods to diagnose and study RP have been developed over time, but only nailfold capillaroscopy has been consistently introduced in the clinical practice. Already in 1925 Brown and O'Leary were using nailfold capillaroscopic analysis to show evidence of microvascular abnormalities in RP secondary to systemic sclerosis (Fig. 1.5) [46]. Much later, the seminal work of Maricq and LeRoy in the 1970s gave the impetus for the capillaroscopy to become a major tool to study RP and to discriminate primary versus secondary disease. The use of this method allowed Maricq and LeRoy not only to meticulously describe specific nailfold capillary patterns in different connective tissue disorders, but also to observe specific functional variations.

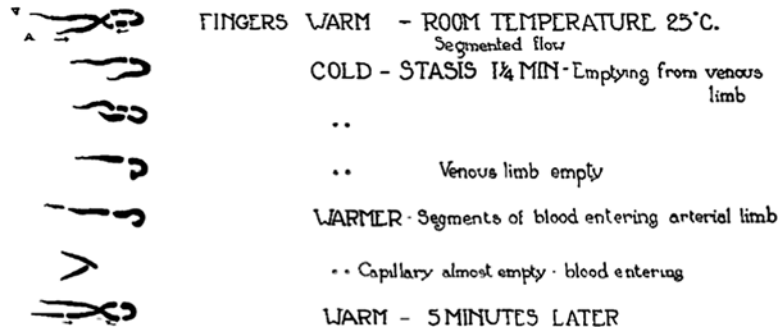

Fig. 1.5 Artistic representation of nailfold capillary pattern in response to cold in patients with Raynaud's phenomenon (Brown and O'Leary 1925) [46]

In fact, they noted that after cooling, the capillary blood flow is completely "standstill" in patients with scleroderma and "intermittent" in primary RP, while it remains "continuous" in healthy individuals [47, 48]. The technique to conduct the capillaroscopy was further developed under the impulse of several investigators up to the present time [49]. Other diagnostic tools such as videomicroscopy, thermography, angiography, and laser Doppler imaging have been used in the research setting and during clinical trials to obtain direct measurements of skin temperature and digital blood flow. However, none of them have as yet become part of the routine clinical assessment in RP patients [50, 51].

Treatment

Since the early nineteenth century, the main approach to cold sensitivity (or RP) has been non-pharmacological and based on recommendations such as the use of warm clothing, improvement of lifestyle, and avoidance of excessive emotional distress [33, 52]. In 1945, Lipkin reported that "mental suggestion" improved RP manifestations in several patients, anticipating the research on the role of biofeedback (1973) and autogenic training (1978) [53–55]. "Swinging the arms counter-clockwise as fast as possible for few seconds" was suggested by others as a helpful practice for RP patients (1978) [56]. Several ancillary aids like electrically heated gloves and socks or chemical hand warmers have also been introduced to help people living in cold climates [57]. Importantly, most of these interventions failed to improve RP when tested in formal trials based on clinical outcomes such as hand temperature recovering time after immersion in cold water [58].

In the nineteenth century, several compounds had been tested for their proven or purported vasodilative effects including amyl nitrite, nitroglycerin, quinine, ergot, and thyroid extract; analgesics such as opium, phenacetin, or cannabis indica; and uricosurics like salicylic acid, sodium phosphate, and piperazidin. Also electricity has been reported as a potential treatment (galvanism and faradism). Typically, the whole body or the hands of the patients were placed in a warm bath and then electricity was directly applied to the water to suppress nerve conduction with the intent of improving circulation [33]. Partial benefit on RP symptoms has been attributed to the application of topical treatments such as oxygen baths, local bleeding, and "fomentations" with sedatives like belladonna or laudanum [33]. An interesting trial evaluating the vasoactive effects of ethylic alcohol has been conducted with some positive results. Vasko and Evans showed that ethanol (10 %) infused intravenously for 2 h (2 ml/kg/h) to eight patients with primary RP resulted in restored pulsatile digital blood flow in five of them [59]. The major challenge with this approach was that large amounts of whiskey, brandy, or other alcohol beverages had to be consumed (90–150 ml) in order to effectively relieve vasoconstriction, carrying considerable risk for intoxication. In fact, no other formal studies have been subsequently conducted using this approach.

Starting in 1862, RP therapy focused mainly on counteracting the sympathetic vasomotor regulation. Maurice Raynaud described beneficial treatments based on the application of ascending electrical current to the spinal cord of his patients with the purpose of achieving a noninvasive sympathetic block [1]. In 1902, Harvey Cushing introduced the use of the tourniquet technique. He noted that the release of a tourniquet from an extremity after limb surgery was inevitably followed by hyperemia associated with a higher than normal skin temperature. That forthcoming winter, this technique was applied for the first time to a young woman with a very painful vasospastic episode. A rubber band was applied tightly to the upper arm for about 2 min. After removal, a "bright flush of the extremity followed with increase of surface temperature and a much more readily palpable radial artery" occurred, in addition to temporary but effective relief of the pain [60]. He hypothesized that the pressure of the tourniquet could disrupt the sympathetic conduction along the artery, therefore interrupting partially the vasoconstrictive tone.

In 1889, cervical sympathectomy was introduced as a treatment for epilepsy. Such approach was unsuccessful and eventually abandoned. However, several patients reported hyperemia of the arms as a side effect of the surgery. These findings brought Adson to perform the first lumbar sympathectomy for RP in a teenage patient with a history of ulcers and painful vasospastic attacks to the feet. The second, third, and fourth lumbar ganglions were resected and the outer sheath of the common iliac arteries was stripped for a distance of about 5 cm. Following the operation, the feet turned warm and pink, with an increase of skin temperature [61, 62]. Since this successful episode, surgical sympathectomy became a widely used treatment for severe RP. Although the surgical technique improved over time, recurrence of symptoms and development of side effects such as ipsilateral paresthesia, Horner's syndrome, or anhidrosis have been frequently reported [62, 63]. More recently localized microsurgical interventions have been developed to achieve a localized digital sympathectomy and more focal beneficial outcomes (1980) [64].

Alternative strategies to block sympathetic efferent impulses have also been pursued. A "chemical" sympathectomy has been introduced in practice using a direct local or intravenous sympathetic block (Bier block, 1974). In the first case, sympatholytic agents such as cocaine, reserpine, lidocaine, and bupivacaine were directly injected in the ganglia or in the proximity of affected districts (i.e., wrist or fingers) [65, 66]. In the Bier block, the veins of the involved extremity were emptied using an elastic bandage, and a blood pressure cuff was inflated to suprasystolic pressure to prevent reperfusion. A sympatholytic agent like guanethidine or reserpine (in 50–100 ml of normal saline) was then injected into a peripheral vein and left in place for 15–20 min before the arterial occlusion was slowly released. More recently, intradigital and palmar botulinum toxin A injections have shown some efficacy in restoring blood flow and achieving pain control [67–70].

The role of αAR was first explored in 1957 with an uncontrolled study on phenoxybenzamine, a nonselective inhibitor. A more refined pharmacological modulation of the sympathetic function was developed later in the 1970s with the use of reserpine and guanethidine. These molecules alter the sympathetic signal at the level of the synaptic terminal reducing the accumulation of norepinephrine and inhibiting the vasoconstricting action of nicotine and acetylcholine. Although in one study the use of reserpine in patients with RP showed an increase in digital capillary blood flow, no difference from placebo was observed in terms of number of vasospastic attacks and skin temperature [71, 72]. The direct inhibition of αARs by methyldopa (1969), prazosin (1979), indoramin (1986), and phentolamine (1987) subsequently emerged as an effective treatment in RP [73–76]. However, these drugs became obsolete due to nonselectivity and association with relevant side effects (i.e., orthostatic hypotension). More recently, after the discovery of the pivotal role played by alpha-2c receptors in mediating cold-induced vasospasm, novel specific αAR modulators are in the pipeline [77].

The direct vasodilator effect provided by nitroglycerin was exploited in RP through

different formulations including sublingual drops (1899), tablets (1983), ointment (1948), tape (1994), and transdermal patches (1995). While beneficial, the use of nitrates has been limited by their short half-life and the frequent occurrence of systemic side effects [78–80].

The observation that RP is associated with the presence of other vasospastic disorders such as Prinzmetal's angina and migraine suggested the possibility that a "diffuse vasospasm" is present in certain individuals [10, 81]. This prompted the introduction of nifedipine, a calcium channel blocker used for coronary vasospasm, as a more targeted therapeutic option to treat RP. The first successful trial with nifedipine was published in 1981 and was soon followed by two other double-blind, placebo-controlled, crossover studies in patients with primary and secondary RP [9–11]. These studies showed consistently a significant reduction of the frequency and the severity of RP attacks.

In the same years, the infusion of prostaglandin-E1 was shown to improve the healing of severe peripheral atherosclerotic vascular disease manifestations and, in 1980, the first trial of intravenous prostaglandin-E1 in RP patients showed great symptomatic benefit as well as improvement in digital perfusion [82, 83]. Similar results were subsequently obtained with infusion of prostacyclin (1981) [12, 13].

The discovery of the prominent role of nitric oxide as a potent vasodilator revolutionized in the late 1990s the treatment of erectile dysfunction with the introduction of phosphodiesterase type 5 inhibitors [84]. Five years later (2003), a rheumatologist from Annapolis, MD (USA), reported the successful use of sildenafil citrate in ten patients with primary or secondary RP [14]. Since then, the efficacy of phosphodiesterase type 5 inhibitors in digital ischemia has been evaluated in several studies showing a significant efficacy both in primary and secondary RP [85–87].

Conclusion

The history of Raynaud's phenomenon is a great example about the ability of great clinicians to translate their expert observations into the discovery of novel clinical phenomena. While major steps have been made over the past three decades to rigorously classify RP, to define specific molecular pathways underlying the dysregulated vasomotor control, and to identify more effective treatments, the challenge of understanding, assessing, and treating Raynaud's phenomenon remains still open. We are confident that new exciting discoveries will soon fill the remaining gaps in "the enigma of Raynaud's phenomenon."

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Definition, Nomenclature, and Diagnostic Criteria

2

Serena Guiducci and Marco Matucci-Cerinic

Abbreviations

RP	Raynaud's phenomenon
ANA	Antinuclear antibodies

Key Points

1. Raynaud's phenomenon is the clinical manifestation of vasospasm of digital blood vessels.
2. A variety of disorders that affect the acral circulation can cause Raynaud's phenomenon.
3. Clinical and laboratory criteria can distinguish uncomplicated primary Raynaud's from RP caused by a secondary disease process.
4. The diagnosis of RP is dependent on a history of cold- or stress-induced color changes (pallor or cyanosis) of the digits of the fingers or toes.

Definition

Raynaud's phenomenon (RP) has fascinated clinicians and researchers since the first description by Maurice Raynaud in 1862 [1] (Box 2.1).

Box 2.1. Raynaud's original criteria for "Raynaud's disease"

1. Discrete episodes of change in color, of the vasospastic type, induced by cold exposure or emotional stress
2. Bilaterality
3. Normal pulsations in palpable stress

The well-demarcated ischemia of the digits is dramatic in presentation with pallor (Fig. 2.1) or cyanosis (Fig. 2.2) ending abruptly at one level on the digits. Some patients have only pallor or cyanosis while others have pallor and cyanosis followed by redness of reactive hyperemia as the vessel reopens (Fig. 2.2). Only one digit or all digits of hands or feet may be involved (Fig. 2.3); although the thumb is usually spared when involved it suggests a secondary underlying cause (Fig. 2.4) [2].

A clear description and definition of RP has been provided [3]. RP is mainly localized to the distal portion of the finger but also toes, nose, earlobes, and tongue can be affected. It consists of two or three phases (bi- or triphasic) characterized by an initial blanching (ischemia), followed by cyanosis (anoxia) and rubor (reperfusion). Pallor is the most specific and rubor the least specific physical sign. In the hand the color changes occur from the fingertip to the base of the finger. RP affects one or more digits, is uncomfortable

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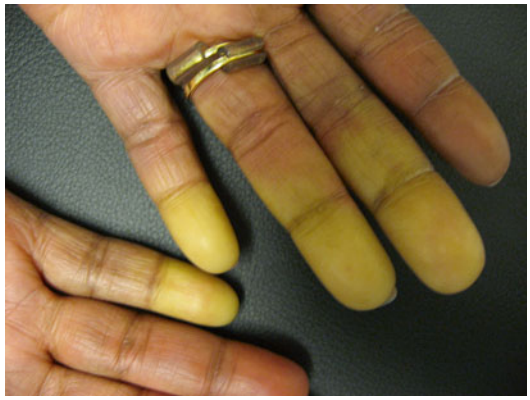

Fig. 2.1 Note the demarcated pale coloration of the fingers typical of the pallor phase of Raynaud's phenomenon

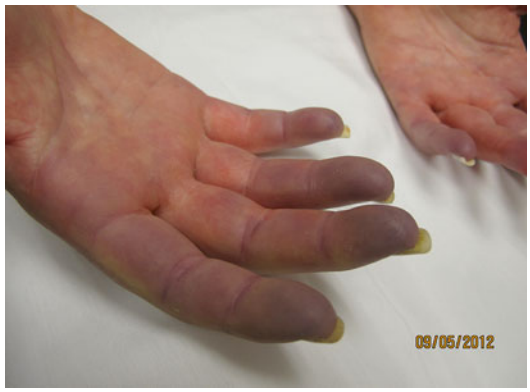

Fig. 2.2 Fingers showing the cyanotic phase of Raynaud's phenomenon in a patient with limited scleroderma

with a numb sensation, and is painful with prolonged ischemia. Attacks are distinctly episodic with symptom-free intervals, and the changes are usually very symmetric in both hands and feet [3]. Involvement of all fingers occurs but events in the thumb suggest a secondary form of RP. It is triggered by cold exposure or emotional stress. It lasts from few minutes to several hours; but typical recovery occurs in 15–20 min after rewarming from cold exposure. Abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses is thought to underlie the disorder (see Chap. 5).

Nomenclature

Ever since Raynaud described the discoloration of hands and fingers in response to cold stimuli, the nomenclature of this phenomenon has progressively evolved [1]. Various terms have been used to describe these cold- and stress-induced events including Raynaud's phenomenon, Raynaud's disease, and Raynaud's syndrome. It is recognized that RP may be the manifestation of several different underlying pathologies and that it can be associated with a heterogeneous group of clinical disorders. Therefore, the dilemma has always been finding the precise definition of RP. Maurice Raynaud by his careful clinical observations recognized the great variety of acral circulatory disorders characterizing the phenomenon. In his preface, Raynaud writes that it is easier to describe a new disease than to bring the great variety with which the phenomenon manifests itself under a common denominator. This prompted him to propose four criteria to identify RP: (1) discrete episodes of change in color, of the vasospastic type, induced by cold exposure or emotional stress; (2) bilaterality; (3) normal pulsations in palpable stress; and (4) absence of gangrene, or only minimal grades of cutaneous gangrene. A patient having vasospastic events meeting these criteria was originally said to have "Raynaud's disease." The nomenclature changed when in 1901 Hutchinson [4] described RP as a "phenomenon" that was either due to an underlying disease, such as an obstruction in the arterial system, or exists without such an obstruction. Thus the astute observations of Raynaud and Hutchinson indicated that RP was linked to a variety of disorders that involved the acral circulation.

In 1932, these observations prompted Allen and Brown [5] to propose a nomenclature and definition for uncomplicated or "primary" RP (Box 2.2). They reviewed and modified Raynaud's original description and proposed the following criteria: (1) vasospastic attacks induced by cold exposure; (2) bilateral involvement of the extrem-

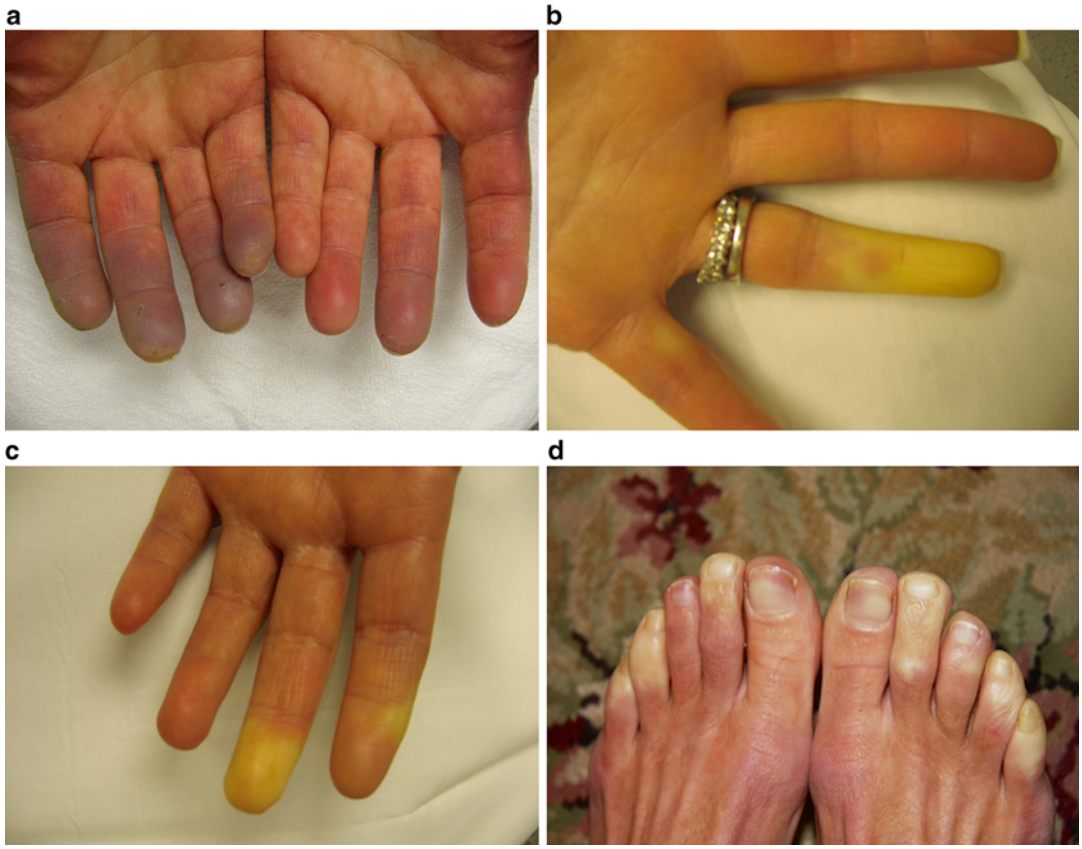

Fig. 2.3 (**a**) The cyanotic phase is seen on the *left* and the *reddened blush* of the hyperemic recovery phase is occurring on the *right*. (**b**) Note the sharply demarcated *white* discoloration of the fourth finger demonstrating the pallor phase of Raynaud's phenomenon. (**c**) Early Raynaud's event involving the distal middle finger. (**d**) The pallor phase of Raynaud's phenomenon involving several toes

ities; (3) absence of gangrene or involvement of only the skin of the fingertips; and (4) a history of symptoms for at least 2 years, with no evidence of an underlying disease. Since that time, a digital phenomenon that met these criteria and showed a cutaneous discoloration from white to bluish to red was called primary RP instead of Raynaud's disease. These criteria allowed the practitioner to distinguish primary RP from other conditions associated with tissue necrosis or from vascular disease of hands and fingers with asphyxia due to local anatomic arterial obstructions. Since then RP in the presence of an underlying disease is labeled "secondary Raynaud's phenomenon" (see Table 2.1).

In 1957, Gifford and Hines also clearly recognized that RP might precede evidence of an underlying disease by many years [6]. Different diagnostic procedures have been used to improve identification of a secondary disease, simplify this nomenclature, and obtain better insights into the pathophysiology of disturbed digital circulation [7–12]. Morphologic studies of the nailfold capillaries with capillary microscopy were described at the beginning of the twentieth century [13, 14] by Brown and O'Leary. Therefore, the evolution of capillaroscopy up to our times has allowed the methodology to be used to distinguish between RP with and without underlying disease [15] (see Chap. 12).

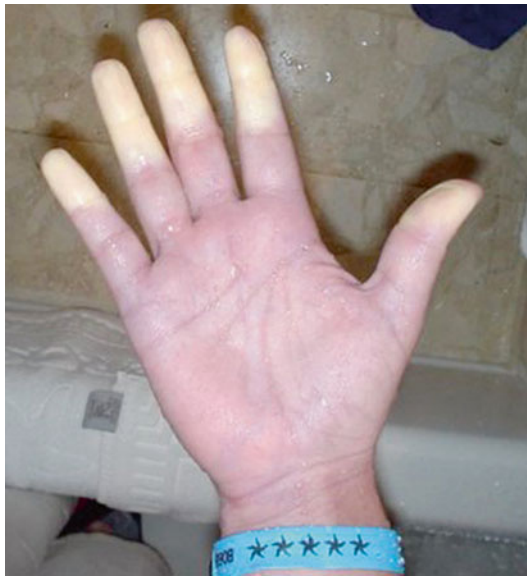

Fig. 2.4 The pallor phase of Raynaud's in several fingers including the thumb in a patient with secondary Raynaud's phenomenon due to scleroderma

Box 2.2. Allen and Brown's original criteria:

1. Vasospastic attacks induced by cold exposure
2. Bilateral involvement of the extremities
3. Absence of gangrene or involvement of only the skin of the fingertips
4. History of symptoms for at least 2 years, with no evidence of an underlying disease

Table 2.1 Disorders and factors associated with Raynaud's phenomenon

Group	Disorders
Rheumatological diseases	Scleroderma
	Systemic lupus erythematosus
	Polymyositis/dermatomyositis
	Sjögren's syndrome
	Undifferentiated connective tissue disease
	Mixed connective disease
Hematologic/ oncologic	Paraneoplastic syndrome
	Cryoglobulinemia
	Cryofibrinogenemia
	Cold agglutinin
	Paraproteinemia
	Coagulopathy
	POEMS syndrome
Endocrine	Hypothyroidism
Vascular	Thoracic outlet syndrome
	Emboli
	Vasculitis
	Prinzmetal angina
	Atherosclerosis
Neurological	Carpal tunnel syndrome
	Migraine headache
Environmental	Vibration injury
	Frost bite
	Emotional stress
Drugs/toxins	Sympathomimetic drugs
	Interferons
	Smoking
	Cocaine
	Ergotamines
	Polyvinyl chloride

Adapted from UpToDate

In 1987, Lemmens defined RP as "a cold-induced critical deceleration of the blood flow which influences the non-Newtonian behavior or thixotrophy [shear thinning of fluid] of the blood along a vicious circle in such a way that the fluidity of the blood is progressively reduced" [16]. In 1986, Jacobs, Lemmens, and colleagues investigated patients with ischemic hand phenomena by hemorheologic (flow properties of blood) and capillary microscopic measurements and differentiated various causes of ischemic hand phenomena. They proposed the following definitions:

1. *Primary Raynaud's phenomenon* is mainly seen in women and characterized by a symmetrical, triphasic discoloration of hands and fingers. It is triggered by exposure to cold or emotional stress, and no underlying cause can be detected. The primary RP has evenly distributed but slightly dilated capillaries in which red blood cell velocity is low as compared with normal subjects, especially after cold provocation, a vasospastic flow disturbance with slight capillaropathy and without rheopathy (abnormal flow properties of liquids).
2. *Secondary Raynaud's phenomenon* is characterized by clinical symptoms similar to those observed in primary RP, but based on an

underlying disease. Secondary RP has avascular areas with giant and extremely dilated capillaries with low red blood cell velocities. Red blood cell aggregation and plasma viscosity are significantly increased. The flow disturbance is associated with marked capillaropathy and rheopathy.

3. Acrocyanosis is a phenomenon in which unilateral or bilateral permanent cyanosis of hands and fingers occurs and no underlying disease can be detected. Show dilated capillaries with low red blood cell velocities. The hemorheologic parameters are not significantly different from those of normal subjects. The flow disturbance in these patients is associated with pronounced capillaropathy but not with rheopathy.

Asphyxia digitorum is characterized by a sharply bordered white, and sometimes cyanotic, discoloration of one or more fingers, especially after cold provocation; the underlying cause is obstructive digital artery disease. The capillary microscopic findings in the non-affected fingers are similar to those observed in normal subjects; red blood cell velocity before and after cold provocation is significantly lower in the affected than in the non-affected fingers; the blood flow is intermittently diminished without capillaropathy or rheopathy and hematocrit value was increased. The basic condition of asphyxia is a local vascular obstruction with a cold-induced, superimposed vascular spasm. *Digitus moriens* [17], or *dying finger*, is an advanced phase of asphyxia digitorum and occurs if both digital arteries are permanently occluded and no collateral circulation can develop.

Criteria for Classification

In 1992, LeRoy and Medsger [18] eventually dropped the term *Raynaud's syndrome* and proposed new criteria to classify RP that could widely approach different diseases and simplify the classification (Box 2.3). They also proposed the sensitive detection techniques of nailfold capillaroscopy and autoimmune serology and removed the principle of a 2-year follow-up as suggested by Allen and Brown, to diagnose a primary RP. They proposed a strict definition of primary RP and also introduced the fact that almost any feature of undifferentiated connective tissue disease or the spectrum of scleroderma-like illnesses qualifies the patients as having secondary RP [18]. They proposed the following criteria for the definition of primary RP: episodic attacks of acral pallor or cyanosis, strong and symmetric peripheral pulses, no evidence of digital pitting scars, ulcerations, or gangrene, normal nailfold capillaries, negative antinuclear antibody test, and normal erythrocyte sedimentation rate. Therefore, they defined the diagnosis of *primary RP* when a patient was characterized by normal capillaroscopy, negative or normal laboratory tests including antinuclear antibodies (ANA) and inflammatory parameters, symmetrical distribution of the phenomenon, absence of skin ulcers, and absence of underlying disease [18, 19]. They proposed also the criteria to define secondary RP that is still used today in clinical practice: abnormal nailfold capillary pattern; positive ANA; presence of digital pitting scars; ulceration or gangrene; esophageal abnormalities; small intestinal, colonic, pulmonary , cardiac, and renal abnormalities; reduced renal blood flow; or creatinine clearance [18]. A panel of 12 experts in the field also agreed on the following criteria for the diagnosis of primary RP: (1) normal capillaroscopy; (2) physical examination is negative for findings suggestive of secondary causes (e.g., ulcerations, tissue necrosis or gangrene, sclerodactyly, calcinosis, or skin fibrosis); (3) no history of existing connective tissue disease; (4) negative or low-titer ANA (e.g., 1:40 by indirect immunofluorescence) [20].

Box 2.3. Current criteria of LeRoy and Medsger:

1. Episodic attacks of acral pallor or cyanosis
2. Strong and symmetric peripheral pulses
3. No evidence of digital pitting scars, ulcerations, or gangrene
4. Normal nailfold capillaries
5. Negative antinuclear antibody test
6. Normal erythrocyte sedimentation rate

Diagnostic Criteria

Cold hands and feet is a very common complaint in the general population and must be distinguished from RP. Cold exposure in normal individuals causes the skin to feel cold and some may witness some skin mottling on cold exposure but not the sharp demarcation of pallor or cyanosis of the digital skin seen in RP. To aid in making a diagnosis, the clinician can use a standard questionnaire which asks three questions: (1) Are you more sensitive to cold than others? (2) Do you notice color changes of your skin? (3) Do your fingers look white or blue on cold exposure? (Box 2.4) Some investigators use actual color photos (Fig. 2.5) of witnessed attacks that the patient must identify [21, 22]. This method has been used in epidemiologic studies investigating the prevalence of RP in the community. The diagnosis is often clearly defined by witnessing an actual event during physical examination of an anxious patient in a cool examination room. Provocative cold testing is not recommended for clinical diagnostic purposes. Clinical criteria describing relative degrees of certainty in the diagnosis of RP have been proposed [23]:

- Definite RP—Repeated episodes of biphasic color changes upon exposure to cold
- Possible RP—Uniphasic color changes plus numbness or paresthesia upon exposure to cold
- No RP—No color changes upon exposure to cold

Box 2.4. Criteria for making a diagnosis of Raynaud's phenomenon: a positive response to these three questions:

1. Are you more sensitive to cold than others?
2. Do you notice color changes of your skin?
3. Do your fingers look white or blue on cold exposure?

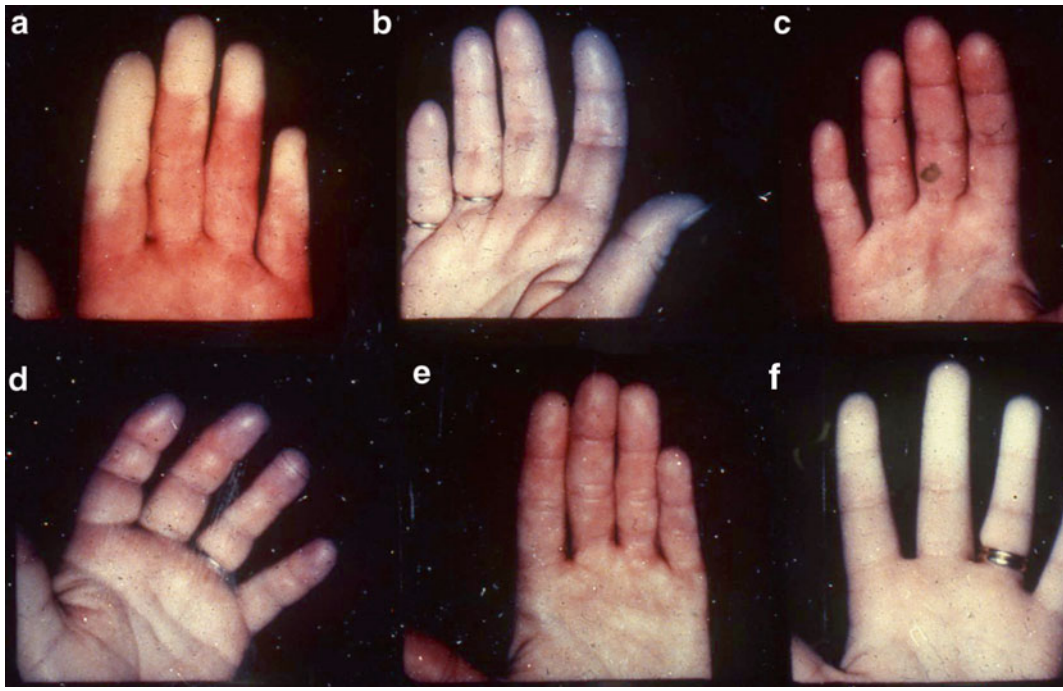

Fig. 2.5 Color chart used to diagnose Raynaud's phenomenon. Photos of color changes of fingers of actual patients during real attack. **a** and **f** = pallor phase; **d** and **b** = cyanotic phase; **e** and **c** = normal variation

The diagnosis of RP in the clinical setting is based upon a history of uniphasic color changes (blue or white events) or direct witnessing of an event during physical examination.

Summary

RP represents a common complaint in clinical practice, particularly among patients with rheumatic diseases [3]. From its original description in the nineteenth century different definitions have been proposed. Today, this event is defined as primary RP when no disease is diagnosed while it is termed secondary RP when an underlying disease is disclosed. This classification satisfies the needs of the physician in practice. Clinical assessment by history and examination is the gold standard for making a diagnosis.

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Epidemiology of Raynaud's Phenomenon

3

Adam Maundrell and Susanna M. Proudman

Abbreviations

ANA	Anti-nuclear antibody
CI	Confidence interval
CTD	Connective tissue disease
DU	Digital ulceration
ESR	Erythrocyte sedimentation rate
GP	General practice
HAQ	Health assessment questionnaire
MCTD	Mixed connective tissue disease
ND	Not described
OR	Odds ratio
RA	Rheumatoid arthritis
RP	Raynaud's phenomenon
RR	Relative risk
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
UK	United Kingdom
US	United States of America
VCM	Vinyl chloride monomer
VWF	Vibration white finger

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Key Points

1. The prevalence of RP in most studies in the general population is between 3 and 5 %.
2. Primary RP accounts for 80–90 % of cases.
3. The prevalence of primary RP ranges from 2 to 20 % in women and 1–12 % in men depending on geographic location, the population studied, the definition of RP used and the method of case ascertainment.
4. Risk factors differ between women and men.
5. Primary RP and RP secondary to autoimmune disease are more common in women than in men.
6. In men, the prevalence of RP increases with age and is more likely than in women to be secondary to occupational exposures such as vibration or atherosclerotic peripheral vascular disease.
7. Up to 50 % of subjects with primary RP have a family history of RP in first-degree relatives, particularly in women and in those with early onset RP.
8. The prevalence of secondary RP depends upon the underlying disease.
9. Progression to secondary RP occurs in 14–37 % of subjects with primary RP.

This chapter discusses the epidemiology firstly of primary Raynaud's phenomenon (RP) and then of the different forms of secondary RP. Points considered include incidence, prevalence, and risk factors. "Risk factors" encompass risk factors for development of RP, for progression

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from primary RP to systemic disease, and (in the patient with systemic sclerosis [SSc]-related RP) for progression to digital ulceration or gangrene.

Primary RP

Incidence and Prevalence of Primary RP

Most studies of RP in the general population report the prevalence to be between 3 and 5 % with primary RP accounting for 80–90 % of cases [1, 2]. The prevalence of primary RP varies according to geographic location and ranges from 2.1 % in a study of 2,155 people randomly selected from an Italian general practice to 11.5 % among 234 people from the electoral roll in New Zealand [3, 4] with the majority of studies reporting a prevalence of less than 5 % (Table 3.1). Rates as high as 21 % in women and 16 % in men were found in general practices in the UK [5]. A large study of 4,182 patients from the Framingham cohort in the USA followed for 16 years reported a prevalence of primary RP of 7.2 % [6]. In Turkey, the prevalence among medical students and hospital staff was 3.6 and 5.9 % among 768 patients attending a medical clinic [7, 8]. In Greece, 5.2 % of 500 randomly selected hospital employees had definite RP [9]. Despite the variation in prevalence, there has been no clear change over time.

The incidence of primary RP has not been widely studied. Suter et al. followed 1,358 healthy individuals in the Framingham Offspring study cohort for a mean 7 years and found an incidence of RP in 2.2 % of women and 1.5 % of men over this 7 year period [10].

Several factors contribute to variation in the rates reported. Most studies have sought to distinguish primary from secondary RP but not all have reported the definition of RP used or they have used differing definitions. The most commonly used definition was proposed by the UK Scleroderma Study Group:

- Definite RP: repeated episodes of biphasic colour changes upon cold exposure
- Possible RP: uniphasic colour changes plus numbness or paraesthesiae upon cold exposure
- No RP: no colour changes upon cold exposure [11]

A less rigorous definition of blanching of the fingers with sensory symptoms in response to cold was used for the UK general practice study, which may also explain the higher prevalence rates observed [5]. Others have used cold-induced single colour change or finger blanching with clear demarcation.

Some studies have assessed prevalence in people randomly selected from the general population. Others have only included people selected from limited populations such as patients attending a particular general practice, medical students or employees and hence are prone to selection bias. While the predominant racial groups have varied amongst studies, the prevalence rates in different racial groups are often not reported. Only one study directly compared two genetically different racial groups. Valter et al. reported a higher prevalence of RP in 4,341 Indo-Europeans compared with 5,248 Finno-Ugric people living in Estonia [12].

Methods of case ascertainment have also varied. Patient- or physician-led questionnaires, telephone interviews and face-to-face assessments with or without the aid of colour charts and photos depicting the triphasic colour response have all been used and may be susceptible to recall bias. Cold challenge testing is a more objective assessment of vasoreactivity but is impractical in population studies.

Risk Factors for Primary RP

Age

While the onset of primary RP can be at any age, it is three times more common in those aged less than 40 years by which time in one prospective study of 424 people with RP, 73 % had developed symptoms [13]. Many patients with RP who are less than 40 years of age have a family history of primary RP [14]. RP appearing after the age of 40 years is considered late onset. In these patients, a positive family history is less common and secondary RP is more likely than primary [13]. Only 3 % of cases develop after the age of 60 [13].

Table 3.1 Prevalence of primary Raynaud's phenomenon

Country	Mean temperatures	Population studied	Ascertainment and definition	Number of people	Prevalence of RP
UK, 1990 [5]	ND	2 groups >15 years of age: patients attending 1 of 5 GPs in London; postal questionnaire to randomly selected patients of 2 GPs	Questionnaire followed by clinical interview; RP if white colour change, precipitated by cold and sensory symptoms	1,532 (413 in postal survey, 1,119 attending GP)	Postal survey: 19 % of women, 11 % of men Questionnaire at GP: 21 % of women, 16 % of men
South Carolina, 1990 [30]	ND	South Carolina residents >18 years	Face-to-face physician interview	5,246	3.5 % of total population 4.3 % of women, 2.7 % of men
Japan, 1991 [31]	ND	Japanese residents	Face-to-face physician interview with aid of photographs	3,873 (1,998 women, 1,875 men)	2.2 % of women, 1.2 % of men
Netherlands, 1992 [32]	ND	508 patients attending a GP	Questionnaire	508	2.9 % of women, 0.5 % of men
USA and France, 1997 [18]	5 regions ranging from warm coastal climates to cold mountainous regions	10,149 randomly selected people in Charleston (USA) and France	Telephone interview followed by face-to-face interview, clinical examination	10,149	5.8–20.2 % of women, 4.1–12.7 % of men Higher rates in cooler regions
USA, 1997 [6]	ND	4,182 (Framingham Study)	Physician-led questionnaire	4,182	All RP: 9.6 % of women, 8.1 % of men Primary RP over 16 years follow-up: 7.2 %
Estonia, 1998 [12]	ND	9,589 people (5,248 Finno-Ugric Estonians; 4,341 Indo-European Slavs)	Questionnaire followed by physical examination	9,589	4.0 % (higher prevalence among Slavs)
USA, 1999 [33]	ND	2,196 randomly chosen African American people living in inner-city Baltimore	Questionnaire, face-to-face interview RP if cold sensitivity plus cold-induced white or blue colour change of fingers	2,196	3.8 %
Greece, 2000 [9]	6.5 °C in winter, 24.8 °C in summer	500 of 756 randomly selected from hospital employees; mean age 33.7 years	Physician-led questionnaire, clinical examination	500	5.2 % 6.4 % of women, 0.9 % of men
UK, 2000 [34]		12,907 of 22,194 randomly selected from GP registration list in England, Wales and Scotland, and from armed forces in Britain; aged 16–64 years	Questionnaire; determined rates of finger blanching with clear demarcation	12,907 (5,994 women, 6,913 men)	4.6 %

(continued)

Table 3.1 (continued)

Country	Mean temperatures	Population studied	Ascertainment and definition	Number of people	Prevalence of RP
Spain, 2001 [35]	11 °C in winter, 22.8 °C in summer	276 people attending a GP in Valencia; mean age 54.4 years No concurrent CTD	Questionnaire	276 (205 women, 71 men)	3.3 % 3.4 % of women, 2.8 % of men Triphasic colour changes: 0 %; pallor only: 100 % of men, 57.1 % of women Pallor/cyanosis: 42.9 % of women
Turkey, 2003 [8]	−10 to 15 °C; 10–37 °C in summer	768 people >18 years (358 women, 410 men) attending GP. Excluded if comorbidities including secondary RP. Mean age 29.21 ± 10.35 years	Questionnaire. Diagnostic criteria as per UK Scleroderma Study group	768 (358 women, 410 men)	Definite RP: 5.9 % (mean age 24.78 years), male:female = 55:45 Probable RP: 7.0 % (mean age 26.94 years)
USA, 2005 [10]	ND	1,358 of 1,525 patients contacted; mean age 53.5 years; (Framingham Offspring study cohort)	RP clinical diagnosis, did not require two colour changes	1,358	10.9 % of women, 7.8 % of men
Italy, 2006 [3]	5.6 °C in winter, 21.6 °C in summer	2,155 of 3,664 randomly selected from 16 GPs in central Italy; aged >18 years (mean age 57.8 years)	Questionnaire, clinical examination RP if experienced pallor and sensory change precipitated by cold	2,155	2.1 % total population Male:female = 88.8:11.2 3.4 % of women, 0.5 % of men Positive for at least 1 criterion of CTD: 4.3 % Subsequently diagnosed with CTD: 0.28 %
Turkey, 2008 [7]	−0.6 to 6.8 °C in winter, 17.2–31.6 °C in summer	1,414 of 1,533 healthy medical students and hospital staff at a hospital in the Edirne Province, northwestern Turkey. Mean age women 27.0 years, men 27.5 years	Questionnaire Diagnostic criteria as per UK Scleroderma Study group	1,414 (838 women, 576 men)	Definite RP: 3.6 %
New Zealand, 2009 [4]	Varied; subtropical to sub-Antarctic	234 of 350 people randomly selected from New Zealand electoral roll	Questionnaire Diagnostic criteria as per UK Scleroderma Study group	234	Definite RP: 11.5 %

ND not described, *GP* general practice, *CTD* connective tissue disease

Female Sex

The prevalence of primary RP is consistently higher in women compared with men, being up to four times more common [15, 16]. This is particularly true for people aged less than 40 years as women are more likely to develop RP at a younger age and the prevalence of RP increases with age in men, as occupational exposures and atherosclerotic disease become more prevalent [17]. Prevalence rates of RP in men only exceed those in women in the setting of occupational exposure to vibration and hand trauma (Chap. 9).

Risk profiles differ between men and women. Fraenkel et al. reported that twice as many women who had been widowed, divorced or separated had RP than those who were married or had never married, suggesting emotional stress may have a role, but this relationship was not observed in men [17]. They also found that alcohol use doubled the risk of developing RP in women but not in men, while smoking increased the risk of RP in men only (odds ratio [OR] 2.6, 95 % CI 1.1–6.3) [17]. In contrast, another study found no association with either alcohol or smoking [18]. In both sexes, a lower body mass index is associated with a higher risk of developing RP, perhaps due to greater sensitivity to cold temperatures [15]. Whether the increased prevalence of RP in women is related to hormonal factors is unknown [17].

Environmental Factors

Relatively few environmental risk factors have been identified and many studies are cross-sectional or do not control for other factors.

In addition to triggering attacks, colder climate may have an aetiologic role. Subjects who have ever lived in colder climates have a higher prevalence of primary RP [19]. Few studies have directly compared the prevalence in different climates [19, 20] but the prevalence is generally higher in cooler locations, with Maricq et al. reporting rates up to 20.2 % in women and 12.7 % in men in cool mountainous regions [19].

The association with occupational factors such as vibration injury in particular, is well known but occupational risks have not been examined in most population studies of primary RP. Exposure to solvents, for example in medical laboratories, is associated with a higher prevalence of RP with symptoms of RP occurring more commonly in the absence of cold [21].

Genetic Factors (Including for Secondary RP)

Up to 50 % of subjects with primary RP have a family history of RP in first-degree relatives, particularly in women and in those with early onset RP [22, 23]. This suggests a genetic susceptibility although shared environmental factors could also contribute. In a study of female twins in the UK, Cherkas et al. found the concordance rates for cold sensitivity, RP and severe RP were all higher among monozygotic than dizygotic twins with heritability of 53 %, 55 % and 53 % respectively. Moreover, a potential contribution from the shared environment for all three traits was rejected [24].

Frech et al. found the relative risk of RP in first-degree relatives of patients with SSc compared with first-degree relatives of controls was 6.38 (95 % CI: 3.4–11.8) with decreasing risk with more distant relationships [25] This was greater than the risk of having SSc (RR 3.07) or an autoimmune disease (RR 2.49) and suggests the vasculopathy of RP is a heritable condition related to the vasculopathy of SSc but large genetic studies in this area are lacking. Polymorphisms of various candidate vasoactive mediator genes were not associated with RP in a small study of 95 cases [23]. Genetic abnormalities in the expression of type I interferon that predispose to abnormal endothelial cell senescence and apoptosis have been linked to SSc vasculopathy [26]. Similarly, a type I interferon signature on gene expression profiling may be associated with RP. This occurs in the setting of biallelic loss of protein expression mutations in the gene for tartrate-resistant acid phosphatase associated with bone dysplasia and increased autoimmunity including RP [27]. A two stage microsatellite-based genome wide study of six multi-case families in 2000 identified the β subunit of the muscle acetylcholine receptor and the serotonin 1B and 1E receptors as possible candidate genes for RP susceptibility [27]. For many common diseases,

single-nucleotide polymorphism-based, genome-wide association studies have been performed to identify genetic risk variants with great success. Despite the supportive evidence for a genetic component to the development of RP, such an approach has not yet been utilised. This is perhaps due to the lack of a sufficiently large collection of suitable cases with DNA available, and/or to the cost of such a study.

Polymorphisms in clotting factors leading to increased microvascular thrombosis do not appear to be increased in patients with primary RP [28].

Genetic factors may also influence the predisposition to secondary RP related to environmental factors such as vinyl chloride monomer (VCM) induced RP. A case-control study of 58 subjects with RP from a population of 305 French workers with a history of VCM exposure, found no association between M1 and GST T1 genetic polymorphisms of glutathione S-transferases, involved in VCM metabolism, and RP when analysed separately but when combined, were significantly associated with RP when compared with other combinations of genotypes (OR = 2.1, 95 % CI = 1.1–3.8) [29]

Secondary RP

Incidence and Prevalence of Secondary RP

Secondary RP occurs less frequently in the general population than primary RP, with a variable prevalence that depends on the underlying disorder (Table 3.2). Only 10 % have a positive family history [36].

In a small study of 118 patients seen in a rheumatology clinic in Italy, patients were classified as primary RP (29.7 %), secondary RP (53.3 %) or a third group with features suggestive of an underlying autoimmune disease but who did not yet meet full diagnostic criteria (16.9 %) [37]. An autoimmune disease was the most common underlying diagnosis in the secondary RP group (42.3 %), with SSc being the most common (25.4 %) followed by RA (7.6 %), SLE (5.9 %) and Sjogren's syndrome (1.7 %). Other major causes included vibrating tools and atherosclerosis (both 2.5 %) [37].

Similarly, a multicentre study in Italy of 761 patients with RP found primary RP in 35.2 % and secondary RP in 64.8 % of patients. SSc was the most common autoimmune disease (28.4 %) followed by SLE (6.8 %) and RA (5 %) [38]. A large proportion of patients (82.5 %) classified as

Table 3.2 Secondary Raynaud's phenomenon

Autoimmune disease
Systemic sclerosis
Rheumatoid arthritis
Sjogren's syndrome
Systemic lupus erythematosus
Dermatomyositis
Polymyositis
Occlusive vascular diseases
Atherosclerosis and emboli
Thromboangiitis obliterans (Buerger's disease)
Haematologic disorders
Cryofibrinogenaemia
Cryoglobulinaemia
Paraproteinaemia
Polycythaemia
Cold agglutinin disease
Neurologic disorders
Intervertebral disc disease
Carpal tunnel syndrome
Thoracic outlet syndrome
Pulmonary hypertension
Drugs
Ergot
Bleomycin
Cisplatin
Clonidine
Beta blockers
Cyclosporin
Interferon- α
Nicotine
Amphetamines
Cocaine
Vibration-induced
Vascular trauma
Hypothenar Hammer hand syndrome
Cold injury

Table adapted from UpToDate, Harrisons Internal Medicine

having primary RP had isolated features consistent with potential future development of an autoimmune disease. Common features included arthralgia (56 %), painless swelling of fingers (23.9 %), dryness of the mouth (21.6 %), migraine headaches (20.5 %), dryness of the eyes (16.8 %) and arthritis (15.7 %). This highlights the limitations of classifying RP into purely primary and secondary subtypes [38].

The annual incidence of secondary RP in the general population is unknown but among 112 patients with RP (73 % with primary RP, 14.3 % with secondary RP and the remainder suspected RP) attending a rheumatology clinic, followed for 5 years, the annual incidence of a concomitant disease that indicated secondary RP was 1.4 % [39].

Aetiology of Secondary RP

Systemic Sclerosis

The most common cause of secondary RP is SSc with rates of >95 % reported [40, 41] although a retrospective study of 61 patients with SSc in Malaysia, found a lower prevalence of 82.6 % [42]. This may reflect a difference in ethnicity, warmer climate or be due to recall bias. In most cases, RP is the initial presenting symptom of SSc and may precede other symptoms by 10 years [43, 44].

Walker et al. found a mean age of onset of RP of 42.9 years old for both limited and diffuse SSc although time until the next disease manifestation was significantly longer for those with limited disease (5 years versus 1.9 years) [41]. Patients who were anti-centromere positive were also found to have a significantly longer duration until the next disease manifestation compared to those who were anti-Scl70 positive (6.5 years versus 2.4 years). Subsequent organ involvement also varied depending on the age of onset of RP. In those who developed RP prior to the mean age of 42.9 years there was a higher rate of digital ulcers, but a lower rate of pulmonary fibrosis, pulmonary hypertension, diastolic dysfunction and arterial hypertension [41]. Age of onset is unrelated to geographic location [45].

Other Autoimmune Diseases

The reported prevalence of RP in RA ranges from 0 to 63 % [46]. Hartmann et al. performed a meta-analysis of 28 studies with 3,730 patients and using a random effects model, the overall estimate of prevalence was 12.3 % [46]. The prevalence fell from 11.2 % in 1977 to 9.4 % in 2012 although the definitions of RP varied amongst studies [46].

Between 12.5 and 33 % of patients with primary Sjogren's syndrome have RP, with the majority of studies reporting a prevalence closer to 33 % [47–53]. RP precedes the onset of sicca symptoms in 31–47 % of patients [49, 51–53], for a mean of 2.1 years in one study [52]. Multiple studies have demonstrated the course of RP to be relatively benign in this setting, with no patients developing acral necrosis [48, 49, 51, 52]. Pharmacological treatment is required in around a third of patients [52]. This subgroup of patients has a higher frequency of extra-glandular features compared to those without RP [48, 49, 53].

RP occurs in 2.5–60 % of patients with SLE [54–56], and is the most common cutaneous manifestation that is not lupus-specific [55]. Furthermore, it is more common in those with cutaneous lupus compared to those without [55]. Choojitarom et al. reported RP in 19.4 % of patients without a prior history of thrombosis but with at least one type of antiphospholipid antibody [57]. These patients had a higher rate of subsequent arterial thrombosis compared to those without RP (54 % compared with 18.5 %). Patients with SLE are also more likely to develop digital gangrene if they have concurrent RP [58].

There are few studies of RP in the idiopathic inflammatory myopathies. The prevalence in 30 patients in Jordan was 26 % although the definition of RP used was not documented [59]. A review of patients with anti-synthetase syndrome reported RP in 50 % of those with anti-Jo-1 antibodies and 40–100 % of those with anti-PL-12 antibodies [60].

Most patients with MCTD have features of SSc and the prevalence of RP is around 85 % [61]. RP also occurs in 46–56 % of patients with undifferentiated connective tissue disease, especially if they are female, have abnormal nailfold capillary microscopic changes and positive anti-RNP antibodies

[62, 63]. Other autoantibodies associated with RP include anti-Ku antibodies (67–79 %) [64, 65] and anti-Ki (42.8 %) [66].

Other Systemic Diseases

Occlusion of larger arteries can cause RP in relatively young people. The prevalence of RP in atherosclerotic peripheral vascular disease has been estimated to be 2.4 % [67]. In 103 patients with RP and no underlying disease, angiography demonstrated atherosclerotic stenoses in 44 patients who had a mean age of 47 years (half of whom had dyslipidemia), peripheral emboli in eight and thromboangiitis obliterans in three patients [68]. A meta-analysis of eight studies with 851 patients with thromboangiitis obliterans estimated the prevalence of RP to be 28.1 % [69]. As this disease causes segmental occlusions in limb arteries, mostly in male smokers, RP typically affects only one or two digits and may lead to severe limb ischemia.

Although studies of RP and increased plasma viscosity have conflicting results, Monti et al. reported that 19.5 % of 913 patients with cryoglobulinaemia had RP [70] and was more frequent in essential cryoglobulinaemia (19.9 %) and cryoglobulinaemia associated with autoimmune disease (36.7 %). This compared with the prevalence of RP in cryoglobulinaemia secondary to other diseases such as chronic liver disease (4.6 %) and lymphoproliferative disease (13.5 %) [70]. Other systemic diseases associated with RP include hepatitis C infection (11.8–22 % of those affected have RP) including those without cryoglobulinaemia (3.5 %) [71], human immunodeficiency virus (17.4 %) [72] and primary biliary cirrhosis, with (28.6 %) or without (8.9 %) pulmonary hypertension [73].

Neurologic Diseases

Rarely, RP complicates compression of the spinal cord or nerve roots due to intervertebral disc disease or tumours, or distal nerve compression in the carpal tunnel. A meta-analysis of eight trials with 675 patients with carpal tunnel syndrome with prevalence of RP ranging from 0 to 60 % estimated the prevalence of RP to be 15.5 % [74].

Thoracic outlet syndrome refers to the obstruction of the neurovascular bundle at the base of the neck. Vascular symptoms develop in approximately 10 % of patients. This can be RP or a non-specific constellation of symptoms of arm weakness, numbness, swelling, cyanosis and cold sensation [75]. No studies have assessed the prevalence of RP alone. It is possible that thoracic outlet syndrome and hand-arm vibration syndrome are interrelated although this is yet to be fully elucidated [75].

Drugs (Chap. 10)

Multiple drugs have been associated with RP, with cisplatin being the best studied. A meta-analysis of 24 studies with 2,749 patients found a prevalence of 0–64.3 % with an overall estimated prevalence of 24 % [76]. The onset of RP can be delayed 3–6 months after completing cisplatin-based chemotherapy regimens and be persistent in 10–49 % of cases [77]. There is a higher prevalence in those who receive five or more cycles of cisplatin [78] or in combination with bleomycin [77].

Meta-analyses of patients taking β-blocker drugs and interferon showed an overall estimated prevalence of RP of 14.7 % and 13.6 % respectively [79, 80].

Occupational Exposure to Vibration (Chap. 9)

Multiple epidemiological studies have demonstrated the association between RP and occupational exposure to vibration. Initially, excessive vibration can cause slight changes in sensation in the fingers, and with continued exposure this progresses to vibration white finger (VWF), also called hand-arm vibration syndrome. VWF is often used interchangeably with RP but there are some important differences. While both can lead to well-demarcated pallor of the fingers in response to cold or emotion, most studies of VWF do not mandate the biphasic or triphasic colour change characteristic of RP. In VWF, symptoms occur exclusively in the areas that have been exposed to vibration, thus do not occur in the toes, and severity correlates with the

degree of exposure [81]. The majority of cases are male and occupational vibration exposure comprises approximately one third of cases of RP in men compared with less than 4 % for women [34].

Studies of forestry workers, mechanics, quarry drillers and shipyard workers have found prevalence rates of VWF of 9.5–26.6 % [82–84], 15 % [85], 30.2 % [86] and 71 % [87] respectively. Bozenzi et al. studied workers exposed to hand-transmitted vibration including grinders, mechanics, caulkers, foundry workers, construction workers, quarry drillers, forest workers and workers in shipyards [88]. The prevalence of VWF was 17.2 %, varying from 9 % for grinders to 51.6 % for foundry workers. One prospective study by Hagberg et al. estimated the incidence to be 13.6 per 1,000 years of exposure [89].

Petersen at al. followed patients with VWF over 1–13 years (mean 5.3 years) [90]. Interestingly, while perceived frequency of attacks remained unchanged in 46 % of cases and increased in 32 %, finger systolic pressure actually improved in 43 %. A less favourable outcome was associated with ongoing vibration exposure, smoking, concurrent vascular disease and an earlier age at initial diagnosis.

Hypothenar hammer syndrome is another occupation-related syndrome in which repeated episodes of hand and wrist trauma result in damage to the ulnar artery, leading to aneurysmal dilatation with resultant embolisation and segmental occlusion. This may present as RP but is usually unilateral and associated with digital ulcers in the areas supplied by the affected vessel in 42.6 % of patients [91, 92]. It accounts for 1.13–1.17 % of all cases of RP, with 93.6 % of all cases being male [92]. Carpentier et al. showed that 13 (36.1 %) of 36 men with known ulnar artery occlusion also had RP, which in 8 (61.5 %), occurred only in the hand ipsilateral to the occlusion. 53.8 % had significant exposure to vibrating tools and 75 % had a history of repetitive palmar trauma. No women were studied [93].

Risk and Prognostic Factors for Progression to Systemic Disease

True primary RP may remit with time. In the Framingham Offspring study, primary RP remitted in 64.1 % in women and 64 % in men [10]. For others, RP may be the first sign of a systemic disease or indicate risk for other conditions such as migraine, unexplained syncope and gangrene.

Almost 99 % of patients with primary RP who progress to secondary RP develop an autoimmune disease [44]. Up to 37.2 % of 3,035 people with primary RP followed prospectively for 4.8 years by Pavlov et al. developed a definite connective tissue disease [94]. Patients who present after the age of 40, with a shorter duration of RP or worsening attacks are at risk of progressing to an autoimmune disease [43, 94, 95]. Patients with features suggestive of an underlying autoimmune disease at baseline are at the highest risk of disease progression [43, 44, 95, 96]. In the study by Pavlov et al., a scleroderma pattern of nailfold capillaries was strongly associated with the subsequent development of SSc and other autoimmune diseases [97].

Hirschl et al. followed 236 patients with primary RP for a mean of 11.2 years [43]. The annual incidence of progressing to suspected secondary RP was 2 % and to confirmed secondary RP was 1 %. The mean duration from suspected secondary RP to confirmation of an autoimmune disease was 5 years. Features that were most predictive included antinuclear antigen (ANA) >1:320, raised erythrocyte sedimentation rate (ESR) and abnormal nailfold capillary microscopy. Koenig et al. followed 586 patients with RP for a median 4 years, with 13.6 % progressing to a confirmed autoimmune disease, 92.6 % of whom developed SSc [96]. Patients with SSc-specific autoantibodies and/or abnormal findings on nailfold capillaroscopy at baseline were at the highest risk, with 47 % having SSc at 5 years and estimates of 69 % at 10 years and 79 % at 15 years. An earlier meta-analysis of ten studies with 639 patients with primary RP

also estimated that 12.6 % of patients developed a secondary disease [44]. As found by Koenig et al., a normal nailfold capillary pattern, negative ANA and absence of swollen fingers, telangiectasiae and sclerodactyly at baseline had a high negative predictive value [44, 96].

RP as Risk Factor for Digital Ischemia, Gangrene and Auto-amputation

Digital ulceration (DU) is a significant clinical problem in SSc-related RP, occurring in 30–58 % of patients [98–102], especially in diffuse SSc [100, 103]. The Canadian Scleroderma Research Group (CSRG) found current DU in 8 % of patients (11.9 % of diffuse SSc and 5.1 % of limited SSc) [100]. The prevalence of current DU was even higher in the German Network for Systemic Sclerosis registry at 24.1 % [102]. As expected, a greater proportion of patients have evidence of previous DU; in the CSRG study, 53.1 % of patients had digital pitting scars, again more commonly in diffuse SSc (63.2 % versus 46.6 % in limited cutaneous SSc) [100].

Studies have consistently shown younger age at onset of RP to be a significant risk factor for the later development of DU in SSc [100, 102]. Other risk factors include male gender, a higher ESR, younger age at first non-RP symptom and anti-Scl-70 antibodies [100]. Patients with DU are more likely to have RP than those without (98 % versus 94 %) [103]. DU typically develop within 5 years of the first non-RP symptom [103] and 32 % of patients experience recurrent or prolonged DU lasting over 6 months [101, 102].

Moderate to severe pain occurs in all patients and may necessitate opioid medication or hospitalisation. Other complications include superficial infections in 50 %, osteomyelitis in 1 %, bone and/or tendon exposure in 43 % and gangrene [99, 101–103]. Ultimately these complications lead to surgical or auto-amputation in 7–20 % due to irreversible tissue loss [101, 102]. The rate of gangrene and/or amputation rises to 30 % in those with prolonged DU of at least 6 months' duration. In those who have required amputation, there is a 1–2 % likelihood of requiring further amputation in the immediate 6–12 months [100] (Chap. 21).

Because of the risk of developing DU and/or gangrene, SSc-related RP may require aggressive treatment. Other causes of RP rarely lead to DU. There are case reports of DU in the setting of SLE and RP has been identified as a risk factor for gangrene, which develops in 0.67 % of patients with SLE [58]. DU occurs more commonly in the setting of antiphospholipid syndrome [104].

RP as Risk Factor for Other Organ Manifestations

The association between primary RP and migraines [23, 105–107] especially if the duration of primary RP is prolonged (OR 2.1, 95 % CI: 1.4–3.3) [108], has been interpreted by some authors to indicate a generalised disorder of vascular tone (Chap. 16).

Headache is a common complaint in patients with SLE, with migraine and tension-type headaches being the two most common subtypes. Studies conflict as to whether RP increases the risk of headache in these patients [109–111]

A small series of three retrospective and eight prospective cases of unexplained recurrent syncope and RP reported that nine also suffered from concurrent migraine with aura [112]. In all patients, syncope resolved after treatment with nifedipine, suggesting a possible relationship between RP and syncope [112].

Morbidity and Function

Primary RP follows a relatively benign course with minimal impact on overall function and quality of life. In many studies, the majority of cases have never presented to the healthcare system previously [34].

The greatest impact of secondary RP on morbidity and function arises from complications from DU and ischemic necrosis, namely pain, infection, gangrene and amputation, with

resultant loss of hand function. Hospitalisations in turn can lead to extended leave from work, financial difficulties and additional stress placed on family members [103].

Negative psychological effects arise from pain, hospitalisation, loss of function and disfigurement that are associated with self-esteem issues and higher HAQ scores [100, 103]. Those with persistent DU have a higher degree of disability [101].

Expert Opinion

Many of the epidemiologic studies of RP have limitations, particularly the lack of standardisation of the many variables that make direct comparison between studies difficult and also lead to a range of reported prevalence rates, for example of primary RP. Ideally, the prevalence of primary RP should be determined from a study sample selected at random from the general population to eliminate selection bias, utilise a standardised definition of RP (such as the UK Scleroderma Study Group definition) with physician-led assessments and account for potential confounders such as climate, race and previous occupational exposures. This is not the case in the majority of studies.

Other risk factors for RP also warrant further investigation. Exposure to cold is often a necessary trigger for RP and it is perhaps surprising that there are only two trials that directly compare prevalence rates of primary RP in different climates. There are no such trials in secondary RP. Many studies assessing the prevalence of primary RP have not included occupational exposure within their questionnaires, which in turn may have led to falsely high prevalence rates of primary RP. Exposure to vibration tools poses a significant risk for the development of RP, and this needs to be separated from primary RP when assessing prevalence rates.

Despite the supportive evidence for a genetic component to the development of RP, SNP based genome wide association studies have not yet been performed. This is perhaps due to the lack of a sufficiently large collection of suitable cases with DNA available, and/or to the cost of such a study.

Studies assessing the prevalence of secondary RP are limited in number, with some causes lacking any trials at all, including multiple drug agents. Within the trials performed, wide variation in results is again seen, reflecting a lack of standardisation of confounders. In addition, there is a lack of trials assessing incidence, both of primary and secondary RP.

On a pragmatic note for the clinician, young female patients who have not developed any additional features 2 years after the onset of RP alone are at low risk for developing an autoimmune disease. Older patients and male patients with RP should be followed as vasospastic symptoms may predate systemic disease by as many as 20 years.

Conclusions

The prevalence of RP in the general population in most studies is between 3 and 5 % with primary RP accounting for 80–90 % of cases. The prevalence of primary RP ranges from 2 to 20 % in women and 1–12 % in men depending on geographic location, the population studied, the definition of RP used and the method of case ascertainment.

Risk factors differ between women and men. The onset of RP in women is more common at an early age and is associated with a family history of RP, suggesting genetic factors may play a role in women as may hormonal and emotional factors. RP secondary to autoimmune disease is also more common in women than in men. In contrast, the prevalence of RP in men increases with age and is more likely to be secondary to occupational exposures such as vibration or atherosclerotic peripheral vascular disease.

The prevalence of secondary RP is related to the underlying disease. Progression to secondary RP occurs in 14–37 % of patients with primary RP. Almost 99 % of patients who progress develop an autoimmune disease, most commonly SSc. Risk factors for progression include positive ANA, elevated ESR, SSc-specific autoantibodies and/or abnormal nailfold capillaroscopy.

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Thermoregulation: The Normal Structure and Function of the Cutaneous Vascular System

4

Nicholas A. Flavahan

Abbreviations

ARs	Adrenergic receptors
AVAs	Arteriovenous anastomoses
BAT	Brown adipose tissue
BP	Blood pressure
NO	Nitric oxide
PVAT	Perivascular adipose tissue
ROS	Reactive oxygen species
SEM	scanning electron microscopy
UCP1	Uncoupling protein-1
WAT	White adipose tissue

Key Points

1. During exposure to cold, our bodies attempt to maintain normal core temperature by restricting heat loss, which is mediated by reducing blood flow to the skin (cutaneous vasoconstriction), and by increasing heat production (shivering and non-shivering thermogenesis).
2. Skin blood vessels are endowed with specialized structural and functional features that enable them to contribute to thermoregulation.
3. Arteriovenous anastomoses (AVAs) are direct connections between arterioles and venules that bypass the skin's nutritional capillaries and allow markedly increased blood flow to the skin. When there is need for heat conservation AVAs remain predominantly closed, whereas during heat elimination they are fully dilated and open.
4. Cold exposure increases the activity of the sympathetic nervous system, which is responsible for initiating cutaneous vasoconstriction and thermogenic responses. Local cooling of the extremities further amplifies the vasoconstrictor response to sympathetic nerve activity.
5. In the cutaneous circulation, sympathetic vasoconstriction and local cold-induced amplification of that response act selectively to restrict blood flow through AVAs, preserving important nutritional blood flow through skin capillaries.
6. Multiple mechanisms can contribute to sympathetic and local cold-induced amplification of vasoconstriction. However, a key component is activation of smooth muscle α_2-ARs, which initiates blood vessel constriction. These receptors are activated preferentially by norepinephrine released from sympathetic nerves in cutaneous blood vessels (including AVAs), and they are much more responsive at cold compared to warm temperatures.
7. The female cutaneous vascular system is especially sensitive to thermal challenges (warm and cold), which likely reflects the influence of estrogen on the blood vessel wall.

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Introduction

The skin is the largest continuous organ in the human body [26, 93, 106]. As with other organs, blood flow to the skin is required to provide rapid transport of oxygen and nutrients (including glucose and amino acids), rapid removal of waste products, and to provide a distribution network for remotely generated hormones, mediators, and cells (including inflammatory and immune cells), thereby enabling optimal activity and survival of skin tissue and the entire organism. The metabolic activity of skin is relatively low and can be accommodated by a fraction of skin blood flow [13, 93]. Most of the blood flowing to the skin does so as part of a complex thermoregulatory process designed to maintain our core temperature within a narrow range [13, 93]. Therefore, blood flow is highest during heat elimination when it can reach 7–8 L/min, and lowest during heat conservation when it can be almost zero [20, 58]. Skin blood vessels are endowed with specialized structural and functional features, which enable them to contribute to this important regulatory process.

General Aspects of the Vascular System and Blood Vessel Wall

The systemic cardiovascular system functions like a sophisticated plumbing system [88]. The heart pump cyclically ejects blood into large elastic arteries that act as distribution pipes and also to buffer the pulsatile pressure and flow coming from the pump [81, 82]. This distribution network branches out to the different organs via large muscular arteries and subsequently to small arteries and arterioles, which are <100 μm in diameter (approximate width of a human hair). These small arterioles function as the faucets within the system and are the major local determinants of organ blood flow [88]. Within this branching network, the number of parallel units increases exponentially, and one main organ artery can supply millions of arterioles. Although the diameter of individual vessels continually decreases in the arterial system, the total cross-sectional area concomitantly increases. This pattern peaks at the level of the capillaries, which have the smallest individual diameter but present the largest combined cross-sectional area [88]. Not surprisingly, capillaries are the major site of nutrient exchange within our organs. The venous system forms a reverse branching system to return blood to the heart. In contrast to the high pressure and low volume arterial system, the venous system is a low pressure and high volume or capacitance system. The venous system is therefore analogous to the storage tank in the plumbing system [88].

Blood flow is dependent on the positive driving force of blood pressure and the negative resistance to flow, which is determined by the blood vessel diameter. Blood vessel diameter is in turn regulated by rapid and reversible constriction of smooth muscle cells encircling the blood vessel lumen. Large proximal arteries have more absolute numbers of smooth muscle cells, but small arteries and arterioles have the largest relative amount of smooth muscle. This translates into the highest wall–lumen ratio for any blood vessel, making them ideal structures to regulate vascular resistance and to function as the vascular faucets [88]. Unlike smooth muscle cells in most blood vessels, those in small arteries and arterioles constrict in response to blood pressure (myogenic autoregulation) [32, 76, 84]. This basal vascular tone is then modulated by stimuli striving to regulate vessel diameter and blood flow (either further constriction or dilatation). The downstream capillaries do not contain smooth muscle cells, comprising essentially a single layer of endothelial cells with smooth muscle-like pericytes providing stability to these tiny but essential structures.

As would be expected in a sophisticated plumbing system, there are pressure sensors (or baroreceptors) located within central arteries that continually monitor blood pressure (BP) [88, 97]. Our ability to maintain BP within physiological limits is essential for our normal function and for our survival. Key regulation of BP begins the moment we step out of bed, because the gravitational impact on our vascular system initiates a decrease in BP that begins to restrict cerebral perfusion [49, 85, 105]. If the fall in BP is not

corrected, then we would quickly pass out and fall back into bed [85]. However, the decreased BP is immediately detected by the baroreceptors, which trigger a corrective increase in the frequency and strength of the heart pump, closure of numerous arteriolar faucets, and mobilization of the venous reservoir to provide more blood to the pump. BP is quickly restored and we can prepare breakfast without considering the calamity that almost befell us. These corrective measures are dependent on a baroreceptor-triggered increase in activity of sympathetic nerve fibers, which supply the heart, small arteries and arterioles, and numerous vessels within the venous system. The increase in sympathetic activity is triggered within the cardiovascular control center in our brain, often called "central command" [49, 85, 86, 105]. For all its sophistication, this process is a primitive survival mechanism and is prewired to respond to threats or perceived threats, often described as the "fight or flight" mechanism. To sustain any fight or flight outcome, blood flow to skeletal muscles (legs, arms) would need to increase dramatically, as would blood flow to the skin (to eliminate heat). Opening of arteriolar faucets within these organs would decrease BP and could precipitate a fainting spell, leaving us at the mercy of the imminent threat. By having a prewired system, whenever we experience stress or a perceived threat, BP rapidly increases as a result of increased sympathetic activity.

Activation of sympathetic nerves results in the release of neurotransmitters from storage vesicles in terminal nerve varicosities located in target organs and tissues. The main sympathetic neurotransmitter is norepinephrine (epinephrine/adrenaline is released from the adrenal medulla), which diffuses to cardiac and vascular cells and excites their activity by stimulating adrenergic receptors (adrenoceptors, ARs) on their cell surface (predominantly α_1- and α_2-ARs in blood vessels, β-ARs in the heart). Unlike hormones such as estrogen, norepinephrine is unable to diffuse through cell membranes and activate intracellular receptors. Once released, norepinephrine also activates "prejunctional" α_2-ARs located on the nerve fibers, which act in a negative feedback to inhibit the release of neurotransmitters and reduce sympathetic responses [22].

Ensuring that blood flow to individual organs matches their individual needs is not achieved through central command, which is predominantly engaged in maintaining blood pressure and therefore in restricting organ blood flow (notable exceptions are the brain, where arteriolar faucets are not functionally connected to the sympathetic system, and the heart, where the faucets contain increased levels of β-ARs that dilate smooth muscle cells) [87]. Key regulation of local blood flow is ultimately achieved at the local level. The arteriolar faucets are embedded within individual organs and are therefore exquisitely poised to detect the local environment and respond directly to those local cues [87]. The most important local cues are byproducts of local cellular metabolism (e.g., decreased O_2, increased CO_2, metabolites such as adenosine) which dilate the nearby arterioles and trigger increased blood flow to match the metabolic needs of the organ [87, 98]. These local metabolic changes can also suppress the activity of sympathetic nerves by inhibiting the release of norepinephrine, and so counter any attempts by central command to decrease blood flow ("functional sympatholysis") [87]. As a result, central command and sympathetic stimulation will be most effective in reducing blood flow to organs with lower metabolic activity (e.g., inactive skeletal muscle). Under physiological conditions, this ongoing conflict between central command and local organ requirements creates a highly efficient and effective control system.

A key component in the local regulation of blood flow and blood vessels is the endothelium, which comprises a single cell layer lining the entire cardiovascular system. Under normal conditions, the endothelium exerts a powerful protective influence on the vascular system, contributing to antithrombotic (inhibits clot formation), fibrinolytic (promotes clot dissolution), anti-inflammatory (prevents pathological effects of inflammatory cells and mediators), and dilator activity [36, 44, 64, 102]. Endothelial production and release of NO (nitric oxide) contributes importantly to the protective role of the endothelium, which includes relaxation of smooth muscle cells to cause blood vessel dilatation and increased blood flow. Production of NO (and

other secondary dilators including prostacyclin) is dramatically increased in response to endothelial cell activation [44, 64]. Numerous locally generated mediators (including byproducts of local cellular metabolism) can activate the endothelium to release NO [65]. The endothelium is also activated by the physical action of blood flowing across the endothelial surface (shear stress) [31, 46]. This flow-mediated response enables dilatation in small downstream arterioles to be conducted proximally to larger arteries, providing effective increases in blood flow to specific sites. Disease processes are associated with marked changes in endothelial function, which contributes to disease progression and pathogenesis (see Chap. 5) [36, 44, 64, 102].

Structural and Functional Organization of the Human Cutaneous Circulation

The vascular system supplying the skin comprises a complex interconnected "body carpet," with regional heterogeneity in vascular density, microvascular structure, and in the organization of the arterial supply system [93]. At the microvascular level, arterioles and venules form two distinct but interconnected systems: an upper network in the papillary dermis and a lower plexus in the dermal–subcutaneous interface [13]. The lower plexus connects with the upper network and also branches into a lateral system to supply sweat glands and hair follicles. The more superficial network has a higher microvascular density and is the source of nutritional capillary loops that extend vertically in an umbrella-like fashion into the dermal papilla [13, 83] (Fig. 4.1). These capillary loops are thought to maintain a similar overall ultrastructure at different skin regions, although their density can vary [13]. In the human finger, on the palmer side these umbrella-like nutritive capillary loops track the lines of our fingerprints ("vascular fingerprint") whereas on the lateral or dorsal side, they are less organized and tend to have reduced density [83] (Figs. 4.1 and 4.2). Under the nail, the orientation of the capillary loops change from vertical to a longitudinal

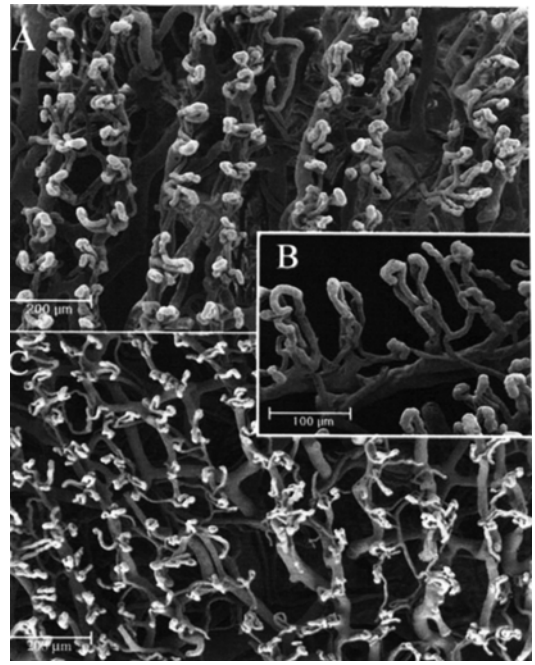

Fig. 4.1 The human cutaneous microvascular system. Three dimensional (3D) structure of the superficial microvascular system of human finger skin obtained by scanning electron microscopy (SEM) of corrosion casts [83]. On the palmer side of the finger (**a**), two rows of umbrella-shaped capillary loops follow the patterning of the fingerprint (see also Fig. 4.2). The capillary loop structures are ~100 µm high and have a dextrogyrate rotation, with a distance between each of ~70 µm (**b**). On the dorsal side, the capillary loops are randomly distributed (**c**) [Images reproduced with permission from [83]]

inclination as a result of the natural growing motion of the nail [83], which makes the capillaries highly accessible to imaging and analysis ("nailfold capillaroscopy," Chap. 10).

During heat stress, our skin contributes to body cooling by the generation and evaporation of sweat, and by dissipation of heat from the blood to the environment [6, 9, 10, 20]. Loss of heat from the skin vasculature is facilitated by the large cross-surface area of the vascular networks running parallel to the skin surface (e.g., Fig. 4.1) and by vasodilatation of skin blood vessels to increase blood flow. The structure and regulation of the cutaneous circulation differs between "hairy" skin (termed non-acral or non-glabrous skin), which covers most of the body surface and non-hairy skin (acral or glabrous), such as in the

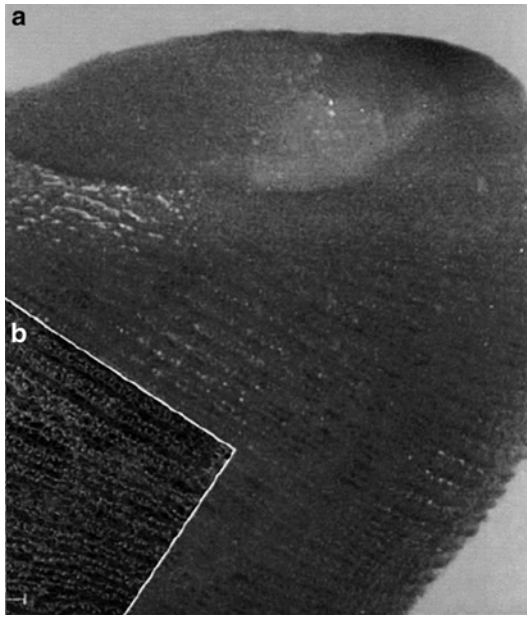

Fig. 4.2 The human microvascular fingerprint. Superimposition of the 3D structure of the superficial microvascular system (obtained by SEM of corrosion casts) (**b**) onto the original structure of the human finger (**a**, obtained earlier in the corrosion process) [83]. There is perfect correspondence between the alignment of the capillary loops and the fingerprint on the palmer side of the finger [Images reproduced with permission from [83]]

palmer aspects of the fingers, and in the nose, ears, palms, and plantar aspects of the feet and toes [72]. Glabrous skin contains a rich concentration of arteriovenous anastomoses (AVAs), which provide direct connections between arterioles and venules [6, 72, 96]. These structures allow blood flow to bypass the nutritional capillary loops, and so AVAs do not contribute to nutritional blood flow (Fig. 4.3). They are key thermoregulatory structures that can rapidly distribute high volumes of blood to the skin surface, enabling optimal regulation of core temperature [6]. Indeed, when there is need for heat conservation AVAs remain predominantly closed, whereas during heat elimination they are fully dilated and open [7]. In skin areas with AVAs, these structures enable blood flow to be rapidly altered by more than 100-fold. Three-dimensional analysis reveals remarkable heterogeneity of AVAs in the human finger, including direct connections (end-to-end, side-to-side, and end-to-side) and more complex structures [53, 69, 83] (Fig. 4.3). AVAs are located in both the lower and upper vascular plexuses [69, 83].

In contrast to most organs, the skin circulation is innervated by two distinct types of sympathetic nerve fibers: a traditional sympathetic adrenergic innervation, which releases norepinephrine to cause vasoconstriction, and a sympathetic cholinergic innervation, which releases acetylcholine to cause vasodilatation. Although non-glabrous skin has sympathetic adrenergic constrictor and cholinergic dilator innervation, glabrous AVA-containing skin lacks influence from the cholinergic dilator innervation [72]. Furthermore, the sympathetic cholinergic vasodilator nerves do not regulate cutaneous blood flow under thermoneutral conditions, and are only activated during hyperthermia [20, 58]. This unusual sympathetic cholinergic innervation also innervates sweat glands and stimulates heat loss via increased production of sweat, the generation of which also requires increased blood flow [9, 10, 20]. The sympathetic adrenergic system provides basal constrictor activity to the skin circulation, particularly in the extremities, contributing to a relatively low skin blood flow even in thermoneutral environments [9, 10, 20]. Body cooling further increases cutaneous sympathetic adrenergic constrictor activity and reduces finger blood flow, whereas body heating inhibits the basal activity of these nerves and increases finger blood flow [9, 10]. In both thermoneutral and cool environments, the sympathetic constrictor outflow to cutaneous blood vessels in the hands and feet is much greater than that to more proximal skin areas including the forearm [9, 10].

AVAs are richly innervated by the sympathetic adrenergic system [6, 67, 72]. In a thermoneutral environment, AVAs display cycles of constriction and dilatation, which occur at a frequency of 2–3/min [6, 14, 27]. This cyclical vasomotion is synchronous between AVAs at different anatomical locations (e.g., hands and feet), and is thought to be mediated by synchronous bursts of sympathetic adrenergic nerve activity [6, 14, 27, 66, 80, 96] (Fig. 4.4). AVA-independent nutritional blood flow in both glabrous and non-glabrous skin does not display such cyclical fluctuations

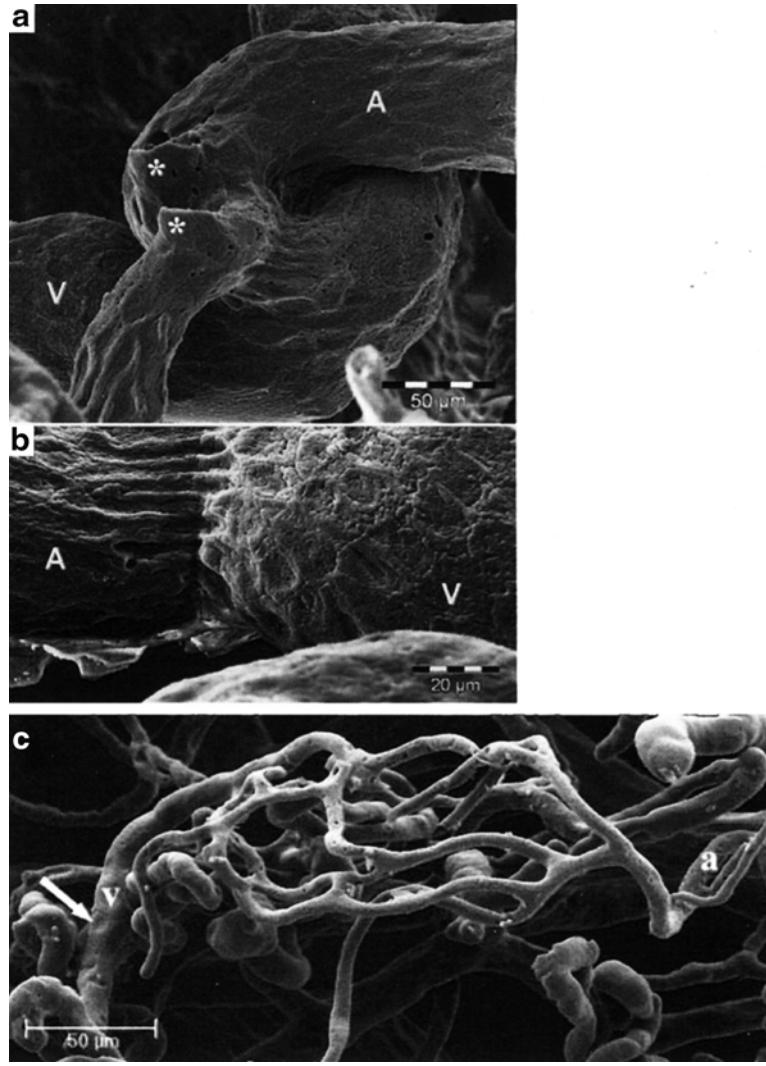

Fig. 4.3 AVAs in human finger skin. Corrosion casting demonstrates the heterogeneity of AVA structures in the cutaneous circulation of the human finger, with end-to-side (**a**), end-to-end (**b**), and more complex structures (**c**) [69, 83]. Within each image, *A*/*a* refers to arterioles and *V* refers to venules [Images reproduced with permission from [69, 83]]

[27, 66, 67, 78, 80, 96]. Reflex changes in sympathetic vasoconstrictor activity in response to changes in environmental temperature have a dramatic effect on AVA blood flow: during whole body heating AVA vasomotion is reduced because the structures are continuously dilated and open, whereas during whole body cooling AVA vasomotion is reduced because the anastomoses are continually constricted and closed [14, 96]. Sympathetic vasoconstrictor activity appears to have a greater impact to restrict blood flow through AVAs compared to nutritional blood flow in glabrous and non-glabrous skin. Indeed, in contrast to blood flow in AVAs, nutritional blood flow in glabrous finger skin is not influenced by increased sympathetic activity during moderate body cooling [27]. This divergence is also evident when sympathetic activity is increased via non-thermosensitive mechanisms, causing reduced digital artery blood flow without affecting nutritional blood flow [78]. Likewise, blood flow to non-glabrous skin is affected less by whole body cooling and reflex cold-induced vasoconstriction than flow through AVAs in glabrous skin [80, 96]. Nutritional blood flow in the digits therefore appears to be protected from sympathetic constrictor activity [78]. Increased sensitivity of AVAs to sympathetic activation is

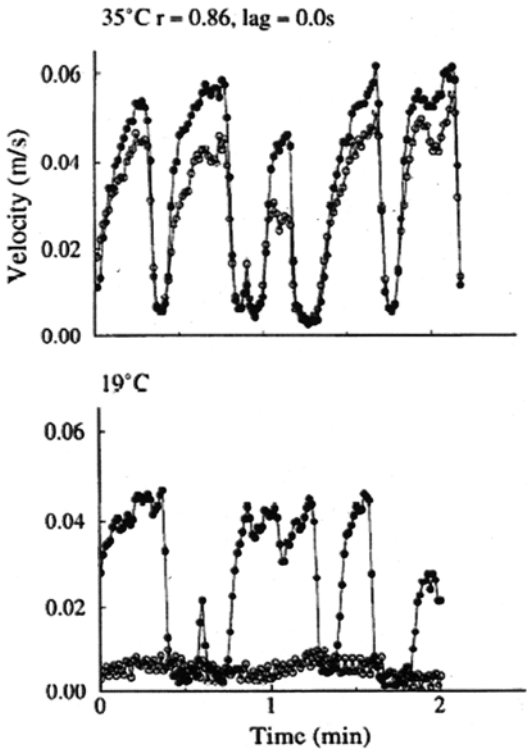

Fig. 4.4 AVA activity. Simultaneous measurement of blood flow velocity in digital arteries of the third fingers from the left (*closed circles*) and right hands (*open circles*) of a control individual when both hands were at 35 °C (*upper panel*) or after the right hand was cooled to 19 °C [7]. Note the remarkable synchrony of blood flow in the fingers at 35 °C, representing the synchronous burst of sympathetic constriction to AVAs in these anatomically distinct locations. During local cooling of the right hand, this vasomotion in the right finger was virtually abolished as a result of sustained closure of the AVAs [7]. Each symbol represents average velocity during 1 heart cycle (image adapted from [7])

also observed in response to local intra-arterial infusion of norepinephrine, which has a greater impact on reducing total digital blood flow and blood flow through AVAs compared to nutritional blood flow [27]. The increased influence of sympathetic activity on AVAs compared to nutritional blood flow may reflect increased expression of α-ARs, increased sympathetic innervation, and increased wall–lumen ratio of AVAs [27].

In addition to reflex increases in sympathetic constrictor activity during body cooling, local skin exposure to cold causes direct constriction of the cutaneous circulation. In the human finger, local cold-induced constriction is caused by constriction of the AVAs as well as the more proximal arteries supplying the finger [7, 8]. During local cooling, the constrictor phase of AVA vasomotion is prolonged, and with more exaggerated cooling there is sustained closure of AVAs and vasomotion abruptly ceases [7, 8, 67] (Fig. 4.4). This constriction is not mediated by an increase in sympathetic outflow but by direct local effects of cooling on the AVAs. AVAs appear to be more sensitive to moderate local cooling than blood flow through non-AVA nutritional arterioles [7]. During prolonged exposure to local cooling (after 5–10 min), the cold-induced vasoconstriction can be temporarily curtailed with periods of vasodilatation (the "hunting reaction"), which is mediated predominantly by transient opening of the AVAs [8].

Contrary to local cooling, which mostly affects AVAs, local warming has a greater impact on nutritional blood flow. AVA vasomotion is not affected by local warming and the accompanying vasodilatation appears to be mediated predominantly by dilatation of arterioles supplying nutritional blood flow [6, 7]. In non-glabrous skin, which does not contain AVAs, local warming of the skin initiates an increase in blood flow that is mediated initially by activation of local sensory nerve fibers and the release of neuropeptide vasodilators including CGRP [58, 72]. Both glabrous and non-glabrous skin are richly innerved with these sensory nerve fibers [72], suggesting that this mechanism likely contributes to local heat-induced increases in nutritional blood flow at both sites. If local heating is maintained, then the prolonged increases in blood flow appear to be mediated by increased activity of NO [58, 72].

Mechanisms Regulating Blood Flow Responses During Cold Exposure

Much of what we know concerning mechanisms that contribute to cold-induced regulation of the cutaneous circulation was derived using preclinical or animal models of the human circulation. Some of these mechanisms have subsequently been confirmed in the human circulation.

Therefore, in each section we consider preclinical models and how these translate into regulation of the human cutaneous circulation.

Modulation of Sympathetic and Adrenergic Constriction

Preclinical Models

Mammalian biological systems function optimally at warm temperatures, which is why our regulatory systems strive to maintain normal core body temperature. It is therefore surprising that a key aspect of that thermoregulation, the activity or constriction of cutaneous smooth muscle cells, actually increases during cold exposure. Indeed, in most blood vessels, moderate and severe reductions in temperature inhibit contractility and cause vasodilatation [100]. Cold-induced dilatation of cutaneous blood vessels can be observed when blood vessels are studied in the absence of stimulation or during constriction to numerous stimuli [100]. An important exception is cold exposure during constriction of cutaneous blood vessels to sympathetic adrenergic activation. Indeed, moderate cooling dramatically increases contraction to sympathetic nerve stimulation in cutaneous blood vessels, but inhibits the response in deep blood vessels [39, 42, 43, 101]. A similar trend was observed when responses to norepinephrine were assessed: cold exposure amplified the constriction in cutaneous blood vessels and inhibited the response in deep vessels [39, 42, 43]. This suggested that a key determinant of the unique cutaneous cold-induced constriction might be at the level of smooth muscle ARs. Although most blood vessels contain one class of α-ARs, the α_1-ARs, cutaneous arteries and veins have a much higher expression and activity of α_2-ARs on their smooth muscle cells [23, 37, 39, 42, 43]. Indeed, when released by sympathetic nerves in cutaneous blood vessels, norepinephrine causes vasoconstriction by preferentially activating α_2-ARs [39, 41]. This increased activity of α_2-ARs contributes to the unique cold-induced constriction of cutaneous blood vessels. Indeed, cooling powerfully amplifies constriction to stimulation of α_2-ARs, but inhibits constriction caused by α_1-ARs [39] (Fig. 4.5). Furthermore, inhibition or antagonism of α_2-ARs (but not α_1-ARs) prevented cold-induced amplification of norepinephrine-induced cutaneous constriction [39]. These experiments provided physiological rationale for increased α_2-ARs activity in cutaneous blood vessels, enabling them to withstand direct cold-induced vasodilatation and instead respond with enhanced vasoconstriction (Fig. 4.6). α_1-ARs also appear to have increased activity in cutaneous blood vessels (relative to deep blood vessels), which provides them with a buffer or reserve capacity to withstand the inhibitory effects of cold exposure on smooth muscle contractility [39, 41].

α_2-ARs comprise three distinct subtypes: α_{2A}-ARs, α_{2B}-ARs, and α_{2C}-ARs [22, 23]. Research that defined the role of these receptor subtypes in responses to cold employed a mouse model of the cutaneous circulation (isolated tail arteries and arterioles) and cultured cells artificially expressing the receptors. Cutaneous smooth muscle cells express α_{2A}-ARs and α_{2C}-ARs, but only α_{2C}-ARs are selectively involved in cold-induced vasoconstriction [22, 23, 25]. At warm temperatures, constriction caused by α_2-AR stimulation was mediated predominantly by α_{2A}-ARs with no evidence for involvement of α_{2C}-ARs [23]. However, although inhibition of α_{2C}-ARs had no effect on α_2-AR constriction at warm temperatures, it powerfully inhibited α_2-AR constriction at cold temperature and abolished cold-induced amplification and vasoconstriction in cutaneous arteries [23]. Antagonism of α_{2A}-ARs inhibited constriction at both temperatures, but cold-induced amplification remained intact, suggesting α_{2A}-ARs were active at both warm and cold temperatures, but were not modulated by temperature [23]. Therefore, α_{2A}-ARs appear to be permissive for cold-induced amplification of the α_{2C}-AR response, which may reflect an indirect or direct interaction between these different receptor species [22]. Temperature regulation of α_{2C}-AR activity reflects an intriguing cold-induced translocation of these receptors from intracellular stores to the cell-surface where they are accessible to stimulation by norepinephrine [2, 3, 22, 54]. Although cutaneous α_2-ARs were

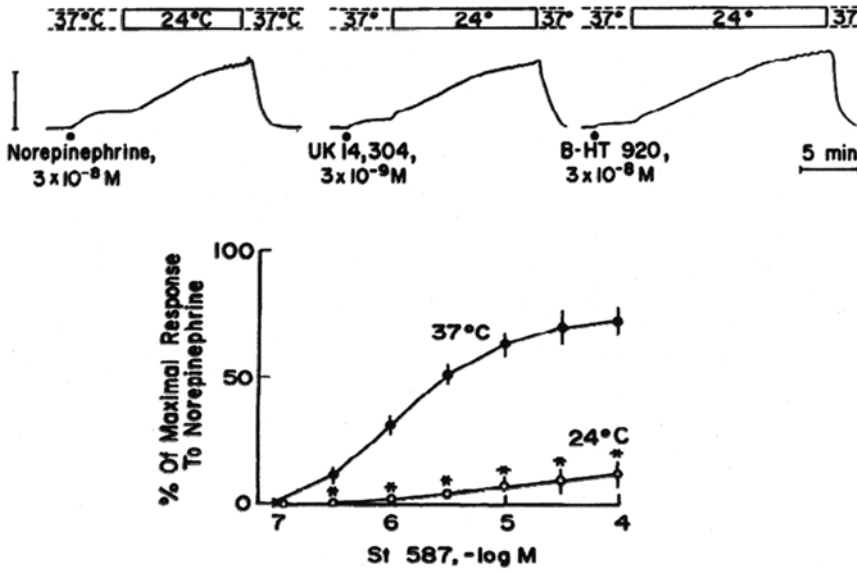

Fig. 4.5 Cooling increases α_2-AR but reduces α_1-AR contractile activity in cutaneous blood vessels. *Upper panel*: Transient cooling (from 37 to 24 °C) causes a dramatic increase in contractile responses to activation of smooth muscle α_2-ARs by norepinephrine or the highly selective α_2-AR agonists UK14,304 and BHT-920 [39]. Upward movement of the trace indicates contraction of an isolated canine saphenous vein, and the *bar* at the *top* indicates the temperature of the blood vessel [39]. *Lower panel*: in contrast to α_2-ARs, contraction of the same blood vessels by the highly selective α_1-AR agonist St 587 is virtually abolished when cooling is applied during the response. Contraction was assessed using a similar approach to the *upper panel*, but contraction is expressed as a % of the maximal response to norepinephrine, and presented as means ± SEM [39] [Images reproduced with permission from [39]]

originally considered to be thermosensors, they are more accurately described as thermo-effectors and are responding to cold-induced signaling within the smooth muscle cells. The key thermosensor appears to be the mitochondria of smooth muscle cells, which on exposure to cold generate a rapid increase in production of reactive oxygen species (ROS) [3]. These signaling intermediaries subsequently activate a signaling pathway RhoA/Rho kinase (ROCK), which promotes cold-induced translocation of α_{2C}-ARs to the cell surface [2, 3, 22, 54]. Indeed, direct activation of this pathway at warm temperatures also mobilizes α_{2C}-ARs to the cell surface [55]. Components of this signaling pathway are also responsible for driving expression of α_{2C}-ARs in cutaneous smooth muscle cells [22, 24, 55, 74], which suggests that the prolonged exposure of cutaneous blood vessels to reduced temperatures might increase expression of these powerful cold effectors.

Confirmation of these results was obtained in an in vivo model that analyzed regulation of blood flow to the glabrous region of the mouse paw [52]. In mice with drug-induced paralysis of sympathetic nerve fibers (tetrodotoxin), local cold exposure caused vasoconstriction that was mediated by activation of α_{2C}-ARs [52]. This reflected cold-induced amplification of vasoconstriction to circulating catecholamines (epinephrine, norepinephrine released from the adrenal medulla) [52]. Indeed, local cooling amplified constriction to activation of α_2-ARs (intra-arterial clonidine) but not α_1-ARs (phenylephrine). Furthermore, selective inhibition of α_{2C}-ARs did not affect α_2-AR constriction at normal temperatures, but abolished the cold-induced increase in constriction [52]. These results also demonstrate that cold-induced modulation of α_{2C}-ARs can amplify responses to circulating catecholamines and does not require functioning sympathetic nerves.

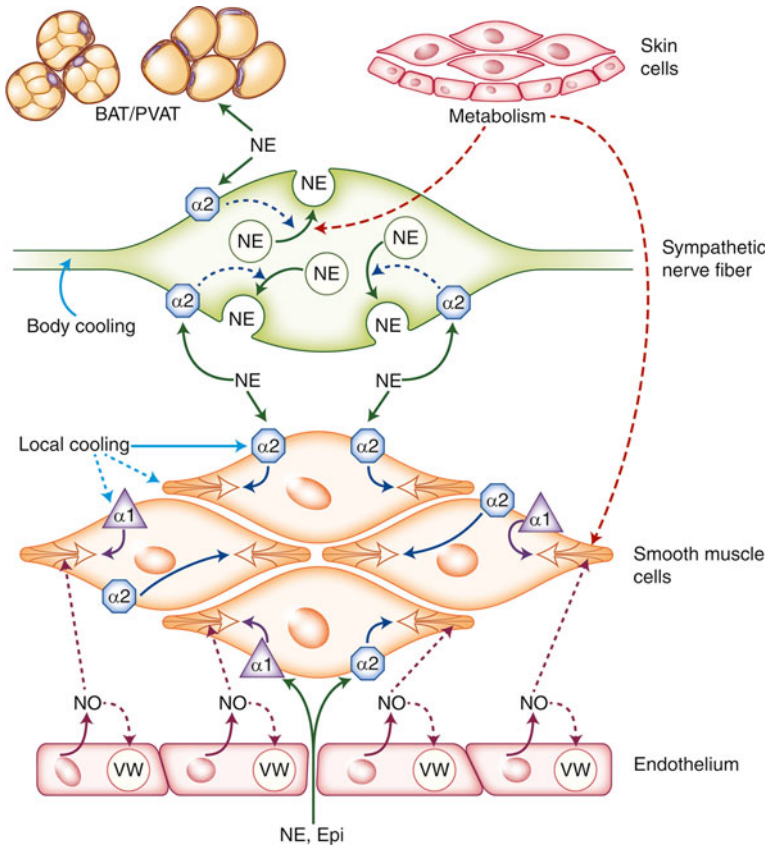

Fig. 4.6 Schematic representation of sympathetic neurotransmission in human skin. In sympathetic nerves, norepinephrine (NE) is located in small storage vesicles. During Body Cooling, there is increased activation of sympathetic nerve fibers and exocytotic release of NE, which causes blood vessel constriction by stimulating predominantly α_2-ARs located on smooth muscle cells. Norepinephrine also activates prejunctional α_2-ARs on sympathetic nerves to inhibit release of neurotransmitters, including NE. Local cooling amplifies α_2-AR constrictor activity, but inhibits smooth muscle constriction and α_1-AR constrictor activity. Smooth muscle α-ARs can also be activated by circulating norepinephrine and epinephrine (Epi) released from the adrenal medulla (and other sympathetic nerves). The endothelium releases NO, which causes dilation of smooth muscle cells. Local cooling is thought to reduce this dilation, which would result in further amplification of α_2-AR mediated constriction. Increased sympathetic nerve activity in response to Body Cooling not only reduces heat loss by initiating cutaneous vasoconstriction but also initiates heat production by activating thermogenesis in brown adipose tissue (BAT). Perivascular adipose tissue (PVAT) has morphological, genetic and proteomic similarity to BAT and may contribute to perivascular thermogenesis. Metabolic activity in neighboring skin and muscle cells (e.g., by releasing metabolic mediators such as adenosine) will dilate nutritional arterioles by inhibiting release of norepinephrine and by directly relaxing the smooth muscle. *Solid arrows* indicate activation, whereas *hatched arrows* reflect inhibition

Defining the role of smooth muscle α_2-ARs (and α_{2C}-ARs) during constriction to sympathetic nerve stimulation is more challenging because of prejunctional α_2-ARs, which act to reduce neurotransmitter release from the nerve fibers (Fig. 4.6). Indeed, in non-cutaneous blood vessels, which are dominated by smooth muscle α_1-ARs, α_2-AR stimulation causes marked vasodilatation during sympathetic nerve activity by inhibiting the release of norepinephrine [77]. α_2-AR inhibition or antagonism has the opposite effect, increasing vasoconstriction to sympathetic stimulation [77]. In cutaneous blood vessels, which are dominated by smooth muscle α_2-ARs, α_2-AR inhibition reduces sympathetic constriction, but this effect is diminished because of

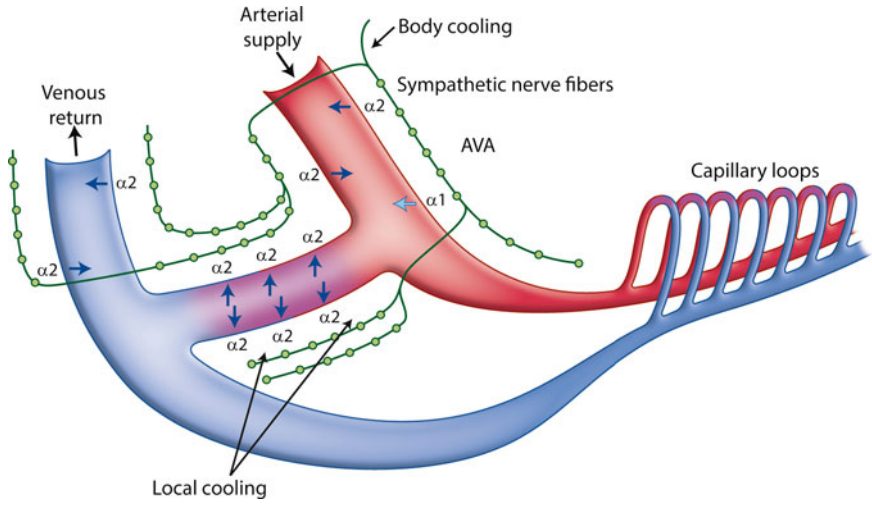

Fig. 4.7 Schematic representation of the cutaneous vascular system in human glabrous skin. The arterial supply system branches to an arteriovenous anastomosis (AVA) and also to nutritional capillary loops. In response to Body Cooling, there is increased activity of sympathetic nerves, which release norepinephrine to cause constriction predominantly of the AVA structures by activating α_2-ARs located on the smooth muscle cells. AVAs appear to have increased activity of this constrictor mechanism, whereas nutritional blood flow through capillary loops is protected from sympathetic constriction and is therefore maintained. Local cooling amplifies sympathetic α_2-AR dependent constriction of AVAs

increased release of norepinephrine and subsequent activation of smooth muscle α_1-ARs [41]. Prejunctional α_2-ARs comprise both α_{2A}-ARs and α_{2C}-ARs, and in contrast to smooth muscle, the neuronal α_{2C}-ARs are already localized to the cell surface [22]. Although α_2-AR blockade abolished cold-induced amplification of constriction to norepinephrine, only combined blockade of α_2-ARs and the constrictor activity of ATP (another transmitter released by sympathetic nerves) was able to prevent cold-induced amplification of constriction to sympathetic nerve stimulation [39, 45]. This likely reflects an increase in ATP release following inhibition of prejunctional α_2-ARs, and a cold-induced increase in smooth muscle contraction to ATP [45].

The Human Circulation

As in preclinical models, the smooth muscle cells of human cutaneous blood vessels have increased expression and activity of α_2-ARs compared to deeper blood vessels [25, 38, 40]. Indeed, the constrictor activity of α_2-ARs increases markedly on going from proximal to distal arteries in human limb arteries, with powerful constrictor activity in small digital arteries [38]. In contrast, the activity of α_1-ARs remains fairly constant [38].

Exposure to moderate whole body cooling caused a dramatic reduction in finger blood flow that was completely prevented by selective inhibition of α_2-ARs (yohimbine) but not significantly affected by selective inhibition of α_1-ARs (prazosin) [29]. This constriction is mediated by a reflex increase in sympathetic nerve activity and reduced blood flow through AVAs. Therefore, the results suggest that the smooth muscle of AVAs in the human finger are richly endowed with α_2-ARs and that sympathetic vasoconstriction of AVAs, including in response to whole body cooling, is mediated preferentially if not exclusively by α_2-ARs (Fig. 4.7). During this reflex increase in sympathetic activity, inhibition of α_1-ARs or α_2-ARs did not significantly affect nutritional blood flow in the finger, confirming the relative protection of finger nutritional blood flow from sympathetic responses [29].

Intra-arterial infusion of α_1-AR or α_2-AR agonists causes profound vasoconstriction of human finger blood flow [29, 48]. Under conditions of body heating (to reduce cutaneous sympathetic

nerve activity), local cooling amplified constriction evoked by activation of α_2-ARs whereas it inhibited constriction to α_1-AR stimulation [48]. In studies restricted to non-glabrous skin, mild local cooling causes rapid constriction that was markedly reduced by selective inhibition of α_2-ARs and only slightly reduced by inhibition of α_1-ARs [35]. Acute cold-induced amplification of α_2-AR constriction in non-glabrous skin is also inhibited by blocking ROCK, which would be consistent with cold-induced mobilization of α_{2C}-ARs [57, 95].

Therefore, results from preclinical models and clinical studies demonstrate that α_2-ARs located on the smooth muscle of cutaneous blood vessels represent a key mechanism for initiating vasoconstriction in response to cold exposure (Figs. 4.6 and 4.7). During body cooling, the resulting reflex sympathetic vasoconstriction in human fingers is mediated by α_2-ARs, confirming the preferential activation of these receptors by nerve-released norepinephrine in cutaneous blood vessels. Furthermore, the increased responsiveness of α_2-ARs at cool temperatures provides a mechanism whereby local cooling can initiate constriction and amplify the response to sympathetic stimulation. Because of the increased responsiveness of AVAs to vasoconstriction by sympathetic stimulation, exogenous norepinephrine and local cooling, the activity of smooth muscle α_2-ARs is likely to be increased in AVA compared to nutritional blood vessels (Fig. 4.7).

Secondary Vasomotor Mechanisms

In non-glabrous skin, although acute local cooling stimulates vasoconstriction that is mediated by α_2-ARs [35], more prolonged cooling (e.g., 40 min [95]) causes constriction that is mostly resistant to inhibition of α_1-AR or α_2-ARs [35, 95]. However, both responses are mediated by ROCK [95]. Therefore, local cooling likely activates Rho/ROCK signaling, as demonstrated in preclinical models, which initiates cold-induced vasoconstriction by amplifying smooth muscle α_{2C}-ARs [2] and then sustains constriction by α-AR independent mechanism(s) [57, 95]. Indeed, Rho/ROCK plays a central role in regulating contraction of smooth muscle cells by increasing the sensitivity of the contractile process to activator calcium ions [2, 95]. Vasoconstriction resulting from this calcium sensitization can be observed in cutaneous blood vessels during cold exposure [2]. It is not yet known if the cold-induced increase in ROS and Rho/ROCK signaling observed in smooth muscle cells also occurs in endothelial cells. If so, Rho/ROCK signaling can inhibit the production of NO through multiple mechanisms [107], whereas ROS can inactivate NO [15, 79]. Although the underlying mechanisms have not been defined, cold exposure inhibits NO-mediated vasodilatation [58, 72] (Fig. 4.6).

As observed in preclinical models, local cooling can also initiate transient vasodilatation in the human cutaneous circulation in humans, although it is most prominent following inhibition of ARs or during very rapid cooling [58, 72, 95]. The mechanisms responsible have not been identified.

Transient Receptor Potential (TRP) Channels

Our perception or ability to sense temperature is mediated by cutaneous thermosensitive sensory neurons. Distinct systems and mechanisms are thought to mediate the sensation of innocuous (15–30 °C) and noxious cool (<15 °C), as well as innocuous and noxious warm temperatures [70, 71]. A key mediator in cold-sensation is TRP melastatin 8 (TRPM8) channels, which respond to innocuous cold temperatures (threshold activation at 22–27 °C) and may also contribute to the sensation of noxious cold [1, 70, 71]. TRPM8 channels can be activated by menthol, which shifts the thermosensitivity of the channels enabling them to be active at warmer temperatures, and is responsible for menthol's pleasantly cool sensation [71]. How TRPM8 channels respond to cold temperatures has not been defined [70, 71]. Sensory nerve endings that express TRPM8 extend to multiple termination zones in glabrous and non-glabrous skin providing an

ideal location to detect and respond to decreases in ambient temperature [33, 91]. However, they are not localized to cutaneous blood vessels and any TRPM8 expression in vascular structures is less than that of sensory neurons [33, 91]. Emerging evidence suggests that cold-induced activation of TRPM8 on cutaneous sensory nerve endings contributes to thermoregulation.

During exposure to cold, we not only have the potential to restrict heat loss through cutaneous vasoconstriction but also to increase heat production through a process termed thermogenesis. Menthol application to the skin of mice initiated thermogenic responses comprising muscle shivering and activation of brown adipose tissue (BAT, see section "Brown and Perivascular Adipose Tissue"), which are responsible for generating heat [89, 90]. Indeed, menthol caused a significant increase in core body temperature, which was reduced in mice with genetic deletion of TRPM8 channels ($TRPM8^{-/-}$) [89, 90]. Furthermore, when exposed to a cold environment, there was minimal effects on core temperature in control animals ($TRPM8^{+/+}$) but a marked decrease in core temperature in $TRPM8^{-/-}$ mice [89]. Therefore, activation of the peripheral TRPM8-dependent sensory system initiates thermogenic responses, which counter the influence of cold exposure on core temperature [89]. Despite the strong activation of thermogenic responses, there appears to be a minimal if any role for the TRPM8 sensory system in preventing heat loss through activation of cutaneous vasoconstriction. Indeed, menthol actually increased skin temperature in control mice, which was reduced in $TRPM8^{-/-}$ animals [89]. This response would be consistent with an increased cutaneous blood flow, presumably in response to the TRPM8-dependent increase in core temperature. Furthermore, exposure to a cold environment caused a dramatic decrease in skin temperatures consistent with cutaneous vasoconstriction, which was the same in control and $TRPM8^{-/-}$ mice [89].

When administered to animals in a cool environment, newly developed inhibitors of TRMP8 caused a profound reduction in core temperature in control but not $TRPM8^{-/-}$ mice [1, 63]. This was associated with suppression of cold-induced activation of thermogenesis in BAT [1]. In contrast, the marked decrease in skin temperature in response to a cold environment was minimally affected by TRMP8 inhibition [1].

These results suggest that the TRPM8 sensory system plays a key role in thermoregulation, although it appears to be preferentially involved in maintaining core temperature by regulating thermogenic responses rather than through minimizing heat loss through peripheral cutaneous vasoconstriction.

There has been surprisingly little research performed on these mechanisms in the human cutaneous vascular system. Application of menthol to human non-glabrous forearm skin caused marked vasodilatation, which appeared to be mediated, at least in part, by acetylcholine [56]. Potential changes in core body temperatures were not assessed. Because sympathetic cholinergic vasodilator nerves are only activated during hyperthermia [20, 58], the vasodilatation to menthol may have occurred in response to an elevation in body temperature (e.g., following BAT activation).

Brown and Perivascular Adipose Tissue

In contrast to white fat or white adipose tissue (WAT), which acts predominantly to store energy, the function of brown fat or adipocytes (BAT) is to convert energy from food and fat stores into heat production [60, 92, 99, 104]. Brown adipocytes contain a large number of mitochondria, and the heat production results from uncoupling of electron transport from the normal mitochondrial process of ATP production. This uncoupling, which at least in rodents is mediated by uncoupling protein-1 (UCP1), causes a leakage of protons into the mitochondrial matrix, bypassing the ATP synthase and thus releasing energy [92, 99, 104].

BAT has long known to be present in rodents and to contribute to thermogenesis. In humans, BAT was known to be present in infants, but was thought to be quickly converted to WAT, so that functional BAT was absent in adults [19, 92]. We

now know that BAT is preserved in discrete fat depots in humans and that it contributes to thermogenesis during cold-exposure [19, 92, 99, 104]. BAT activity is inversely correlated with age and body mass index, and appears to be higher in females compared to males [92, 99, 104]. For example, BAT is threefold more likely to be detected in subjects <50 compared to those >64 years of age [92]. BAT thermogenic activity increases acutely following cold exposure, and BAT depots expand following chronic exposure to cold temperatures (including seasonal variation) [92].

BAT is densely innervated by the sympathetic adrenergic nervous system, which positively regulates its thermogenic activity [99, 104]. Following activation of the sympathetic system by cold exposure, norepinephrine acts via β-ARs to acutely increase thermogenic activity in existing BAT cells (UCP1 activation, stimulation of lipolysis), and under more chronic conditions to amplify and expand BAT activity (UCP1 expression, mitochondrial biogenesis, BAT expansion) [92, 99, 104] (Fig. 4.6). This latter process, termed adaptive thermogenesis also enables white adipocytes to trans-differentiate into brown-like adipocytes [92, 99, 104].

Fat tissue is closely associated with blood vessels throughout the vascular system. This perivascular adipose tissue (PVAT) was generally considered to be a structural support for the vascular system [18, 19]. However, recent research has demonstrated that PVAT has morphological, genetic and proteomic features that are similar to BAT and clearly distinct from WAT [18, 19] (Fig. 4.6). Moreover, studies performed in mice with genetic deletion of PVAT have demonstrated that during acute cold exposure, PVAT contributes to thermogenic activity and maintenance of intravascular temperatures [18, 19]. PVAT thermogenic capacity is further increased during chronic exposure to low temperatures [18, 19]. Interestingly, increased thermogenic activity of PVAT is associated with improved endothelial function and protection from vascular disease [18, 19]. In the arterial system, sympathetic nerve fibers are located in the exterior of the blood vessels, which would enable norepinephrine to diffuse into the blood vessel wall to activate vasoconstriction and also towards PVAT to activate thermogenesis (Fig. 4.6).

The status of PVAT surrounding cutaneous blood vessels, including the human circulation is unknown. By enabling local heat production, PVAT could counter the severity of cold-induced vasoconstriction in the cutaneous circulation. Brown adipocytes express cold-sensitive TRPM8 channels, which may enable BAT to respond directly to cold temperatures [68]. Likewise, PVAT may express these same channels and respond directly to reduced temperatures (TRPM8) as well as to cold-induced reflex increases in sympathetic stimulation (ARs) (Fig. 4.6). Interestingly, smooth muscle and PVAT adipocytes are thought to be derived from a common precursor [18, 19]. Given their shared heritage, it is especially intriguing that mitochondria are involved in initiating the cold-induced mobilization of α_{2C}-AR in smooth muscle and in driving thermogenesis in adipocytes. Indeed, ROS, which are generated by smooth muscle cells in response to cold exposure, increase the uncoupling activity of UCPs. Therefore similar mechanisms may be operative in both cell types to enable the cutaneous system to counter the effects of cold exposure through a reduction in heat loss (smooth muscle) and increased heat production (PVAT) [3, 12, 73].

Gender-Dependent Changes in Cold-Induced Vasoconstriction

The female cutaneous vascular system is especially sensitive to thermal challenges. Several studies have demonstrated that in a thermoneutral environment, hand and finger blood flow is higher in young men compared to young women [11, 30, 47, 94]. Indeed, under these conditions, the low levels of finger blood flow in young women can be comparable to the low levels observed in individuals with primary RPh [11]. However, this gender difference is not observed after menopause. In a thermoneutral setting, finger blood flow in young men and postmenopausal women are similar and markedly higher

than in young women [11]. This reduced blood flow in premenopausal women reflects increased sympathetic vasoconstriction [30]. Indeed, sympathetic-mediated cutaneous vasoconstriction is so intense in young women (and in primary RPh) that mental stress causes vasodilatation and an increase in finger blood flow, whereas in men only vasoconstriction is observed [30, 51]. This is thought to reflect concomitant vasodilator and sympathetic vasoconstrictor responses to mental stress, with the vasodilator response only visible when sympathetic constriction is almost maximal [30, 51]. Body warming, which inhibits sympathetic discharge (thermal sympatholysis) markedly increased blood flow in men and women, such that after combined local and body warming, hand blood flow in women actually surpassed that in men [30].

Cutaneous digital vascular responses to both local cooling (constriction) and local warming (dilatation) are highest in premenopausal women and those taking oral contraceptives, lowest in men and intermediate in postmenopausal women [4].

- The digital arterial blood flow of young women displays less tolerance to cold exposure than that of young men [94]. In response to local cooling, finger and hand blood flows are reduced to much lower levels in young women compared to young men [4, 11, 30]. There is also a more prolonged recovery time before normal blood flow is restored [11]. Furthermore, the digital arteries of young women were found to constrict in response to local cold exposure, whereas this was not observed in young men [75].
- The vasodilatation and increase in finger and hand blood flow during intense local warming was highest in premenopausal women (and those taking oral contraceptives) compared to men and postmenopausal women [4, 30, 103].

The increased thermosensitivity of the female cutaneous circulation is thought to be mediated by estrogen [30, 34, 50]. The sensitivity of the cutaneous circulation to local cold exposure appears to be highest during the mid-luteal phase of the menstrual cycle, and the recovery time correlated (in a negative manner) with serum levels of 17β-estradiol [5, 50, 94]. The reduced digital blood flow and increased sensitivity to cold-induced constriction can translate into cooler finger temperatures in women compared to men [4, 61, 94]. The concept of "cold hands, warm heart" reflects the higher core temperature of women, particularly in the luteal part of the menstrual period, while at the same time displaying reduced finger skin temperature [61]. Indeed, women feel colder during the luteal phase compared to other points of the menstrual cycle, even at a similar body temperature [50]. The exaggerated response of the cutaneous circulation to cold-induced constriction during this phase may reflect in part an increase in the thermoneutral set point [50].

Increased cold-induced vasoconstriction is likely mediated by an estrogen-dependent increase in adrenergic sensitivity [30, 34, 50]. Indeed, inhibition of α_2-ARs but not α_1-ARs prevented the amplified cold-induced finger vasoconstriction observed in females compared to males [16]. 17β-estradiol increases expression of cold-sensitive α_{2C}-ARs in human cutaneous smooth muscle cells [34], and causes a selective increase in cold-induced amplification of constriction to α_2-ARs in cutaneous arteries [34]. However, intra-arterial clonidine caused vasoconstriction of finger blood flow that was significantly greater in males compared to females [47]. This likely reflected the increased sympathetic activity in females and the prejunctional inhibitory influence of clonidine. Indeed, during indirect heating to partially reduce sympathetic activity, constriction to clonidine was significantly increased in females but not in males [47]. Local intra-arterial phenylephrine caused constriction that was either the same or greater in males compared to females, and was not influenced by indirect heating [28, 47].

In addition to increasing expression of constrictor adrenergic receptors, estrogen also increases the expression of endothelial nitric oxide (NO) synthase and endothelial production of NO [62]. Indeed, cyclical elevations in estrogen levels during the menstrual cycle are associated with increased vasodilatation to endothelial stimulation and increased vasoconstriction to norepinephrine [17, 59]. Local vasodilatation to

warming is enhanced when estrogen and progesterone are elevated compared to the low-hormone phase of the menstrual cycle, which is thought to reflect estrogenic amplification of NO or other mechanisms underlying the response [21, 58]. NO-mediated dilation is thought to contribute to the vasodilation caused by local skin warming (see section "Structural and Functional Organization of the Human Cutaneous Circulation").

The dual role of estrogen in increasing constriction and dilatation pathways likely explains why the female cutaneous system is more sensitive to cold-induced constriction and warm-induced dilatation.

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5 Pathophysiological Regulation of the Cutaneous Vascular System in Raynaud's Phenomenon

Nicholas A. Flavahan

Key Points

1. In a thermoneutral environment, digital blood flow is lower in individuals with Raynaud's phenomenon (RP) compared to control subjects, and this falls to dramatically low levels during exposure to cooler temperatures. In control subjects, body cooling selectively reduces blood flow through arteriovenous anastomoses (AVAs), whereas in RP both AVA and nutritional blood flow is decreased with more severe effects in secondary (SSc) compared to primary RP.
2. The reflex increase in sympathetic outflow in response to cold exposure is similar in control and RP subjects. However, the resulting cutaneous vasoconstriction and the ability of local cooling to amplify the sympathetic response are increased in RP. The increase in sympathetic activity can precipitate vasospasm in RP digital arteries, although this vasoconstrictor influence is dramatically increased by local cooling. In contrast, digital arteries of control subjects are minimally affected by these interventions. Increased reactivity of RP vasculature to cold exposure appears to be mediated by increased activity of smooth muscle α_2-ARs.
3. During cold exposure, the partial interruption of nutritional blood flow in primary RP reflects expansion of sympathetic constriction into digital arteries and arterioles, whereas the more severe disruption in SSc likely reflects additional dysfunction in endothelial flow-mediated dilation in these individuals.
4. Increased insight into cold-induced modulation of AVAs, arterial and venous compartments highlights the vascular basis of skin color changes that characterize RP episodes.
5. In contrast to primary RP, the secondary RP condition of SSc is associated with progressive structural deterioration and loss of the cutaneous nutritional microvasculature and a systemic vasculopathy.
6. Increased insight into RP and SSc highlights novel approaches to treating these disorders.

Introduction

Raynaud's phenomenon (RP) is an inappropriate, exaggerated response of the cutaneous circulation to cold exposure, which results in vasospasm and the characteristic pallor of the skin (Fig. 5.1). It commonly affects the fingers, but is also observed in the toes, nose, and ears. These areas of the skin are also prominent locations of arteriovenous anastomoses (AVAs), which are specialized thermoregulatory structures (see Chap. 4). RP is more prevalent in females compared to males (see Chap. 4), and can occur as a primary condition or secondary to an underlying disease

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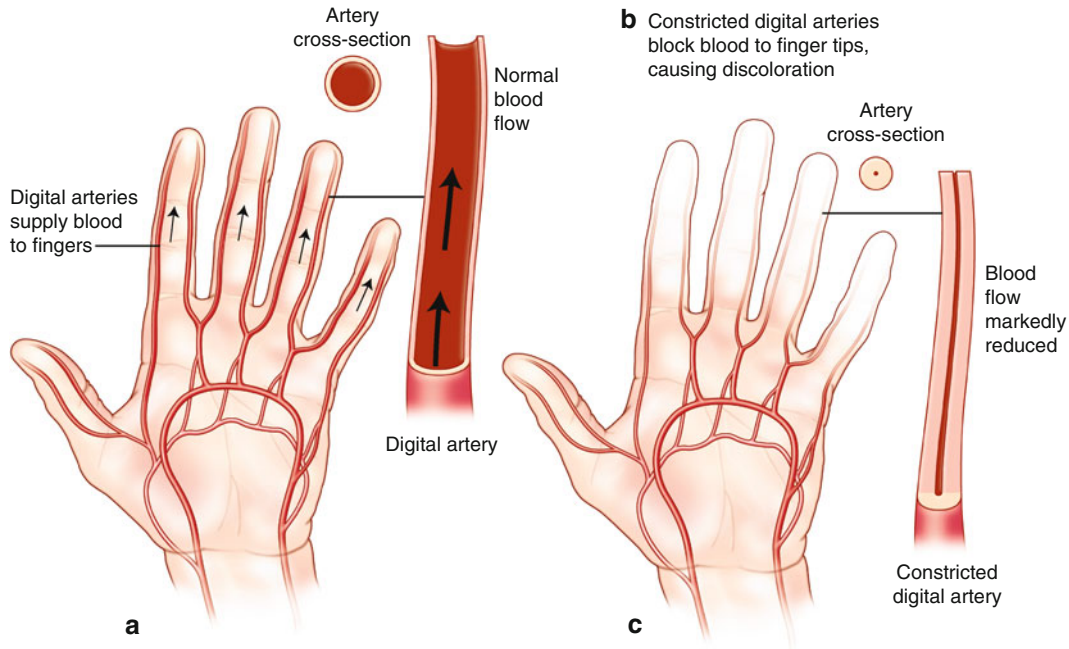

Fig. 5.1 RP. Schematic represention of RP demonstrating cold-induced constriction and vasospasm of the digital arteries, which precipitates a marked reduction in finger blood flow and contributes to the characteristic color changes

process or trauma. This chapter reviews the regulatory control of the cutaneous vascular system in primary RP and in secondary RP (in particular scleroderma—SSc).

Cutaneous Vascular Responses to Cold Exposure in RP

Numerous studies have observed that even in a thermoneutral environment, finger blood flow is lower in RP (primary and secondary) compared to control subjects [19, 22, 31, 58, 60, 78, 125]. During body cooling or a reduction in ambient temperature, blood flow falls to markedly low levels in individuals with RP [19, 31, 58, 78]. Indeed, blood flow can fall to absolute zero in secondary RP (SSc), although this was not observed in individuals with primary RP [31]. In response to localized cooling of the fingers or hands, individuals with primary and secondary forms of RP demonstrate increased sensitivity to cold, with more severe and more prolonged (slower recovery) reductions in finger blood flow [8, 67, 78, 109, 125]. Interestingly, during local warming, finger blood flow was higher in individuals with primary RP compared to control subjects, but remained significantly lower in SSc subjects [147]. This reduced ability of SSc subjects to dilate or increase blood flow is thought to reflect at least in part structural limitations of the SSc circulation (see section "Structural Changes in Cutaneous Circulation"). The ability of local warming to normalize finger blood flow in individuals with RP (including SSc) has been reported by other investigators [67, 109].

Finger blood flow comprises both nutritional blood flow and flow through AVAs (see Chap. 4). In control subjects, total and AVA blood flow are reduced in cool compared to warm environments, but nutritional capillary flow is unaffected and remains constant [19]. In contrast, nutritional, AVA and total flows were all significantly reduced when RP subjects are exposed to a cooler environment [19]. The decrease in nutritional blood flow was most marked for individuals with SSc compared to those with primary RP, whereas the reductions in AVA and total flow were not significantly different between individuals with primary RP and SSc [19]. The increased sensitivity of RP

nutritional blood flow to changes in ambient temperature was confirmed by imaging capillaries in the finger nailfold [91] A cool environment did not interrupt nutritional flow in control subjects but had a marked inhibitory effect in individuals with RP [91]. All SSc patients displayed severe disruption in nutritional blood flow, with most presenting a complete "standstill" and others with intermittent "stop and go" pattern of flow [91]. These changes were observed with less severe cooling in RP than was achieved with control subjects. In contrast to SSc patients, individuals with primary RP experienced milder effects on nutritional blood flow, with mostly intermittent standstill of flow [91].

In response to local cooling, digital arteries of individuals with Raynaud's phenomenon (primary and secondary) constrict more markedly than control subjects, resulting in vasospasm [103, 124, 125] (Fig. 5.2). At a relatively warm skin temperature (35 °C), the diameter of digital arteries was similar between control and RP subjects (luminal diameter of ~1.2 mm) [124]. When finger temperature was gradually reduced, the digital arteries of control and RP individuals initially behaved in a similar manner with slight constriction [124]. However, over the course of a narrow temperature range, digital arteries of RP subjects displayed a dramatic sensitivity to cooling, culminating in vasospasm of RP digital arteries at an average skin temperature of 19.2 ± 0.5 °C ($n = 12$, mean ± SEM) [124] (Fig. 5.2). In contrast, control arteries demonstrated only a slight constriction in response to cold even when skin temperatures were reduced to 14 °C [124] (Fig. 5.2). Similar results were obtained when the hands of control subjects and individuals with RP were exposed to abrupt local cooling (10 °C), which caused slight constriction of digital arteries in control subjects (8.7 %) but dramatic vasoconstriction in individuals with RP (92.4 %), with no significant difference between those with primary and secondary forms of the disease (including SSc) [103] (Fig. 5.2). Interestingly, local cold-vasospasm of RP digital arteries occurs over a similar temperature range as the local cold-induced closure of AVAs observed in control individuals (see Chap. 4, and section "Endothelial NO" in this Chapter).

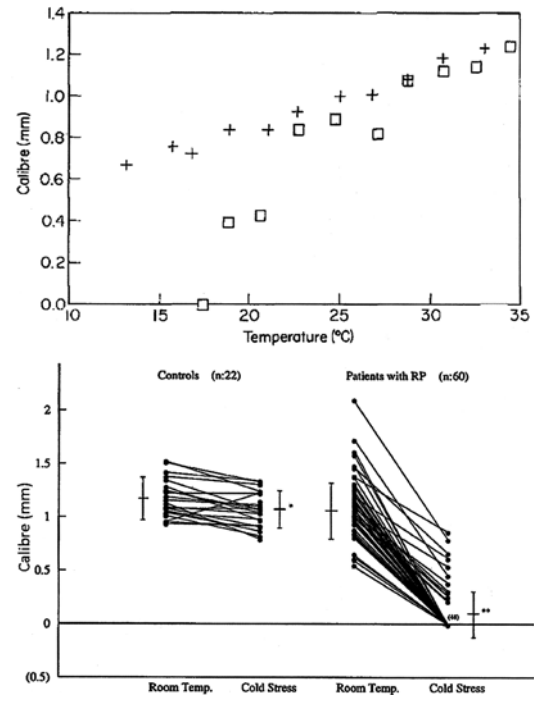

Fig. 5.2 Cold-induced vasospasm of digital arteries in RP. The diameters of digital arteries (index or middle fingers) in control subjects and in individuals with RP were determined using ultrasound imaging [103, 124]. *Upper panel*: Digital arterial diameters were determined in control subjects (+) and in individuals with RP (*open square*) during progressive local cooling of the finger. Vasospasm was complete in all RP subjects by 17 °C, whereas control subjects displayed only small decreases in diameter. Symbols represent average diameter values [124]. *Lower panel*: Digital artery diameters were determined in control and RP subjects at room temperature and after local cold stress (hand in 10 °C bath for 5 min) [103]. The cold stress had minimal effects in control subjects, but caused marked constriction in individuals with RP (48 had complete closure) [103]. Closed circles represent individual responses, whereas vertical bars indicate means ± SEM [103] [Images reproduced with permission from [103, 124]]

Mechanisms Contributing to Altered Vasoconstrictor Activity in RP

Sympathetic and Adrenergic Responses

Exposure to a cool environment (body cooling) causes an increase in sympathetic nerve fiber activity to the human cutaneous circulation (Chap. 4). This increase in sympathetic discharge

or nerve fiber activity is similar in control subjects and individuals with RP [32]. However, the constrictor response to that sympathetic stimulation [and to the sympathetic neurotransmitter norepinephrine [48]] is increased in RP compared to control individuals, and this increased reactivity is thought to be responsible for the enhanced cold-induced vasoconstriction summarized in section "Cutaneous Vascular Responses to Cold Exposure in RP."

Increased reactivity of the RP cutaneous circulation to sympathetic stimulation is especially evident in the important regulation of nutritional blood flow. Increased sympathetic activity during body cooling does not impact finger nutritional blood flow in control subjects, but causes a significant reduction in individuals with RP (section "Cutaneous Vascular Responses to Cold Exposure in RP"). This reduction in RP nutritional blood flow was prevented and nutritional flow restored to normal by intra-arterial treatment with low doses of reserpine, which blocks the release of norepinephrine from sympathetic nerve fibers [19]. When control subjects were exposed to the same cool environment, there was no change in nutritional blood flow and no significant effect of inhibiting norepinephrine-induced vasoconstriction on nutritional flow (inhibition of α_1-ARs or α_2-ARs) [21]. Therefore, sympathetic-mediated constriction expands from predominantly AVAs in normal individuals to additionally encompass the nutritional vasculature in individuals with RP. Indeed, nutritional blood vessels of individuals with secondary RP (SSc) have a marked increase in constrictor activity of smooth muscle α_2-ARs, but no change in activity of α_1-ARs [36].

The digital artery vasospasm occurring in RP (section "Cutaneous Vascular Responses to Cold Exposure in RP") is also dependent on sympathetic nerve activity. Reflex increases in sympathetic activity in response to body cooling can precipitate vasospasm in the absence of local cooling, especially in those with secondary disease [12]. However, the vasospastic potential of sympathetic activity in RP is dramatically increased by local finger cooling, and is more marked in individuals with secondary compared to primary forms of the disorder [12]. In contrast, when sympathetic nerve activity is decreased by body warming, the constrictor response to local finger cooling in RP is dramatically reduced [12]. Therefore, vasospasm of digital arteries in RP appears to reflect an increased activity of these blood vessels to sympathetic stimulation and also an increased cold-induced amplification of the response, compared to control subjects [12]. Local cooling of the fingers also amplified sympathetic-mediated constriction of hand blood flow (in response to neck cooling) to a significantly greater degree in RP compared to control subjects, which the authors proposed was mediated by a greater cold-induced amplification of α-AR constriction in RP [67].

Within the local sympathetic process, key mediators of cold-induced amplification are α_2-ARs located on the cutaneous smooth muscle cells, which have increased constrictor activity at cool temperatures (Chap. 4). However, assessing smooth muscle constrictor activity of α_2-ARs within the intact cardiovascular system is a daunting task. Because of inhibitory prejunctional α_2-ARs on vascular sympathetic nerves, α_2-AR inhibition will augment sympathetic transmission, increase the release of norepinephrine and promote vasoconstriction (see Chap. 4). Likewise, α_2-AR agonists will reduce sympathetic transmission and promote vasodilatation. These responses are the opposite of effects resulting from the inhibition or activation of smooth muscle α_2-ARs. This divergence is especially evident following systemic administration of α_2-AR ligands. α_2-ARs located in the central nervous system powerfully inhibit the sympathetic outflow [15]. Indeed, the preferential α_2-AR agonist clonidine was used clinically to treat hypertension, and reduce blood pressure by inhibiting sympathetic activity [110]. Likewise, oral clonidine was evaluated as a potential therapy for RP resulting from hand arm vibration syndrome (HAVS), with the goal of reducing the heightened sympathetic activity in digital arteries [112]. However, clonidine actually provoked RP in some individuals [112]. The observed effects of α_2-AR agonists and antagonists will be dependent on the activity of sympathetic nerves, and on whether they are administered locally or systemically. Smooth muscle constrictor activity

of α_2-AR agonists is best observed when sympathetic activity is low. Likewise, inhibition of sympathetic constriction by α_2-AR antagonists will occur only if the response is mediated predominantly, if not exclusively by α_2-ARs [39]. The analysis is further complicated by potential deficiencies in the selectivity and activity of the agonists or antagonists. For example, clonidine is a partial agonist with weak activity at α_2-ARs and very weak activity at α_{2C}-ARs [36]. Where possible, high efficacy agonists should be used (e.g., brimonidine—UK14,304) [36].

Local selective inhibition of α_2-ARs abolished cold-induced vasospastic attacks in individuals with primary RP, whereas inhibition of α_1-ARs had no effect [45]. In primary RP, the low finger blood flow during exposure to a cool environment was dramatically increased by local selective inhibition of α_2-ARs (sevenfold) or combined non-selective inhibition of α_1-ARs and α_2-ARs (sixfold), whereas local selective inhibition of α_1-ARs had a much smaller effect (twofold) [20]. In a separate study, under thermoneutral conditions, α_1-AR inhibition had a greater effect to increase blood flow in controls compared to primary RP, such that the difference in blood flow between controls and RP actually increased [22]. In contrast, α_2-AR inhibition caused greater dilatation in RP compared to controls and therefore diminished the differences in blood flow between these groups [22]. In individuals with primary RP, inhibition of α_1-ARs or α_2-ARs prevented vasoconstriction in finger blood flow to moderate local cold exposure [22]. This contrasts with other studies where α_1-AR blockade did not prevent cold-induced vasoconstriction in human finger blood flow in normal or RP subjects [18, 30]. In individuals with secondary RP (HAVS), cold-induced vasoconstriction was abolished after local selective inhibition of α_2-ARs [85].

Molecular expression of α-ARs on RP cutaneous arteries has not been determined. However, expression of α_2-ARs on circulating platelets is increased in individuals with primary RP compared to controls [28, 69]. Furthermore, the constrictor activity of smooth muscle α_2-ARs is dramatically and selectively increased in RP (SSc) compared to control arteries, which would be consistent with increased receptor expression [36] (Fig. 5.3). Similarly, when administered intra-arterially in a thermoneutral setting, the preferential α_2-AR agonist clonidine caused vasoconstriction in human fingers that was significantly increased in primary RP compared to control subjects [20] (Fig. 5.3). In contrast, constriction to the preferential α_1-AR agonist phenylephrine was similar between the two groups [20] (Fig. 5.3). Other studies confirmed this increased responsiveness to clonidine in primary RP compared to control subjects, although they also observed increased responsiveness to phenylephrine [49, 50]. When assessed during body heating (to reduce sympathetic activity), local cooling increased the constriction of finger blood flow to the preferential α_2-AR agonist clonidine in individuals with primary RP, whereas in control subjects local cooling actually inhibited responses to the agonist [49]. Local cooling did not affect constriction to the preferential α_1-AR agonist phenylephrine in controls or RP subjects [49]. In contrast to these analyses of finger blood flow, when constrictor activity was assessed directly in non-glabrous skin, norepinephrine or the α_2-AR agonist BHT933 evoked cutaneous vasoconstriction that was similar in control and secondary RP individuals (HAVS), whereas phenylephrine caused constriction that was reduced in RP (HAVS) [29].

Despite the caveats surrounding analysis of smooth muscle α_2-ARs, the ability of selective α_2-AR antagonists to prevent the vasospastic attacks of RP and to inhibit cold-induced vasoconstriction of finger blood flow in RP strongly implicates increased activity or expression of smooth muscle α_2-ARs in the pathogenesis of this disorder. This conclusion is reinforced by the increased constrictor activity of the preferential α_2-AR agonist clonidine in individuals with primary RP and increased contractile response to the highly selective α_2-AR agonist UK14,304 in secondary RP arterioles (SSc). Increased activity of α_2-ARs would explain the increased constrictor activity of the sympathetic nervous system (e.g., in response to body cooling), and the increased cold-induced amplification of that constriction in RP (Fig. 5.4). A key component of RP pathogenesis is the

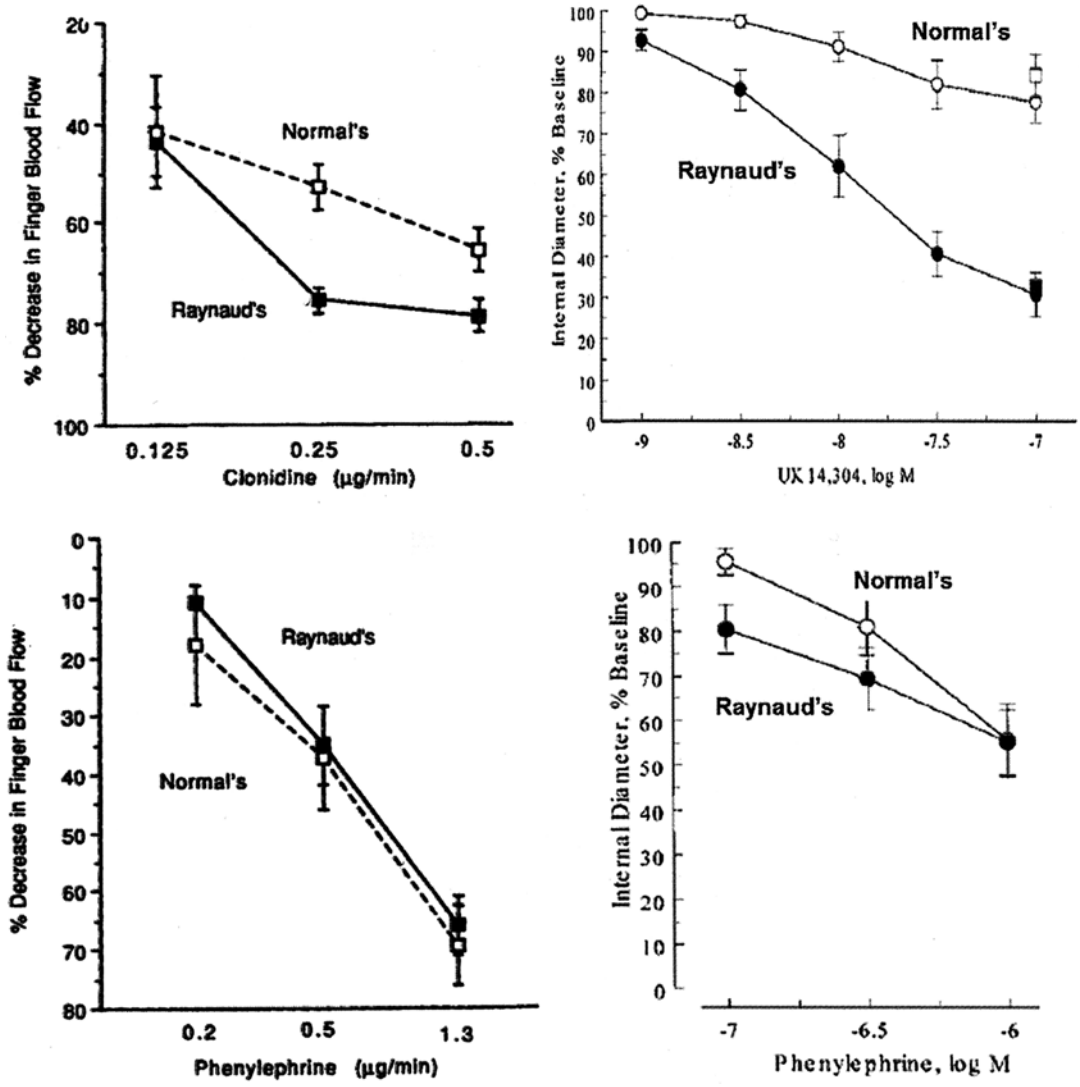

Fig. 5.3 α_2-AR vasoconstriction is selectively increased in RP. *Left panels*: Fingertip blood flow was assessed in control subjects (*open square*) and in individuals with primary RP (*closed square*), under basal conditions and in response to increasing intra-arterial doses of the preferential α_2-AR agonist clonidine (*top*) or the preferential α_1-AR agonist phenylephrine (*bottom*) [20]. Constrictor responses to clonidine were increased in RP compared to controls, whereas responses to phenylephrine were similar in control and RP individuals [20]. *Right panels*: Contractile responses of nutritional arterioles isolated from control subjects (*open circle*) and individuals with secondary RP (SSc, *closed circle*) were assessed in response to the selective α_2-AR agonist UK 14,304 (*top*) or the α_1-AR agonist phenylephrine (*bottom*). In addition, the response to UK 14,304 is also presented for endothelium-denuded arterioles (*open* and *closed squares*). SSc arterioles had increased reactivity to α_2-AR stimulation, whereas responses to α_1-AR were not significantly different between control and SSc arterioles

expansion of powerful sympathetic-mediated vasoconstriction from predominantly AVAs in control subjects to digital arteries and arterioles in individuals with RP (Fig. 5.5). This expansion of sympathetic constriction, which is also likely to be mediated by increased activity of smooth muscle α_2-ARs, explains the interruption in nutritional blood flow that occurs in primary RP and to a greater degree in secondary RP (SSc) (Fig. 5.5) (see also section "Endothelial NO").

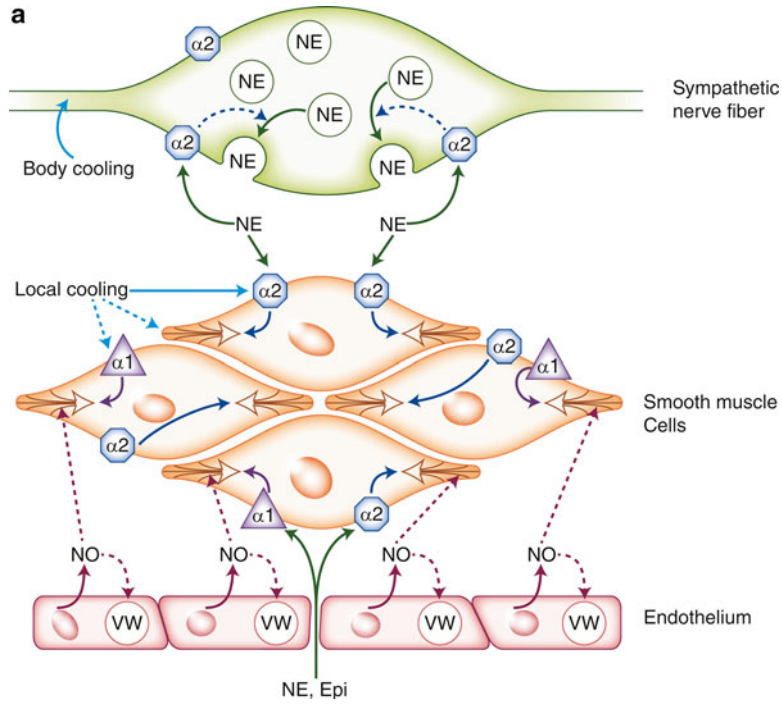

Fig. 5.4 Schematic representation of sympathetic neurotransmission in cutaneous blood vessels and its likely modulation in RP. Norepinephrine (NE) is located in small storage vesicles within sympathetic nerve varicosities. (**a**): *Controls*. During Body Cooling, there is increased activation of sympathetic nerve fibers and exocytotic release of NE, which causes blood vessel constriction by predominantly stimulating α_2-ARs located on the smooth muscle cells. Norepinephrine also activates prejunctional α_2-ARs located on the sympathetic nerves to inhibit release of sympathetic neurotransmitters. Local cooling amplifies α_2-AR constrictor activity, but inhibits smooth muscle constriction and α_1-AR-mediated responses. Smooth muscle α-ARs can also be activated by circulating norepinephrine and epinephrine (Epi) released from the adrenal medulla (and other sympathetic nerves). The endothelium releases NO, which causes dilatation of smooth muscle cells. Local cooling is thought to reduce this dilatation, which would result in amplified α_2-AR constrictor activity. (**b**): *Primary RP*. Increased activity of α_2-ARs on smooth muscle cells is likely responsible for the increased constriction to sympathetic nerve stimulation (including during Body Cooling) and to increased amplification of sympathetic constriction in response to local cooling. (**c**): *SSc*. SSc is additionally characterized by a marked change in endothelial function with reduced activity of NO, precipitating increased constrictor responses to α_2-AR stimulation and increased exocytosis of ET-1 and ULVWF (VW). This latter response appears to be most evident in superficial blood vessels and the resulting constriction to ET-1 is likely most prominent in nutritional arterioles. SSc arteries are also associated with intimal fibrotic lesions mediated by mesenchymal cells. *Solid arrows* indicate activation, whereas *hatched arrows* reflect inhibition

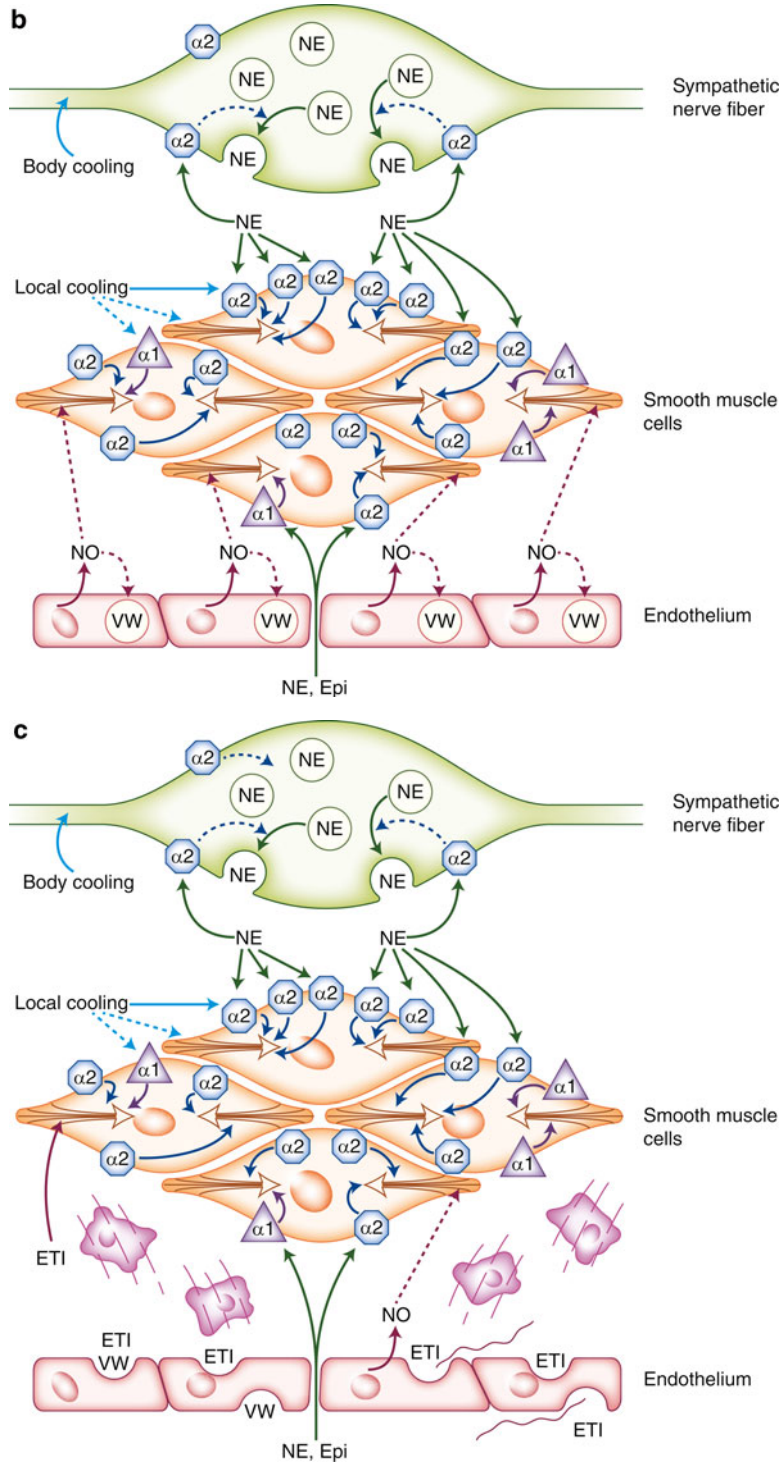

Fig. 5.4 (continued)

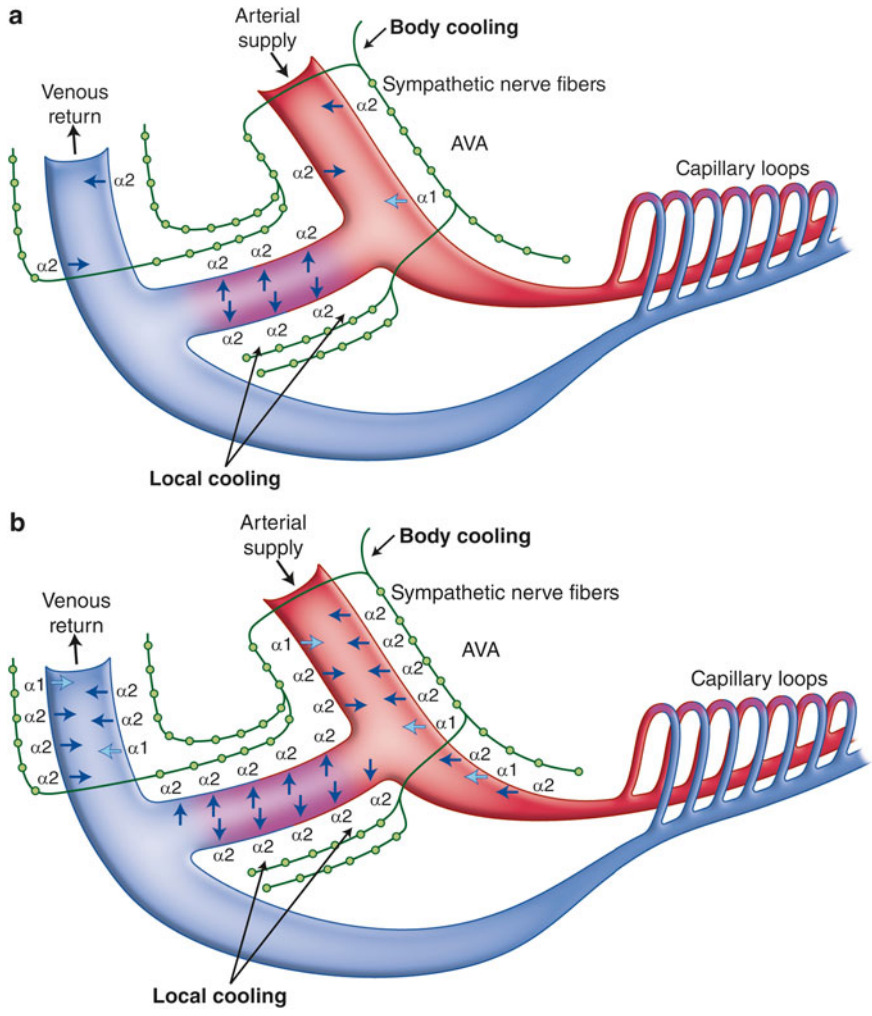

Fig. 5.5 Schematic representation of the cutaneous vascular system in human glabrous skin in control (**a**), primary RP (**b**), and SSc (**c**) subjects. The arterial supply system branches to an arteriovenous anastomosis (AVA) and also to nutritional capillary loops. (**a**): *Controls*. In response to Body Cooling, there is increased activity of sympathetic nerves, which release norepinephrine to cause constriction predominantly of the AVA structures by activating α_2-ARs located on the smooth muscle cells. AVAs appear to have increased activity of this constrictor mechanism and nutritional blood flow through capillary loops is protected from sympathetic constriction and is therefore maintained. Local cooling amplifies sympathetic α_2-AR dependent constriction of AVAs. (**b**): *Primary RP*. In Primary RP, Body Cooling causes the same increase in activity of sympathetic nerves, but cutaneous blood vessels have a more pronounced response to the sympathetic neurotransmitter(s). This likely represents increased expression of smooth muscle α_2-ARs causing increased constriction of cutaneous veins, AVAs and the arterial supply. Increased expression of constrictor α_2-ARs would also cause these blood vessels to be more responsive to local cooling. This expansion of sympathetic and local cold-induced constriction to more proximal arteries and to nutritional arterioles is responsible for the vasospasm of digital arteries and for slight disruption in nutritional blood flow to capillary loops. (**c**): *SSc*. In SSc, in addition to increased sympathetic constriction, there are structural changes in the vascular system comprising intimal lesions in arteries and arterioles and disruption of the nutritional capillaries. Because of these changes and the additional dysfunction in arterial endothelial flow-mediated dilatation, the profound constriction occurring in the upstream arterial system causes profound disruption in nutritional blood flow and ischemic injury

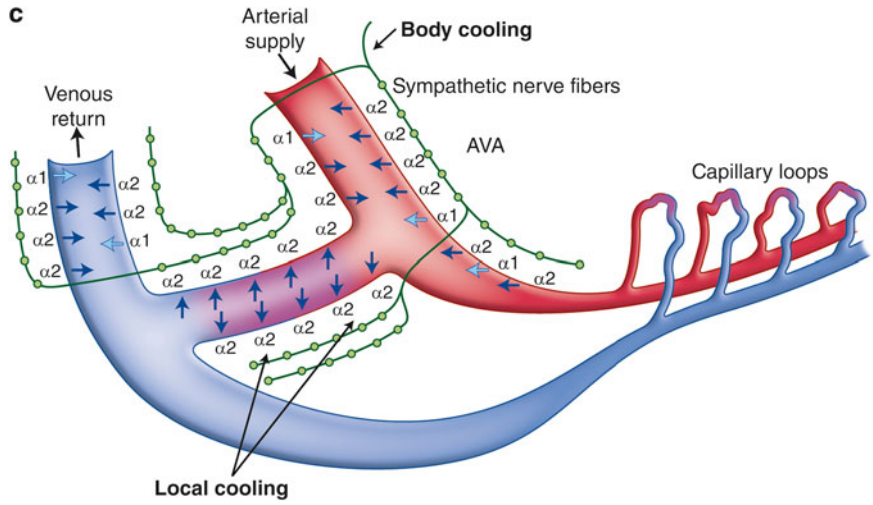

Fig. 5.5 (continued)

Vascular Mechanisms Underlying the Characteristic Color Changes of RP

RP episodes are generally associated with progressive color changes: initial pallor or blanching followed by cyanosis then rubor, which has been likened to the French tricolor of white, blue and red [74] (Fig. 5.1). The initial pallor of affected skin reflects cold-induced digital artery vasospasm, which will cause an abrupt and marked reduction in arterial inflow. However, the remarkable whitening suggests that cutaneous veins also undergo severe cold-induced vasoconstriction (venous spasm), which would rapidly remove blood from the low pressure, large volume venous system (see Chap. 4 for discussion). Veins are generally considered as weak and sluggish effectors. Although this is often the case in deep veins, cutaneous veins exert very powerful and rapid responses to sympathetic activation [39, 41]. Furthermore, sympathetic neurotransmission can actually be more effective in cutaneous veins compared to arteries. In arteries, because of their high pressure, nerve fibers are restricted to the outer circumference of the blood vessel wall, and norepinephrine diffuses between smooth muscle cells to regulate vascular contractility and diameter (Fig. 5.4). In contrast, in the low pressure cutaneous venous system, sympathetic nerve fibers penetrate the blood vessel wall and release norepinephrine directly on smooth muscle cells. The smooth muscle of cutaneous veins also has an exceptionally high activity of α_2-ARs, making them highly responsive to local cold-induced amplification of sympathetic constriction [17, 37, 42].

The initial pallor of the skin can be followed by the cyanotic phase (Fig. 5.1). This is often ascribed to hypoxia or lack of oxygen causing inappropriate deoxygenation (and hence blueing) of the blood. However, it is likely mediated by early vasodilatation of the cutaneous venous system while the AVAs remain in a highly constricted state. The dilated cutaneous venous system would therefore expand with deoxygenated blood flowing from nutritional capillaries and from deeper veins. The venous system in glabrous skin likely has a high volume or capacity, which would be required to accommodate high levels of AVA blood flow during heat stress. Therefore, the dilated cutaneous venous system will provide a high capacity for deoxygenated blood and also a low flow rate, resulting in the unusual cyanotic appearance. More rapid dilatation of cutaneous veins compared to AVA could reflect the more intimate association of sympathetic nerves with

venous smooth muscle, which would allow for more rapid removal of norepinephrine (via neuronal uptake), or from differences in smooth muscle contractile dynamics in veins versus AVAs.

The cyanotic phase is followed by rubor or reddening of the skin. This phase is often attributed to ischemic dilatation of the skin's nutritional blood supply (hyperemia). However, a more likely explanation is that it predominantly reflects the delayed dilatation of AVAs allowing a large influx of fully oxygenated blood (AVA flow bypasses the nutritional capillaries) into the dilated venous system. The high flow of this richer red blood through the dilated venous system will displace the bluer deoxygenated blood and provide the rubor appearance of the skin.

Finally, normal sympathetic regulation of the cutaneous arterial system, the AVAs and venous system will restore normal coloration to the skin.

Endothelial NO

Endothelial cells respond to numerous stimuli by increasing production of the powerful vasodilator and protective mediator NO, as well as secondary vasodilators such as prostacyclin (Chap. 4) (Fig. 5.4). Indeed, even norepinephrine acting on endothelial α_2-ARs can initiate endothelium-dependent vasodilatation [40]. Although endothelial α_2-ARs are most active in the coronary circulation, they have the potential to initiate dilatation in cutaneous arteries [23, 40]. The physical action of the blood stream is a key endothelial activator, with increasing blood flow causing increased production of endothelial dilators and endothelium-dependent dilatation [26, 44].

Endothelial NO activity is generally reduced in vascular disease resulting in a diminution in its protective activity and precipitating pathological functional and structural changes in the blood vessel wall, including enhanced constriction, vascular cell death (apoptosis), vascular inflammation, and vascular remodeling [34, 43, 84, 140]. Most studies have found that endothelium-dependent dilatation is normal in individuals with primary RP, including in response to increased flow (flow-mediated dilatation) [2, 73, 88, 114]. However, some reports have reported increased and decreased endothelial responses [71, 72], although this variation could reflect in part differences in gender and/or age between the experimental groups. In individuals with RP secondary to SSc, studies have consistently demonstrated impaired vasodilatation to endothelial activators including flow-mediated vasodilatation, and that this dysfunction occurs early and worsens as the disease progresses [1, 2, 46, 47, 80, 82, 83, 88, 93, 116, 117] (Fig. 5.4). Vasodilatation to endothelium-independent, direct smooth muscle dilators (NO-mimics: nitrovasodilators) may be preserved [46, 47, 128] or reduced in SSc [2, 80, 82, 83, 93, 117]. Therefore, the decrease in SSc endothelial dilatation may progress from dysfunction localized to the endothelium, to pathological changes throughout the blood vessel wall including structural changes that limit vasodilatation. These pathological changes in the SSc cutaneous circulation are part of a widespread systemic vasculopathy [4, 6, 25, 132, 133] (section "Structural Changes in Cutaneous Circulation") (Fig. 5.4).

Endothelial dilatation is likely to have an especially important role in glabrous skin including the finger circulation, where high blood flow through AVAs will expose proximal digital arteries to high shear stress and endothelial activation. Interestingly, RP is restricted to areas that are rich in AVA, with digital artery vasospasm occurring over a similar temperature range as cold-induced closure of AVAs (see section "Cutaneous Vascular Responses to Cold Exposure in RP"). The closure of AVAs, by reducing shear stress-induced activation of digital artery endothelium, may shift the balance towards sympathetic vasoconstrictor activity. Although diminution in shear stress-induced endothelial activity would also occur in control subjects, they would continue to be protected from vasospasm by a reduced sympathetic stimulus for digital artery constriction [12, 141] (Fig. 5.5).

Alterations in endothelial-dependent dilatation also likely contribute to the differing influence of cold exposure on nutritional blood flow in primary RP and secondary RP (SSc). As discussed above, during cold exposure, nutritional blood

flow is markedly disrupted in secondary RP (SSc) compared to the minor impairment observed in primary RP. Endothelial flow-mediated vasodilatation enables dilation in distal compartments of the circulation (e.g., terminal arterioles) to be conducted upstream and provide graded and targeted increases in blood flow (see Chap. 4). Therefore, despite the remarkable whitening in primary RP, metabolic vasodilation (Chap. 4) in nutritional arterioles will provide an endothelial dilator stimulus to maintain nutritional blood flow (albeit somewhat restricted because of profound arterial constriction). This low-level blood flow will quickly exit the constricted venous system and therefore not influence the pallor of the skin (see section "Vascular Mechanisms Underlying the Characteristic Color Changes of RP"). In contrast to primary RP, there is severe endothelial dysfunction in SSc. Therefore, although metabolic activity may dilate the local SSc nutritional arterioles, reduced flow-mediated dilatation will prevent this dilation from being conducted upstream to proximal arteries, which will continue to markedly restrict blood flow. Therefore, unlike primary RP, there will be a more profound interruption in SSc nutritional blood flow, precipitating SSc tissue injury.

A reduction in endothelial NO activity would also be expected to amplify vasoconstrictor episodes in SSc arteries, and to promote further pathological changes in the vascular system including thrombotic and inflammatory signaling and vascular remodeling. Indeed, expression of cold-sensitive α_{2C}-ARs in human cutaneous smooth muscle cells is amplified by inflammatory stress [15–17].

Endothelin-1 and Endothelial Exocytosis

Endothelin-1 (ET1) is a powerful vasoconstrictor, inflammatory and fibrotic mediator that can be produced and stored (as its precursor, Big ET1) within the vascular endothelium [56]. Following appropriate stimulation, endothelial cells quickly release stored proteins including Big ET1 by exocytosis [56]. Big ET1 is rapidly converted to ET1 during this exocytotic process [56]. There has been considerable interest in the potential role of ET1 in contributing to the vasospastic attacks of RP and to pathological vascular and tissue remodeling in SSc. Indeed, endothelial exocytosis can apparently be activated by exposure to cool temperatures [152]. However, under normal physiological conditions, the endothelium neither synthesizes nor releases sufficient quantities of ET1 to initiate vasoconstriction [56]. Furthermore, NO is a powerful endogenous inhibitor of ET1 expression and of endothelial exocytosis [56]. Although early research suggested that circulating ET1 levels were higher in individuals with primary RP compared to controls, and were further increased by local cold exposure [153], subsequent studies revealed conflicting results and ET1 is not thought to be involved in the vasospastic episodes of RP [27, 125, 146].

Endothelial exocytosis mediates the release of other stored proteins including ULVWF (ultra large von Willebrand factor), which promotes hemostasis and thrombosis [13, 56]. ULVWF is unfurled by blood flow and is subsequently cleaved by an endothelial surface protease ADAMTS13 to generate (circulating) VWF fragments with reduced thrombotic potential [13]. Release of ULVWF occurs in parallel with the release/generation of ET1 [56]. In controls and in individuals with primary RP, there is minimal evidence for endothelial exocytosis of ULVWF in cutaneous blood vessels [75]. In contrast, there is exuberant release of ULVWF in SSc superficial skin blood vessels with concomitant loss of ULVWF storage in the associated endothelium [75] (Fig. 5.4). The extent of endothelial exocytosis is related to SSc disease progression [75]. A similar pattern is evident with the circulating level of VWF, which is normal in primary RP but significantly increased in individuals with SSc and correlates with disease severity [9, 57, 64, 89, 90]. The circulating level of VWF is not influenced by cold exposure [9]. Increased exocytosis of ULWF, which will be a powerful stimulus for thrombosis and vascular inflammation, may reflect diminished activity of NO in SSc (Fig. 5.4). The contents of endothelial storage

granules can be regulated to increase expression of pathological mediators, including Big ET1. Indeed, the expression and storage of Big ET1 is dramatically increased in vascular aging [56]. There is increased presence of ET1 in cutaneous blood vessels of SSc subjects compared to control individuals, and as occurred with ULVWF release, ET1 is localized predominantly to superficial blood vessels [138]. Therefore, as occurs during aging, SSc endothelium likely has increased expression of ET1 precursors, with ET1 being formed during endothelial exocytosis (Fig. 5.4). Indeed, individuals with secondary RP (including SSc) have markedly increased circulating levels of both VWF and ET1, with close correlation between them [119, 139]. Short-term treatment with bosentan, which antagonizes ET_A (mediates smooth muscle constriction) and ET_B receptors (mediates endothelial generation of NO, and sometimes smooth muscle constriction), has shown promise in significantly reducing the formation of new ulcers in SSc subjects, although it does not significantly influence vasospastic attacks of RP [76, 92, 106]. This may reflect an increased role of ET1 in the nutritional microcirculation rather than in proximal digital arteries, which is consistent with the increased prominence of endothelial exocytosis in more superficial blood vessels.

There have been promising preliminary results obtained with botulinum toxin A (botox) in treating severe RP (including SSc), reportedly improving pain, perfusion and ischemic lesions [51, 104, 105, 121, 135, 137]. It remains unclear how this agent might mediate beneficial effects in this disease spectrum. Botulinum toxins specifically inhibit the molecular machinery involved in exocytosis, targeting macromolecular "SNARE" complexes involved in vesicle fusion with the plasma membrane [97, 144]. They can therefore inhibit the exocytotic release of neurotransmitters from nerve fibers. Botulinum toxin A comprises a heavy chain (Hc) and light chain (Lc), with the Hc involved in the binding and internalization of the toxin and the Lc subsequently degrading the SNARE protein SNAP25 [97, 144]. Cell surface receptors for the toxin comprise high affinity proteins (SV2, synaptic vesicle protein 2) and low affinity glycolipids called gangliosides [97, 144]. The toxin is thought to have preferential activity to inhibit cholinergic neurotransmission (including the neuromuscular junction in skeletal muscle) because of a higher expression of SV2 receptors [97, 144]. Indeed, when administered in low doses to human non-glabrous skin (forearm), botulinum toxin A selectively inhibited the vasodilatation and sudomotor (sweating) responses caused by heat stress-induced activation of the sympathetic cholinergic system [70, 122] (see Chap. 4 for description). In contrast, it had no effect on the sympathetic adrenergic cutaneous vasoconstriction caused by body cooling or the neuropeptide-mediated vasodilation evoked by local warming [70, 122]. However, when used in higher concentrations, the toxin can access sympathetic nerves to cause proteolytic degradation of SNAP25 and inhibition of sympathetic neurotransmission [98, 99, 126]. Indeed, botulinum toxin A also powerfully inhibits endothelial exocytosis [108], and will therefore inhibit the release of ULVWF and ET1. Although cold-induced translocation of smooth muscle α_2-ARs involves fusion of transport vesicles with the plasma membrane [100], it is not clear if this pathway involves SNARE complexes. The potential therapeutic effects of botulinum toxin A will therefore be determined by the dose and route of administration, but also the ability of the toxin to access target cells and the role of SNAP25 in mediating vesicle fusion in those cells. Based on available data, the most likely therapeutic targets include sympathetic-mediated vasoconstriction and endothelial exocytosis of ET1 and ULVWF. Endothelial production of NO is not dependent on exocytosis and should not be influenced by the toxin. However, the toxin may have a negative impact on responses to body warming (cholinergic dilatation, sweating) and local skin warming (neuropeptide dilatation).

Others

Although the vasospastic episodes of RP reflect abnormal thermoregulatory responses, we lack insight into thermoregulation in these individuals.

During cold exposure, processes are initiated to restrict heat loss (cutaneous vasoconstriction) and to generate heat (thermogenesis) (see Chap. 4). Analysis of the RP population has so far been restricted to the process of cutaneous vasoconstriction and reduction in heat loss, with no studies assessing thermogenesis (including shivering and activation of brown adipose tissue, BAT). Activation of thermogenesis has the potential to diminish the role of heat conservation and cutaneous vasoconstrictor mechanisms. Indeed, if perivascular adipose tissue (PVAT, Chap. 4) of cutaneous blood vessels can participate in thermogenesis, then such local heat production could diminish the influence of local cold exposure on cutaneous vasoconstrictor mechanisms. Despite the exuberant cold-induced cutaneous vasoconstriction in RP, core temperature was actually lower in RP in a thermoneutral environment and fell more during a reduction in ambient temperature, when compared to control subjects [58, 59]. However, core temperatures of control and RP individuals were similar in a warm environment [58]. This preliminary analysis suggests that thermogenic responses may be impaired in RP.

The density of CGRP-containing nerve fibers in finger skin (non-glabrous) is reported to be reduced in individuals with primary RP and further decreased in SSc [11]. Although CGRP is a vasodilator and has specific efficacy in terminating ET1 activity [81, 94, 95], no studies have provided evidence that a deficiency in this mediator contributes to heightened vasoconstriction in RP. As discussed in Chap. 4, activation of CGRP-containing nerve fibers appears to be involved in the immediate cutaneous vasodilatation to local warming [68]. However, cutaneous blood vessels of RP subjects dilate more to local warming than control subjects, with SSc subjects displaying an intermediate or reduced response [141, 147]. Therefore, there appears to be no functional deficit in the neuropeptide response to warming in primary RP, and the dysfunction present in SSc may represent a structural limitation of the SSc vasculature (see section "Structural Changes in Cutaneous Circulation").

Increased activity of reactive oxygen species (ROS) may play an important role in acute vasospastic episodes of RP and in the vascular and tissue remodeling occurring in SSc [1, 62, 146]. Increased ROS activity contributes to cold-induced cutaneous vasoconstriction by stimulating smooth muscle α_{2C}-AR mobilization and potentially by inhibiting NO dilatation, impairs the protective role of the endothelium, and participates in vascular and tissue fibrosis [5, 35, 62, 146].

Structural Changes in Cutaneous Circulation

Although subtle structural changes may be present in the cutaneous microvasculature and proximal arteries of primary RP, the underlying defect in this condition is generally considered to primarily reflect a change in functional activity of the vasculature [10, 62, 63, 101, 146]. In contrast, the secondary RP condition of SSc is associated with progressive structural deterioration and loss of the cutaneous nutritional microvasculature [24, 62, 63, 78, 132, 146] (Fig. 5.5). This reduction in microvascular density (also termed "microvascular rarefaction") will remove nutritional support to the underlying tissue and precipitate skin lesions. A major functional difference between primary and secondary RP (including SSc) is the profound reduction in nutritional blood flow occurring in response to cold exposure (section "Cutaneous Vascular Responses to Cold Exposure in RP"). This reduction can result in severe bouts of ischemia–reperfusion, which in turn may contribute to inflammatory activation and subsequent destruction of the fragile microvascular system. Upstream digital arteries are also structurally compromised in SSc with severe occlusive intimal fibrosis, characterized by increased deposition of collagen, elastin fragmentation, and evidence of prior thrombosis [63, 115] (Fig. 5.4). SSc is associated with diffuse tissue fibrosis including the presence of activated fibroblasts and increased collagen deposition, which results in skin thickening, tightening and contractures [24, 132]. These changes, including intravascular (i.e., intimal lesions) and extravascular fibrosis, occur in a systemic manner affecting multiple organs including the heart, kidneys and lungs [24, 132]. As with skin tightness, when these fibrotic

changes occur in the vascular wall, they increase arterial stiffness [120]. Several reports have observed that SSc is associated with intimal fibrotic lesions and increased stiffness in the central arterial system [25, 82, 133]. Therefore, pathological changes occur throughout the entire vascular system in SSc, including microvascular rarefaction and intimal fibrotic changes in proximal and central elastic arteries.

Endothelial to Mesenchymal Transition

Recent research has highlighted a potential common mechanism for the pathological structural changes occurring in the vasculature and tissues of SSc subjects. Endothelial to mesenchymal transition (EndoMT) refers to the transdifferentiation of ECs to a mesenchymal or myofibroblast cell phenotype. This process is characterized by a progressive loss in endothelial-specific proteins and acquisition of mesenchymal-specific markers (including α-smooth muscle actin) [52, 154, 156]. EndoMT-derived cells have a highly invasive and proliferative phenotype, with intense fibrotic activity including marked production of collagens and fibronectin, which increase tissue and vascular stiffness [3, 52, 54, 77, 111]. Indeed, EndoMT-derived myofibroblasts can play a key role in the pathological development of intimal fibrotic vascular lesions (including transplant arteriosclerosis) and interstitial organ fibrosis (including heart, kidneys, lungs) [3, 14, 111, 155, 156]. The associated loss of endothelial cells also contributes to microvascular rarefaction [7, 54, 113, 145, 156].

TGFβ and Smad2/3 signaling are considered central mediators of EndoMT acting to suppress expression of endothelial genes and upregulate mesenchymal genes [54, 61, 77, 86, 96, 111, 136, 156]. Induction of EndoMT by TGFβ is amplified by inflammatory cytokines and activation of the inflammatory transcription factor NFκB [87, 113, 129]. Indeed, local TGFβ activity may itself be induced by inflammatory stimuli, in particular angiotensin II (ANGII) signaling [127, 142, 143]. ANGII, TGFβ or inflammatory cytokines are all known to induce endothelial dysfunction, resulting in diminished activity of NO and increased expression of ET1. Indeed, EndoMT is associated with decreased expression of NO synthase and increased ET-1 expression [87, 96, 113], with endothelium-derived ET-1 acting as a key initiator of EndoMT [145].

SSc should provide a highly permissive environment for EndoMT. The disease process is associated with increased activity of ANGII, TGFβ, ET1 and inflammatory cytokines, which stimulate the EndoMT process. Indeed, exposure of endothelial cells to the abnormal extracellular matrix of the tight skin mouse ($Tsk^{+/-}$, a preclinical model of SSc) was sufficient to induce EndoMT [151]. Likewise, in a new preclinical model of the SSc disease process, chronic infusion of ANGII to mice caused skin fibrosis that was associated with EndoMT-derived myofibroblasts, as well as a marked increase in TGFβ expression, collagen deposition, and inflammatory/immune cell infiltration [127]. These intriguing results highlight the possibility that EndoMT may be a crucial driving force behind the pathological microvascular rarefaction, intravascular (intimal lesions) and extravascular fibrosis occurring in SSc.

Mechanism-Based Approaches to Treating the Vascular Pathogenesis of RP

Therapeutic intervention in RP should strive to be mechanism-based and to target processes or mediators involved in the disorder. In primary RP, the disorder represents primarily a dysfunction of vasomotor activity and it is likely that vasodilator therapy (in particular, targeted to the cutaneous circulation) will continue to be a major focus. In evaluating vasodilator therapies, special emphasis should be placed on nutritional blood flow (especially in secondary RP), rather than solely analyzing total blood flow or skin temperature changes. Nutritional blood flow is crucial to maintain tissue integrity, represents only a minor fraction of total finger blood flow, and is clearly regulated differently in controls and in individuals with primary

and secondary RP. Furthermore, skin temperature can be an imprecise measure of skin blood flow [31]. Therapeutic intervention in SSc should strive to not only prevent acute reductions in blood flow associated with RP but more importantly to prevent and reverse the obliterative structural vasculopathy in this condition.

Vasoconstrictor α_2-ARs likely play a crucial role in the abnormal responsiveness and cold-induced vasospastic episodes of RP. However, because of inhibitory central and prejunctional α_2-ARs (including α_{2C}-ARs) (section "Sympathetic and Adrenergic Responses"), it is highly unlikely that α_2-AR antagonists can be used effectively in therapy. Although systemic administration of the preferential α_{2C}-AR antagonist OPC-28236 had significant beneficial effects to increase thermal recovery following cold exposure in secondary RP (SSc), there was also a tendency for the antagonist to increase blood pressure and to reduce digital skin blood flow [149]. Similarly, oral administration of the purportedly selective α_{2C}-AR antagonist ORM-12741 increased the circulating levels of norepinephrine and reduced thermal and blood flow recovery from a local cold challenge in subjects with secondary RP (SSc) [65]. The detrimental effects of these antagonists likely reflect increased sympathetic activity following blockade of central/prejunctional α_{2A}-ARs or α_{2C}-ARs [OPC-28236 inhibits both receptor subtypes [66], no published data is available for ORM-12741]. The impressive effects of α_2-AR inhibition to combat cold-induced vasospasm and to increase blood flow in primary RP were achieved following local administration, which would diminish actions on central α_2-ARs to increase sympathetic activity. Attempts to chemically or surgically reduce sympathetic nerve activity in cutaneous circulation may be self-limiting, because interrupting nerve activity can increase the sensitivity of constrictor α_2-ARs and enhance their activation by circulating catecholamines [38, 66, 67]. The preferred approach would be to selectively inhibit smooth muscle α_2-ARs. This cannot currently be achieved using receptor antagonists, although treatment options could reduce the cell-surface mobilization of α_{2C}-ARs.

Statins have numerous, direct, protective effects on the blood vessel wall (in particular, endothelial cells) independently of lowering circulating LDL levels that would be expected to be beneficial in RP and SSc. Statins increase eNOS expression and NO production, reduce oxidant stress, decrease expression of ET1, inhibit endothelial apoptosis, increase mobilization of endothelial progenitor cells, and increase neovascularization (microvascular growth) [123, 157, 158]. Statins also inhibit the process of EndoMT [134], which may contribute to the systemic vasculopathy and tissue fibrosis occurring in SSc. In individuals with secondary RP (SSc), chronic treatment with statins (8 weeks to 4 months) significantly reduced the severity of RP vasospastic episodes and improved endothelial dilator function, which was associated with increased NO levels, a reduction in oxidant and inflammatory stress, an increased number of endothelial progenitor cells, and a decrease in the elevated circulating levels of VWF (and in markers of thrombotic activity) [1, 53, 79]. Statin treatment also significantly reduced the number of digital ulcers and the formation of new ulcers, significantly reduced overall disease severity and increased functionality, including hand grip [1]. The direct, protective, vascular effects of statins (the so-called pleiotropic effects) are thought to be mediated predominantly by inhibition of Rho/ROCK signaling [134, 157, 158]. This is a key pathway contributing to cold-induced modulation of the cutaneous circulation (Chap. 4). Indeed, although never studied, statins would be expected to reduce cold-induced mobilization of α_{2C}-ARs. The effects of ROCK inhibition in this disease spectrum have not been adequately evaluated. Acute administration of the ROCK inhibitor fasudil (2 h) did not significantly alter thermal recovery of skin temperature following cold challenge in RP with SSc [33]. There may have been a dose dependent improvement in digital skin blood flow both at warm and cold temperatures, but because of variability in flow measurements, this was not statistically significant [33]. In separate studies, ROCK inhibition with fasudil inhibited cold-induced vasoconstriction in non-glabrous skin [130, 131]. Clearly, the potential

therapeutic benefits of statins and Rho/ROCK inhibitors need to be thoroughly evaluated in RP and SSc.

The potential role and therapeutic applications of non-shivering thermogenesis in RP is a highly promising but unexplored area. Indeed, expansion and activation of BAT reservoirs could theoretically provide a rapid and effective mechanism to combat the local and centrally mediated processes of cold-induced cutaneous vasoconstriction. Local thermogenesis (e.g., cutaneous PVAT) could buffer cutaneous blood vessels from exposure to cool temperatures and directly initiate local warming-induced vasodilatation. Likewise, systemic thermogenesis (e.g., central or deep BAT reservoirs) would be expected to diminish reflex cold-induced increases in sympathetic constrictor activity and could initiate cholinergic vasodilatation (Chap. 4). Indeed, available evidence suggests that TRPM8 channel activators (including menthol) may be able to selectively activate BAT/PVAT reservoirs and initiate thermogenesis-mediated vasodilatation of the cutaneous circulation (Chap. 4). The positive impact of PVAT activation on endothelial function (Chap. 4) is also a compelling reason to pursue the role and therapeutic potential of this process.

In addition to cold-sensitive TRPM8 channels, distinct subtypes of TRP channels can respond directly to heat. Indeed, activation of TRPV1 channels on sensory nerves (and potentially on endothelial cells) is thought to contribute to cutaneous vasodilatation in response to local warming in human skin, which is mediated by neuropeptides (e.g., CGRP) and increased NO activity [68, 107, 118, 148, 150] (Chap. 4). Activation of TRPV1 channels (e.g., by capsaicin) can mimic the effects of local warming and stimulate cutaneous vasodilatation [55, 68, 102, 107, 118]. However, a current deficiency in using this approach to combat cold-induced vasoconstriction is that activation of sensory TRPV1 channels (by warm-mimics such as capsaicin) also initiates pain and inflammation [55, 102].

The potential role and therapeutic implications of EndoMT in SSc is a highly promising but under-explored area. Effective inhibition of TGFβ and ANGII signaling (AT1 receptor antagonists, e.g., losartan, or inverse agonists, e.g., valsartan) should continue to be explored as therapeutic strategies to combat the microvascular rarefaction, and intravascular (intimal lesions) and extravascular fibrosis that drive pathology in this disease process.

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Primary Raynaud's Phenomenon

6

Ariane L. Herrick

Abbreviations

PRP	Primary Raynaud's phenomenon
RP	Raynaud's phenomenon
SSc	Systemic sclerosis

Key Points

1. Primary Raynaud's phenomenon (PRP) is common especially in women.
2. PRP (unlike systemic sclerosis) does not progress to irreversible tissue injury: therefore if ulcers or digital pitting are present then this is *not* PRP and a secondary cause should be looked for.
3. Patients with PRP should have no features on history and examination of an underlying secondary cause. They should have a normal full blood count normal erythrocyte sedimentation rate, negative antinuclear antibody and normal nailfold capillaroscopy.
4. Most patients with PRP can be reassured and do not require drug treatment: in many patients symptoms improve spontaneously over the years.
5. If drug treatment is required a calcium channel blocker is the first choice.

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Introduction

Primary (idiopathic) Raynaud's phenomenon (PRP) is important to both clinician and researcher for several reasons. First, it is very common (and is by far the most common cause of Raynaud's phenomenon [RP]). Second, although generally considered "benign" in that it does not progress to digital ulceration and critical ischaemia, PRP can be associated with significant pain and disability in those severely affected. Third, PRP must be distinguished from early systemic sclerosis (SSc), of which RP is often a presenting feature [1–3] and from RP secondary to other causes. Fourth, researchers often compare PRP to SSc-related RP in order to understand why patients with SSc (but not with PRP) progress to ischaemic injury.

A comprehensive review article on PRP should cover definition, epidemiology, genetic factors, pathogenesis, presenting features (history and examination), investigations and management, and also "transition" from primary to secondary RP. However, many of these different topics are covered in other chapters. The aim of this chapter is to give a short overview with cross-referencing to other chapters for further details. To put the problem into context, first a case of "typical" PRP is described.

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Case History

A 21-year-old student consults her general practitioner complaining of coldness and colour changes of her hands for approximately 3 years, worse when out of doors or in other cold environments. In the cold her fingers turn pale/blotchy (Fig. 6.1) then purple. Her feet tend to feel cold but less so than her hands. She is worried because her symptoms have become worse since she recently started working two evenings a week in a local supermarket: if she packs in the freezer areas (which she does much of the time) her fingers become numb and painful as well as change colour. She is on no drug treatment and is a non-smoker. Her mother has similar symptoms and is in good general health: her maternal aunt has heart trouble as well as cold hands.

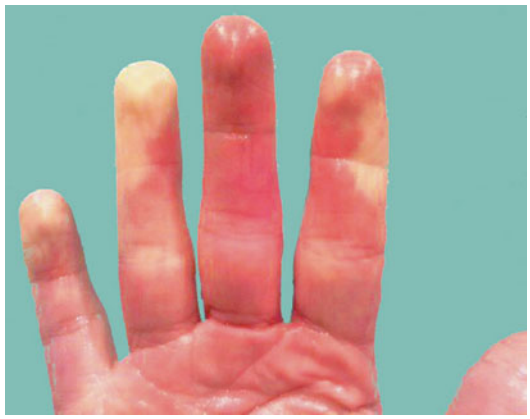

Fig. 6.1 Pallor phase in a patient with PRP

On examination there are no abnormalities. The skin of her fingers is cool but normal. Her upper limb peripheral pulses are easily felt.

Her general practitioner thinks that there is unlikely to be any significant cause of concern but arranges some further checks. Full blood count and erythrocyte sedimentation rate (ESR) are both normal and antinuclear antibody (ANA) testing negative. Nailfold capillaroscopy, performed at the local rheumatology department, is normal (Fig. 6.2).

A diagnosis of PRP is made. The patient is advised to speak to her employer and ask if she can change to working in warmer parts of the store: if this proves impossible then she is aware that it would be best to seek alternative part-time work. She is given a leaflet on RP, which gives information on keeping warm. Her doctor discusses starting nifedipine, but both he and the patient feel that this may not be necessary and the patient is concerned about the possibility of developing headaches, especially because this is

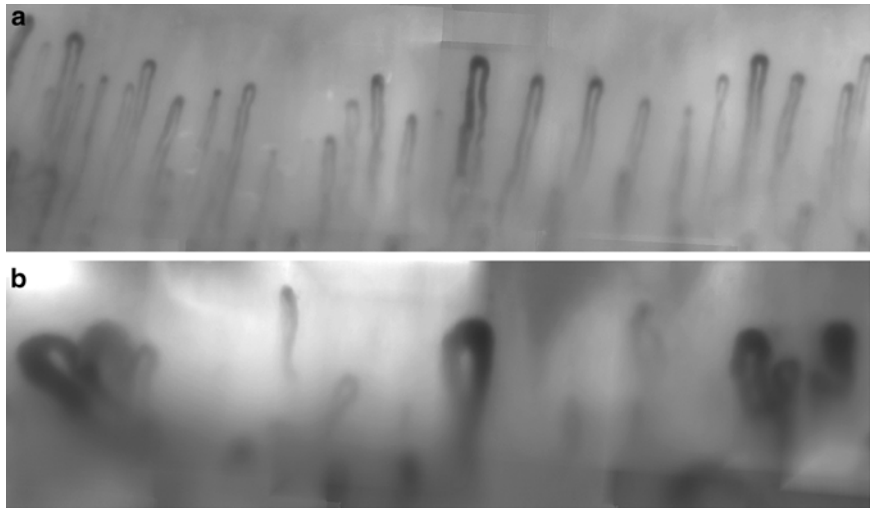

Fig. 6.2 Normal nailfold capillaries (**a**) compared to abnormal dilated capillaries in a patient with SSc, with areas of avascularity (**b**)

her final year at university and she has a number of examinations coming up.

Definition

When RP is "primary" this means that it is idiopathic (of unknown cause). Importantly for the clinician, there is no underlying disease or condition to which it is secondary, and which might require specific treatment.

Allen and Brown in 1932 [4] discussed criteria for what was then termed "Raynaud's disease". More recent criteria proposed by LeRoy and Medsger in 1982 [5] (already discussed in Chap. 2) are summarised in Table 6.1, and are worthwhile considering in turn, because these highlight a number of key features relevant to the history, examination, and investigation plan:

Episodic attacks of acral pallor or cyanosis: RP attacks are intermittent and resolve. This is usually true also for secondary RP, and so this criterion does not discriminate between PRP and secondary RP.

Strong and symmetric peripheral pulses: This helps to discriminate PRP from RP secondary to structural disease of large arteries, for example atherosclerosis or thromboangiitis obliterans (Buerger's disease). However, this finding will not discriminate between PRP and RP secondary to SSc-spectrum disorders, nor to several other causes discussed in Chap. 10, when the problem lies primarily in the microcirculation and/or in intravascular factors (for example RP secondary to hyperviscosity syndromes).

No evidence of digital pitting (Fig. 6.3), *ulceration or gangrene*: This is a key point: by definition if a patient has progressed to irreversible tissue injury then this is not PRP and a secondary cause, for example SSc, *must* be looked for. It should be noted that (in contrast) the Allen and Brown criteria [4] included "gangrene or trophic changes limited in a large degree to the skin" and so could have included digital ulcers and scars which are now considered by most clinicians to be indicative of underlying disease.

Table 6.1 Proposed criteria for primary Raynaud's phenomenon [5]

Episodic attacks of acral pallor or cyanosis
Strong and symmetric peripheral pulses
No evidence of digital pitting, ulceration or gangrene
Normal nailfold capillaries
Negative antinuclear antibody (ANA) test (titre <1/100)
Normal erythrocyte sedimentation rate (ESR)

Fig. 6.3 Digital pitting in a patient with SSc. Copyright Salford Royal NHS Foundation Trust

Normal nailfold capillaries: As discussed later, abnormal nailfold capillaries are predictive of a SSc-spectrum disorder.

Negative antinuclear ANA test (titre <1/100): A positive ANA is of concern, as this associates with connective tissue disease, especially when present in a high titre.

Normal ESR: Many secondary causes of RP, including connective tissue disease, malignancy and haematological disorders including diseases associated with hyperviscosity are associated with a raised ESR. A raised ESR demands an explanation.

It is worth mentioning that the criteria of LeRoy and Medsger [5] were a proposal: the diagnosis of PRP is not straightforward as discussed below under "transition". An example of one of the challenges for clinicians is the definition of "normal nailfold capillaries", as discussed in Chap. 12 and below under "investigation".

Epidemiology

As already stated, PRP is very common. Women are more often affected than men. A detailed description of incidence and prevalence is given in Chap. 3. Community based studies which are questionnaire based usually do not include checking of all the parameters listed in Table 6.1 and will therefore most likely include some patients (for example) with abnormal nailfold capillaries or a positive ANA. However, pragmatically most individuals with RP who are not aware that they have an underlying causal disease/condition will have PRP.

Estimates of prevalence of PRP vary widely, as discussed in Chap. 3. To take two examples, a UK community study reported prevalences of RP of 19 % in patients attending surgeries and of 15 % in patients responding to a postal survey: attending surgeries, 21 % women and 16 % men affected; postal survey, 19 % women versus 11 % men affected [6]. A United States community-based study reported prevalences of 11 % in women and 8 % in men [7].

PRP typically presents in the teens or twenties. It is therefore especially important that a secondary cause is excluded when RP develops in older age groups. Children also may present with PRP [8]. The prevalence of RP in 12–15-year-olds has been estimated to be 15 % (18 % in girls, 12 % in boys) [9].

Pathogenesis

The pathogenesis of PRP is not fully understood, although in recent years there have been major advances in our understanding of the cellular and molecular basis of vasospasm, as discussed in Chaps. 4 and 5. The key point to make here is that the episodic imbalance between vasoconstriction and vasodilation which occurs in PRP is thought to be purely *functional*: structural vascular change does not occur. On this basis, abnormal nailfold capillaries exclude a diagnosis of PRP (Table 6.1). Although subtle abnormalities in nailfold capillaries have been reported in PRP [10] this may relate to the fact (discussed below) that the distinction between PRP and early SSc is not absolute.

The pathophysiology of RP is discussed in full in Chap. 5 and only a few points will be made here. When studying pathophysiology, investigators often compare patients with PRP to patients with SSc-related RP and to healthy controls: when abnormalities are found in patients with PRP, these may be less marked than in patients with SSc-related RP. Abnormalities in patients with PRP include reduced endothelium-dependent vasodilation [11–13], reduced expression in finger skin of the vasodilator calcitonin gene-related peptide [14], increased protein kinase activity and tyrosine phosphorylation [15], platelet activation [16–19], white blood cell activation [20] and oxidative stress [21]. Although some studies have suggested a role for endothelin-1 [22–24] the evidence (as discussed in Chap. 5) is conflicting. Genetic factors have also been implicated in the pathogenesis of PRP [25, 26], as discussed in Chap. 3.

History and Examination

The approach to diagnosis of the patient with suspected or definite RP is summarised in Fig. 6.4. The clinician must differentiate primary from secondary RP, and gauge the severity of the RP because this will inform treatment decisions.

In diagnosing and assessing severity of PRP, the key points in the history are:

1. The typical colour changes of the fingers and toes (usually in response to cold exposure or emotional stress). Classically the fingers turn white (ischaemia), then blue (deoxygenation) then red (reperfusion), although many patients report only a uniphasic or biphasic response (including white or blue). The colour changes are confined to distal to the metacarpophalangeal joints, and can last variable lengths of time, but in patients with PRP usually resolve quickly (within minutes) after rewarming. Patients often report cold sensitivity rather than colour change of the feet which are less visible. The nose, ears and nipples [27] may also be affected (Fig. 6.5). Although attacks tend to be symmetrical, some fingers may be

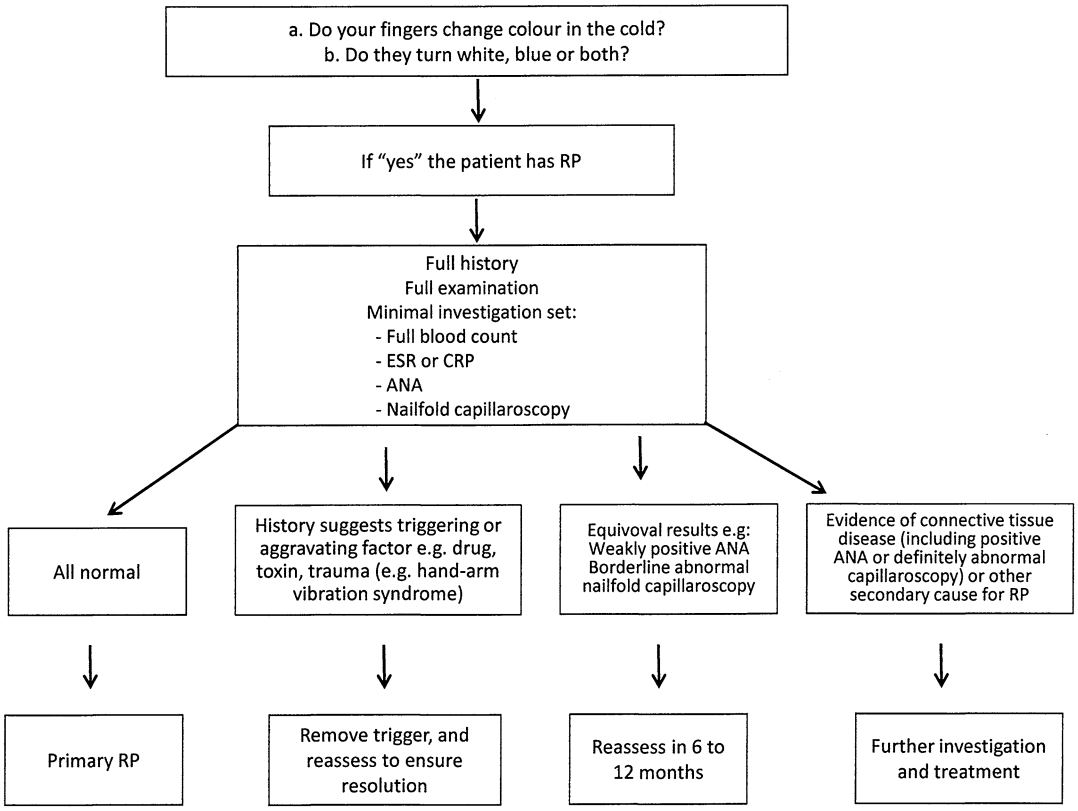

Fig. 6.4 Flow chart summarising the approach to diagnosis of RP

Fig. 6.5 Cartoon of the "cold skin zones" in healthy control subjects (fingers, hands, toes, feet, knees, nose, ears): these are exaggerated in patients with PRP

more affected than others. The thumbs are often spared, and if affected then this should prompt the clinician to be especially careful to exclude an underlying connective tissue disease [28]. It is worth highlighting that many people are cold sensitive, but for a diagnosis of RP, there must be colour change (Fig. 6.4).

2. Absence of any symptoms suggestive of a connective tissue disease or of any of the other causes of secondary RP (Table 3.2). Therefore, it is essential to take a comprehensive history including a full systems enquiry (connective tissue disease can present with a wide range of symptoms, e.g. recent onset of heartburn could suggest oesophageal dysmotility), drug history, social history (with full occupational history including vibratory tool exposure, industrial chemical exposure) and family history (many patients with PRP have a family history of RP).
3. Assessment of severity. Are the attacks painful and interfering with activities of everyday living?

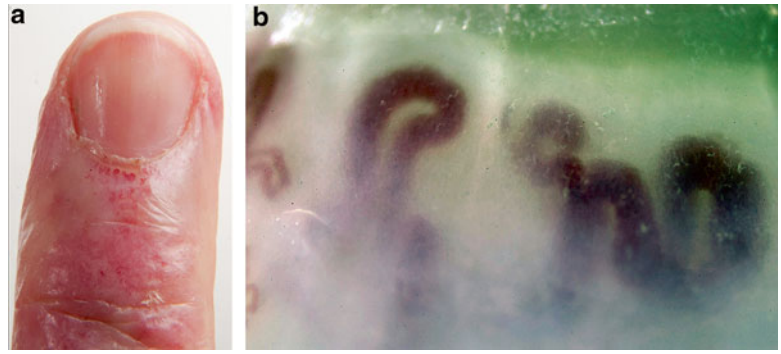

Fig. 6.6 Nailfold capillaries that were so dilated as to be visible to the naked eye (**a**) and as shown by capillaroscopy (**b**). This patient had dermatomyositis. Courtesy of H Chinoy. Copyright Salford Royal NHS Foundation Trust

On examination, the fingers and face should be carefully examined for sclerodactyly, digital pitting, digital ulcers, calcinosis, periungal erythema, telangiectases, and any capillary dilation or haemorrhages (at the nailbed) which are so marked as to be visible to the naked eye (Fig. 6.6). The peripheral pulses must be checked. A full examination is required for the same reason as a full history (e.g. basal crackles might indicate connective tissue disease-associated interstitial lung disease).

Investigations

As directed by the criteria for PRP (Table 6.1), the basic set of investigations comprises a full blood count, ESR, ANA and nailfold capillaroscopy (Fig. 6.4). Many clinicians would also include a biochemical profile with thyroid function tests and (especially if symptoms are unilateral) a thoracic outlet radiograph to look for a cervical rib (Fig. 6.7). All should be normal in the patient with PRP.

Many clinicians do not have access to nailfold videocapillaroscopy, which is the "gold standard" capillaroscopy technique (Chap. 12). A lower magnification technique should then be used: a stereomicroscope, dermatoscope [29, 30] or ophthalmoscope [31, 32]. There has been recent increased interest in the dermatoscope, which is a small portable hand-held piece of equipment which can be used in the office or outpatient clinic [33]. An advantage of lower magnification is that the whole nailbed is included in one field of view, although it is likely that more subtle abnormalities seen with high magnification videocapillaroscopy are missed. Figure 6.8 shows example images using the dermatoscope and videocapillaroscopy.

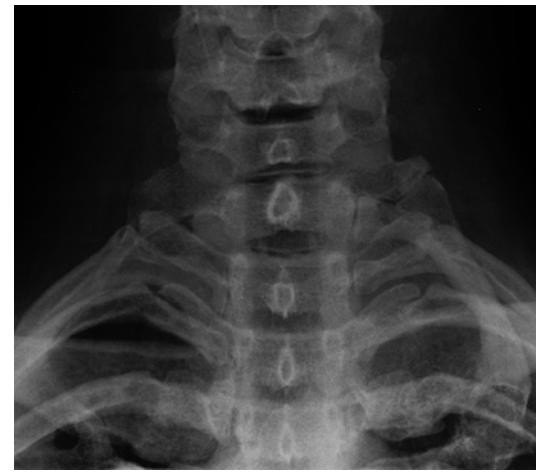

Fig. 6.7 Bilateral cervical ribs

It is worth highlighting that the interpretation of nailfold capillaroscopy images can be difficult. As discussed in Chap. 12, there is a wide range of "normality": healthy controls do not all have evenly shaped "hairpin" loops (Fig. 6.2a) but can have considerable tortuosity of their capillaries. Figure 6.9 shows examples of capillary appearances which are not definitely "scleroderma-spectrum" but which nonetheless are not entirely normal. Also, it is not always possible to visualise everyone's capillaries and this should not be mistaken for avascularity. However, definite abnormalities of a systemic

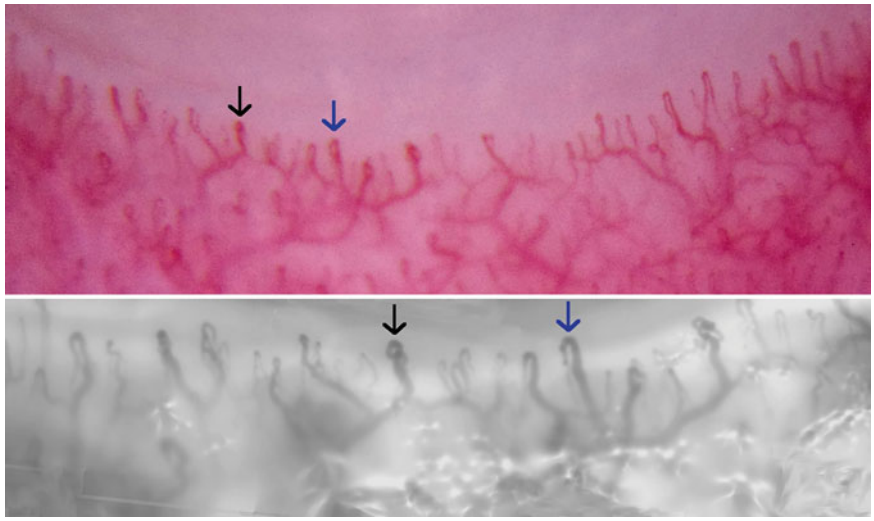

Fig. 6.8 Normal capillaries in a patient with PRP, imaged with a dermatoscope (*top*) and videomicroscope (*bottom*). The *arrows* indicate the position of the same capillaries using each technique. The higher magnification gives more detailed visualisation of the individual capillaries

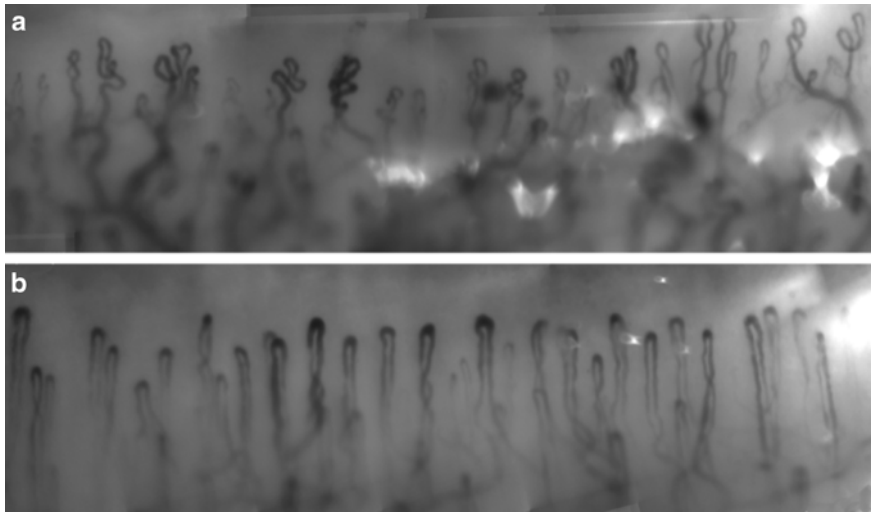

Fig. 6.9 Nailfold capillaries in healthy control subjects showing (**a**) marked tortuosity (**b**) regular capillaries but with some variation in apical diameters. These images demonstrate the challenges in defining "normality"

sclerosis-spectrum disorder, for example giant capillaries, are not consistent with a diagnosis of PRP (Chap. 12).

Thermography, which measures surface temperature (Chap. 13), can help to differentiate primary from secondary RP, but is available only in certain specialist centres. Most thermography protocols will include a temperature challenge (Fig. 6.10), usually a cold challenge [34–36].

A number of other methodologies which are used in research studies can help to distinguish between PRP and SSc-associated RP. These include laser Doppler flowmetry, laser Doppler imaging, finger systolic pressure measurement and plethysmography. They are discussed in Chap. 13.

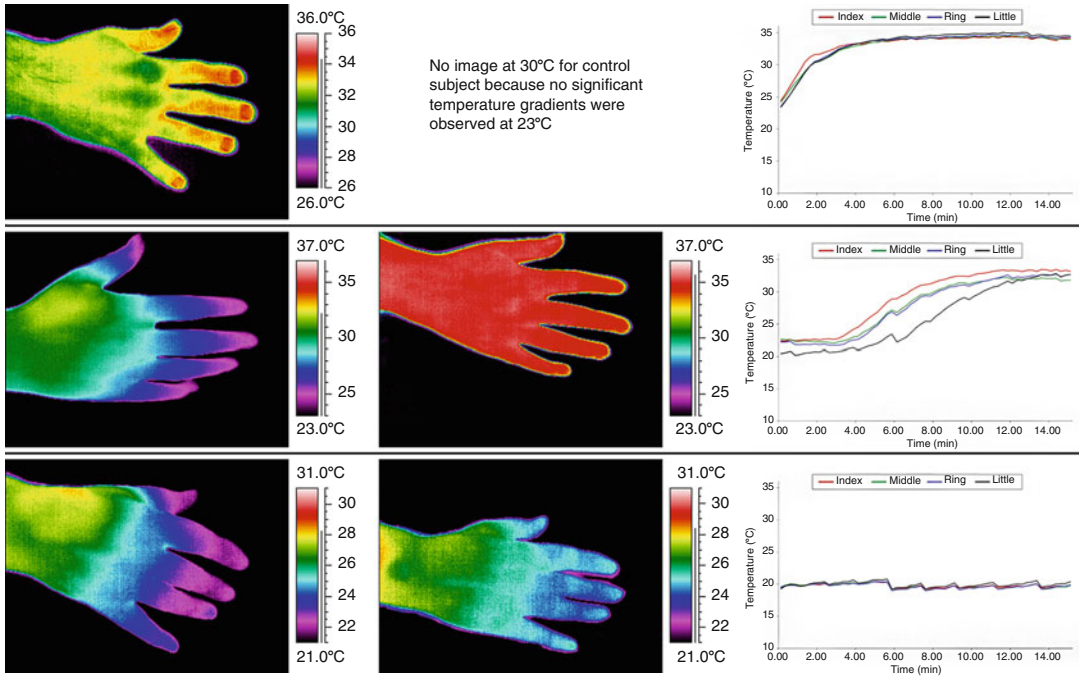

Fig. 6.10 Thermograms from a healthy control subject (*upper*), a patient with PRP (*middle*) and a patient with SSc (*lower*). The thermograms on the left are at 23 °C, and on the right at 30 °C. Although in both patients the fingertips are cold at 23 °C, this temperature gradient along the fingers normalises at 30 °C in the patient with PRP, but not in the patient with SSc (suggesting underlying structural vascular disease). The rewarming curves on the right show rapid rewarming in the healthy control subject, delayed (but complete) rewarming in the patient with PRP, and no rewarming within the 15 min observation period in the patient with SSc

Treatment

Many patients with PRP do not even seek medical advice, and most do not require drug treatment. Once the diagnosis of PRP is made, a key point is to reassure that patient that there is no evidence of any underlying condition, and that the aim of treatment is to minimise symptoms. Treatment of RP is discussed in detail in Chaps. 19 and 20, but some general points especially relevant to PRP will be made here.

Patient Education/General Measures

This is probably the most important aspect of management, discussed in Chap. 19. Patients should be advised to minimise the impact of changes in temperature by dressing warmly (not only warm socks, gloves and hats but also keeping centrally warm). Many patients use handwarmers, and some find electrically heated gloves and socks helpful. Leaflets describing RP and ways to keep warm are published by patient support groups (Fig. 6.11).

If patients smoke, they should be advised to stop. Of interest is that a survey in the Framingham Heart Study Offspring Cohort suggested an association between current smoking and Raynaud's phenomenon in men (adjusted Odds ratio 2.59, 95 % confidence interval 1.11–6.04) but not in women [37], consistent with findings of an earlier study [38].

In many patients with PRP, symptoms improve over time [7, 39], possibly at least in part because patients become less concerned about them, or make lifestyle modifications which prevent attacks.

Fig. 6.11 Examples of patient education leaflets. Copyright Salford Royal NHS Foundation Trust

Drug Treatment (Table 6.2)

This should be considered in the patient who does not respond to general measures and is discussed in detail in Chap. 20.

Most clinicians recommend calcium channel blockers [40] as their first choice, although adverse effects are common, including vasodilatory side effects such as headache, flushing and dizziness. Sustained release preparations tend to be better tolerated, and a key point is to commence at low dosage and gradually increase. Despite the widespread use of calcium channel blockers in PRP, these were reported to be only minimally effective in a recent Cochrane review [41] which included seven randomised trials (four examining nifedipine, three nicardipine) and 296 patients. Overall, the number of RP attacks per week was reduced by 1.72 (95 % CI 0.60–2.84) meaning that calcium channel blockers could reduce the weekly number of attacks by as few as 0.6 or as many as 2.8 [41].

Table 6.2 Drugs used in the patient with PRP, in whom general ("non-drug") measures are insufficient to control symptoms

Calcium channel blockers (e.g. nifedipine, amlodipine)[a]
Angiotensin II receptor antagonists (e.g. losartan).
Angiotensin-converting enzyme inhibitors
Alpha-adrenergic blockers (e.g. prazosin)
Serotonin reuptake inhibitors (e.g. fluoxetine)
Phosphodiesterase inhibitors (e.g. sildenafil)
Topical nitrate therapy (this causes both systemic and local vasodilation—doses used for systemic effects are often poorly tolerated, and at present there is no licensed formulation available for local application)
Intravenous prostanoids (seldom used for PRP)

[a]First line treatment

There is even less evidence base to support the use of any other class of drug in patients with PRP, as discussed in two other recent reviews [42, 43]. This lack of evidence base is due at least in part to the difficulties in mounting clinical trials of RP. However, it seems reasonable, if a calcium channel blocker is ineffective or not tolerated, to

prescribe an alternative vasodilator. Other drugs used in the treatment of PRP include angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and alpha-adrenergic blockers (Table 6.2). Phosphodiesterase inhibitors are being prescribed increasingly, at present more for secondary than for primary RP. To date there has been very little research into the effects of phosphodiesterase inhibitors in patients with PRP: one study in 15 patients with PRP suggested that a single dose of 100 mg sildenafil improved finger blood flow during local cooling [44]. Topical glyceryl trinitrate (GTN, nitroglycerine), applied locally to the fingers has recently been revisited in a clinical trial including both patients with PRP and with SSc-related RP [45], but at present there are no formulations available specifically for applying to the fingers in patients with RP (this is an area requiring further research). When GTN is given by transdermal patch for its systemic effects [46], it tends to be poorly tolerated and is therefore seldom used, although a recent report suggested that this was useful in childhood RP [47]. Intravenous iloprost is occasionally prescribed for patients in whom PRP attacks are particularly severe, but this treatment is generally reserved for patients with secondary RP, progressing to digital ulceration.

A challenge to clinicians is the patient with PRP and a low blood pressure, intolerant of vasodilator preparations. General (non-drug measures) should be revisited. Some clinicians try a selective serotonin reuptake inhibitor [48] which may be better tolerated than the therapies already mentioned.

Treatment efficacy in primary versus *secondary RP*: Some clinical trials have included patients with both PRP and SSc-related RP and compared treatment effect between subgroups. The caveats of subgroup analysis, discussed in Chap. 18, should be borne in mind. Given that the evidence base for treatment of both PRP and secondary RP [49] is weak, in general it is usually difficult to say whether treatment effect is greater or less in patients with PRP. However, it might be reasonable to assume that patients with PRP are more likely to respond to vasodilator therapy than patients with SSc-related RP, because they do not have structural vascular disease. This is borne out by some studies which suggest greater efficacy in PRP than in SSc-related RP, for example the study by Chung et al. [45] of topical GTN, which included 69 patients with PRP and 150 with secondary RP (131 of whom has SSc), and studies of fluoxetine [48] and losartan [50].

Other Treatments

Although botulinum toxin has been recommended for primary as well as secondary RP [51], there is no good evidence base for this approach. There is no role for surgery is in the treatment of PRP.

Transition from Primary to Secondary RP

This is a difficult area and has already been referred to in Chap. 3. The literature suggests in the order of 1–3 % of patients per year with what appears to be PRP or "isolated" RP progress to SSc or other underlying disease [52, 53]. A key issue is how carefully RP is "vetted" before classed as primary. A study which followed 586 patients with RP over 3,197 patient years (median follow-up 4 years) reported rates of progression to SSc as follows [54]: 1.8 % of patients with neither an abnormal nailfold capillary pattern nor a SSc-specific autoantibody; 25.8 % of patients with an abnormal nailfold capillary pattern; 35.4 % of patients with a SSc-specific autoantibody; 79.5 % of patients with both an abnormal nailfold capillary pattern and a SSc-specific autoantibody. Another level of complexity is the definition of transition. For example, Cutolo et al. [55] reported that 14.6 % of 129 patients with PRP (normal nailfold capillaries, ANA negative) developed abnormal nailfold capillary patterns over a mean of 29.4 months. The conclusion must be that the separation between PRP and early connective tissue disease-associated RP is not absolute, and that abnormal nailfold capillaries and SSc-specific autoantibodies (although not diagnostic in themselves) are "red flags". This has been acknowledged in the American

College of Rheumatology/European League Against Rheumatism 2013 classification criteria for SSc [56, 57], which include both abnormal capillaroscopy and SSc-specific autoantibodies.

If the clinician is unsure, for example a patient has a positive ANA of 1/100 and equivocal nailfold capillaroscopy (e.g. normal architecture, but one or two areas of haemorrhage, or some borderline widened capillaries) then the pragmatic approach is to review the patient and repeat the capillaroscopy 6–12 months later (Fig. 6.4).

Expert Opinion

PRP is common, and does not progress to irreversible tissue injury. An important aspect of management is to make the correct diagnosis (i.e. not miss a secondary cause) and then reassure the patient accordingly. A patient with PRP should have no worrying features on history and examination and investigations (full blood count, ESR, ANA and nailfold capillaroscopy) should all be normal.

Many patients with PRP will respond to reassurance and general (non-drug) measures: in those with persisting symptoms requiring drug treatment, a calcium channel blocker (sustained release) is generally the first choice, starting at low dosage and gradually increased as tolerated and indicated. If the maximum tolerated dose is ineffective, an alternative vasodilator should be tried.

In the research setting, comparing patients with PRP to those with SSc-related RP may help to elucidate why patients with SSc, but not those with PRP, may progress to digital ulceration and critical ischaemia.

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Raynaud Phenomenon in the Pediatric Age

7

Francesco Zulian and Clare Pain

Abbreviations

ANA	Antinuclear antibody
CCBs	Calcium channel blockers
CRPS	Complex regional pain syndrome
CTD	Connective tissue disease
JSSc	Juvenile systemic sclerosis
LDI	Laser Doppler imaging
NFC	Nailfold capillaroscopy
RP	Raynaud phenomenon
SSc	Systemic sclerosis

Key Points

1. RP in children can be either primary (idiopathic) or secondary: even young children can be affected.
2. RP in children (as in adults) can be the presenting feature of connective tissue disease.
3. Children with RP should have a full history and examination looking particularly for an underlying connective tissue disease.
4. Investigations should include full blood count, ANA and nailfold capillaroscopy (which are usually possible even in young children).
5. Management depends on severity including impact on function and whether or not there is tissue damage.
6. If general measures fail and drug treatment is required, calcium channel blockers are most commonly used as first line.
7. Iloprost is used in children with severe disease, for example those with digital ulcers.
8. There have been no randomized controlled clinical trials in children with RP: these are much needed to provide an evidence base for treatment.

Introduction

Raynaud phenomenon (RP) in children may, as in adults, be primary (idiopathic) or secondary to rheumatic diseases, drugs, or other conditions (Table 3.2). This chapter aims to present a practical approach to clinical assessment and treatment of children with RP, with supporting evidence from studies specific to the pediatric age group. As with adults, RP can be the presenting feature of connective tissue disease (CTD). However, risk factors for progression from RP symptoms to a defined CTD phenotype are less well defined in children. The differentiation between primary and secondary forms of RP is important as those with primary RP have a good outcome and can be

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managed with non-pharmacological approaches and, where necessary, vasodilatory drugs with reassurance to the child and family that this condition is relatively benign. Identification of a child with secondary RP or at high risk to progression to secondary RP based on history, examination, and investigations is important to allow more careful monitoring and follow-up, with the aim to detect evolving CTD early.

There are no pediatric specific definitions of primary and secondary RP and many studies use the LeRoy and Medsger classification criteria [1]. This is not universal and differing definitions between studies can make it difficult to make comparisons. Published guidelines for investigation and management of children with RP are not widely available, in part because of a lack of robust pediatric specific evidence.

Epidemiology Including Secondary Causes

It is difficult to establish the true prevalence of RP in children. The lack of a well-defined reproducible diagnostic test makes it difficult to obtain reliable estimates, and pediatric studies have used differing definitions of RP [2–4].

A study conducted in the UK in 720 schoolchildren, aged 12–15 years, identified Raynaud's symptoms in 15 % of the subjects, by the use of a self-administrated questionnaire [5]. The rates were higher in girls (18 %) compared to boys (12 %) with a tendency for prevalence to increase with age. These rates are similar to those reported in adults [6]. No studies have been performed to identify prevalence of RP in younger children. It has previously been thought that primary RP particularly in very young children is rare. Larger pediatric studies of RP have included only a few [2] or no children under 6 years of age [3, 4]. Cases of primary RP occurring in infants and toddlers are reported [7, 8] although long-term follow-up to provide outcomes is not available. Very young children can also present with secondary RP and critical ischemia [9]. Age at onset of RP did not appear to differ between children with primary compared to secondary RP [2], although there were few younger children included in this study. Because of the paucity of prospective data on young children with RP, many clinicians would continue to follow up such children to monitor for evolving CTD.

RP can be the presenting feature of CTD in children. In juvenile systemic sclerosis (JSSc) RP is the first sign of disease in 61–70 % of patients [10, 11]. Several studies have demonstrated a significant delay between first symptoms and diagnosis in JSSc, ranging from 7 months to 2.8 years [10, 12, 13] suggesting that there is a period of time where children present with RP before a diagnosis of JSSc is made. Better identification of those at risk of progression to JSSc would facilitate earlier diagnosis and treatment. Indeed, 72–84 % of children with a definite JSSc diagnosis develop RP during the course of the disease; by adulthood almost all patients report RP [12, 14]. RP is not a feature of juvenile localized scleroderma with rates reported as 2–3 % which is much lower than the prevalence observed in healthy children [15, 16].

RP can be observed in other rheumatologic conditions such as mixed connective tissue disease, where it has been reported in 58 % of patients at disease onset [17]. RP is reported in 15 % of children with juvenile systemic lupus erythematosus [18]. Around 10 % of children with Sjögren's syndrome can present with RP during the disease course [19].

Clinical Features

History

The complaint of cold hands or feet is quite common especially in young female teenagers and should be distinguished from RP, which involves both cool skin and cutaneous color changes. A detailed patient history should be taken and should include which extremities are affected, color changes experienced, and associated symptoms such as numbness, pain, and itching. Frequency, severity, and duration of attacks including impact on functional ability are important to aid decision making on need for vasodilatory therapies. Children should also be asked about possible

triggers such as cold, wind, or emotion. Exposure to cold temperature triggers RP but, more frequently, the provocation occurs during relative shifts from warmer to cooler temperatures. As a result, mild cold exposures such as air conditioning or the cold of a refrigerator may cause an attack.

Not all children with RP will have triphasic color change and this is not necessary to make a diagnosis. In a retrospective review of 123 pediatric patients, Nigrovic and colleagues reported that 24 % of children with primary RP and 19 % of children with secondary RP reported triphasic color changes, while 40–50 % had only monophasic color changes; number of color changes could not differentiate between primary and secondary RP [2].

Symptoms associated with CTD such as unexplained fever, fatigue, rash, digital ulcers, morning stiffness, arthralgia, myalgia, dysphagia, peripheral edema, lymphadenopathy, or oral ulcers should be enquired about.

Drug history may identify certain drugs known to cause secondary RP. In children, an important issue is the use of stimulants for attention-deficit hyperactivity disorder, which may exacerbate vascular dysfunction [20]. Family history of RP or CTDs should be sought.

Examination

A full examination of the child should be performed to look for signs of CTD including musculoskeletal, skin, cardiac (including peripheral pulses and blood pressure), respiratory, and abdominal examinations. In particular, the hands can provide clues for differentiating primary from secondary RP; digital pitting scars, ulcers, sclerodactyly, puffy hands, arthritis, joint contractures, and abnormal nailfold capillaries should be actively looked for.

Investigations

Most specialists would recommend a minimum blood work-up of a complete blood count, inflammatory markers, and antinuclear antibody (ANA) in children with RP and no suspicion of CTD. However, depending on the level of concern raised during history and examination, more thorough laboratory testing is recommended and may include a complete blood count, inflammatory markers, renal and liver function, muscle enzymes, thyroid function tests, urinalysis, complement (C3 and C4), and wider autoantibody profiling. If ANA is positive, tests for specific autoantibodies may assist with confirming the diagnostic suspicion including systemic sclerosis (SSc)-specific antibodies (e.g., anti-centromere, anti-topoisomerase (Scl-70), anti-Th/To, anti-RNAP), anti-double-stranded DNA, antiphospholipid antibodies, and extractable nuclear antigen antibodies (e.g., anti-SSA [Ro], anti-SSB [La], anti-ribonucleoprotein, anti-Smith, and anti-Jo-1).

If secondary RP is suspected due to CTD, children may require more organ-specific investigations such as ECG, ECHO, pulmonary function tests with DLCO, and/or high-resolution CT thorax.

Nailfold Capillaroscopy in Children

Nailfold capillaroscopy (NFC) is an important investigation to help differentiate between primary and secondary RP and should be performed in all children presenting with RP. There are different methods of examination: nailfold capillaries can be examined simply with an ophthalmoscope, auroscope, dermatoscope, or higher magnification devices such as video capillaroscopy. Even most young children will tolerate nailfold capillaroscopy and the only technical issue is the ability of a child to stay still [21] (Chap. 12).

Studies have examined NFC in healthy children and children with CTD, although definitions of abnormality are less well defined than in adults with considerable variation. It is likely that definitions of capillary appearance into "normal," "nonspecific," and "scleroderma pattern" can be applied to children; at present validation of these definitions in the pediatric age is lacking. Normative data for NFC in healthy children have been described although nonspecific microvascular abnormalities are common and have been

reported in 37 % of children without disease [22]. Capillary length, density, and width are age related with younger children having wider and fewer capillaries [23–25]. However, children with CTD had more defined abnormalities (such as avascularity, giant loops, hemorrhage) with significantly higher rates of abnormalities in mixed CTD ($p=0.008$), JSLE ($p=0.0002$), and juvenile dermatomyositis ($p<0.0001$) compared to healthy children [24]. Of the small cohort of JSSc patients included in this study 5/8 had scleroderma pattern abnormalities at disease onset. Children with juvenile dermatomyositis can have scleroderma pattern abnormalities and the degree of NFC may help to predict the outcome [22, 24, 26–28].

Prospective evaluation of serial NFC in 40 children and adolescents with Raynaud's phenomenon identified three children who developed progressive NFC changes with two developing scleroderma pattern (one developed mixed CTD and the other hypothyroidism with digital ulcers and puffy hands). Nonspecific changes seen on initial NFC were entirely normal in all four children at follow-up and some patients who were ANA positive also became negative on retesting [4]. This highlights that repeat NFC and autoantibody assessment is important as changes can occur and may alter the level of concerns regarding a child's risk of progression to a CTD. Repeat NFC 6 monthly, particularly in new onset RP, may be indicated [3, 4].

Other Imaging Techniques

Thermography, often incorporating dynamic imaging such as cold challenge, is well described in adults and can help differentiate primary from scleroderma-related RP [29] (Chap. 13). Pediatric studies are limited and include a small pilot study showing that the re-warming curve gradients were significantly lower and time to re-warming was increased in children with RP compared to healthy children [30]. A further study (including 12 healthy children, 32 children with primary and 17 children with secondary RP) did not detect significant differences between the groups in terms of re-warming rate [31].

There is a single report of the use of laser Doppler imaging (LDI) to assess functional abnormalities in blood flow in children with RP [32]. This pilot examined NFC and LDI in five children with JSSc, five with primary RP, and 5 healthy children who were age and gender matched. Children with JSSc had increased numbers of enlarged capillaries and deletion scores compared to the other groups. Mean finger blood flow was significantly reduced in the JSSc group compared with healthy children. After cold stimulus, healthy children showed blood flow recovery by 20 min, whereas those with primary RP and JSSc did not. However, LDI did not appear to differentiate between primary RP and JSSc.

Larger studies are needed to further evaluate whether these techniques can be useful in differentiating children with secondary RP from those with primary disease.

Predictors of Progression to CTD

We do not have clear information on how many children with RP develop a CTD over time. A prospective study of 250 patients with RP, 44 % of whom were aged 10–16 years, showed that 23.6 % evolved into a definite CTD: undifferentiated CTD in 11.3 %, SLE in 3.5 %, scleroderma spectrum in 5.2 %, and juvenile idiopathic arthritis/rheumatoid arthritis in 4 %. The mean time from the first RP and the development of a CTD disease was 2.4 years [3].

Interestingly, a retrospective study showed that 7/85 patients (8 %), who were initially classified as primary Raynaud's, developed a definite CTD in a follow-up period of 1.3 ± 2.1 years [2].

As for possible risk factors for the progression to a definite CTD in children, NFC abnormalities and the presence of autoantibodies are the most important [2, 3].

In the cohort of 250 patients with RP previously mentioned, 10 (4 %) had sclerodermatous type changes on NFC before the progression to a CTD: eight developed scleroderma spectrum disorders, one undifferentiated CTD, and one SLE [3]. However, nonspecific NFC changes are common in healthy children and those with primary RP.

It is the specific "scleroderma pattern" which incurs a high risk of progression to CTD [3, 4, 23, 33].

The presence of positive autoantibodies is another important risk factor for the development of a CTD. The retrospective study in children with RP [2] showed that ANA is present with a significant higher frequency in secondary RP (85 %) versus primary RP (25 %, $p<0.001$) and that positive ENA screen was positive in 67 % of children with secondary RP compared to 6 % of those with primary RP ($p<0.001$). NFC were borderline or abnormal in 68 % of secondary RP compared to 23 % of patients with primary RP ($p<0.001$). The vast majority (93 %) of those with CTD have one or both of ANA or abnormal NFC as compared to 39 % of those classified as primary disease [2]. Age at onset, gender, or number of color changes did not differ between the two groups. The authors defined primary RP as episodic reversible color change in the extremities without established or suspected CTD rather than based on ANA or NFC findings.

It is important to recognize that while most pediatric patients with secondary RP will have a positive ANA, a significant number of those with primary RP also have a positive ANA without evidence for an associated rheumatic disorder. Healthy children can be ANA positive and low-level titers and transient positivity are less of a concern. Current evidence suggests that children with RP and ANA positivity should be followed up more closely than those that are ANA negative as they may be at increased risk of development of CTD and it is likely that those with specific autoantibodies (for example anti-topoisomerase (Scl-70) or anti-centromere) are at higher risk.

Differential Diagnosis

As in adults, the differential diagnosis for RP includes a long list of disorders but those that more frequently are considered in clinical practice are *acrocyanosis*, *perniosis*, or chilblains, and, more rarely, *frostbite, carpal tunnel syndrome, erythromelalgia*, and *complex regional pain syndrome*.

Acrocyanosis is a painless, vasospastic disorder causing persistent coldness and bluish discoloration of the hands and, less commonly, of the feet [34]. Patients with acrocyanosis have cold and diffusely cyanotic color changes that can involve the entire hand and foot, extending proximally without a sharp demarcation between affected and unaffected tissue. It is aggravated by cold exposure and is often associated with hyperhidrosis of hands and feet. Both acrocyanosis and RP are more common in individuals, mostly female, with low body weight or who have anorexia nervosa [35, 36]. Acrocyanosis is common in infancy and is usually self-limiting with a recent study showing that 30 % of newborns had acrocyanosis and 4 % had cutis marmorata (a reticular cutaneous vascular pattern which can affect the whole body) [37]. Both these conditions are related to an exaggerated physiological vasomotor response in infants which improves with age. It is important to differentiate acrocyanosis from central cyanosis. This can be done easily with pulse oximetry. Rarely, acrocyanosis can be due to methemoglobinemia although it more commonly causes a central cyanosis [38].

Unlike RP, acrocyanosis rarely responds to vasodilator therapy.

Perniosis, or chilblains, is a cold-induced condition characterized by painful, erythematous, papular, or nodular lesions, usually located on the fingers and toes. In a pediatric series the ratio of girls to boys was 4.5:1 with mean age at presentation 13.5 years. All children presented with prolonged capillary refill time and 82 % had finger swelling. All had normal NFC and 25 % were ANA positive [39]. Digital ulceration is also reported and cold dry weather has been reported to cause clustering of cases [40]. As with RP, perniosis may present as an idiopathic process or in association with systemic disease (i.e., JSLE). It is distinguished from RP by the lack of blanching.

Frostbite can occur in cold climates and can have prolonged sequelae including persistent cold sensitivity.

Carpal tunnel syndrome is quite rare in children and is usually secondary to juvenile idiopathic arthritis, lysosomal storage disorders, or idiopathic [41]. Numbness and reduced manual dexterity are the more characteristic symptoms while color changes or cold sensitivity are absent.

Since the nerve compression or percussion test (Tinel's sign) is often non-diagnostic in pediatric patients, electrophysiological testing is indicated to confirm the diagnosis.

Erythromelalgia is a rare condition of paroxysmal vasodilation and can be considered as the opposite of RP. Symptoms consist of episodic burning pain accompanied by erythema, warmth, and swelling of hands and/or feet often triggered by heat, exercise, or friction. Patients report dramatic relief with application of ice or cold water. Primary erythromelalgia presents in childhood and can be familial (autosomal dominant) or sporadic. A retrospective pediatric cohort showed substantial morbidity and poor response to treatment with 59 % of children having evidence of small-fiber neuropathy [42]. In the primary form, a gain-of-function mutation of SCN9A, the gene that encodes the voltage-gated sodium channel Na(v)1.7, has been recently described [43]. Secondary erythromelalgia can be associated with essential thrombocytosis, hypertension, or Fabry's disease [44].

Complex regional pain syndrome (CRPS), or reflex sympathetic dystrophy, presents with unilateral distal limb involvement, with altered coloration (red, pale, or mottled) of the affected area showing differences in temperature (warmer or colder) and color compared with the unaffected side [45]. These patients refuse to move the affected limb and it may appear hyperhidrotic compared to the contralateral limb. Children often have severe diffuse persistent allodynia, hyperalgesia, paresthesia, or other abnormal sensations which are the main differentiating factors from RP.

Cervical Ribs

Cervical ribs or thoracic outlet obstruction should be considered in children presenting with unilateral symptoms. However, a large pediatric series of 322 children with cervical ribs did not identify RP as a presenting feature [46]. Upper extremity pain and paresthesia were uncommon and most children (88.8 %) were asymptomatic. Of those with symptoms the majority had either a neck mass or pain.

Treatment

Similarly to adults, the treatment choices for RP depend on the severity of symptoms, the impact on function, and in secondary RP the presence of tissue damage as indicated by digital ischemia, ulcers, or pitting scars. There are no randomized or controlled trials of treatment in children with either primary or secondary RP and evidence is often extrapolated from adult literature. Studies have also not explored in depth the impact that RP has on children in terms of function, quality of life, or pain.

Children with primary RP may report color change without any pain or discomfort with no impact on function. Thus, a conservative, non-pharmacological approach is often sufficient and most appropriate for these patients. However, some children with primary RP can have significant discomfort and pain during attacks which can impact on functional ability. An approach to management of a child with RP should include assessment of the impact of the symptoms on the child and family. For example, does RP affect the child's ability to write and has this had an impact during exams? Have symptoms interfered with the child's ability to perform adequately at sports or music? Does the mother of the toddler with RP avoid going out in cold weather because an attack will be triggered which may cause the child to cry?

By comparison, children with secondary RP are more likely to have more severe attacks including progression to tissue damage and therefore to require pharmacological agents to achieve symptomatic control and prevent ischemic events.

General Measures

Non-pharmacological therapeutic interventions include avoidance of triggers such as cold temperatures, sudden temperature changes, wind or air conditioning, and certain drugs. The use of warm and layered clothing can be extremely effective and families and children should be advised to wrap up before exposure to cold. Persuading a young child or adolescent to wear

layers and warm clothing is not without its challenges.

Techniques to terminate an attack, such as massage, windmill motions of the arms, and immersion in warm water, can be helpful. Some children may find that attacks are triggered by stress or emotions, although this was not shown in one study where there was no association with RP and psychosocial factors [5]. A letter from a clinician to a child's school explaining the diagnosis and the importance of these general measures may be helpful if wrapping up and layering of clothes breach school uniform policy. The impact of symptoms on examination performance should also be considered.

If a child is regularly taking drugs that are known to cause or exacerbate RP, the need for these medicines should be reviewed before pharmacological therapies to treat RP are discussed. However, it may not be feasible to stop aggravating drugs. This is a particular problem in children on stimulants for treatment of attention-deficit hyperactivity disorder as the side effects of coming off such therapies may cause more harm than the symptoms from secondary RP. This requires careful discussion with the family and the clinicians involved in the care of the child.

Pharmacological Measures

In children with primary RP, a decision on whether to start vasodilator therapy should be based on the impact of symptoms on the child and a discussion of benefits and side effects of drugs, so the family and child can make an informed decision on whether to commence treatment. This is in part because aims of treatment are to alleviate symptoms rather than to prevent tissue injury.

Titrating to lowest effective dose and use of medications only during periods of expected cold exposure (e.g., winter months) can help to minimize medication exposure in patients with primary RP.

One drug may be effective in one patient, whereas a different agent is effective in another. If one drug is ineffective it is therefore worth trying others, one at a time, until the desired effect is obtained.

Due to structural vascular abnormalities, patients with secondary RP are likely to require more aggressive therapy. Aims of therapy in these patients include reduction of pain/discomfort and improved function but also the major goal is to prevent or limit new digital ulceration and episodes of ischemia.

The most commonly used vasodilator agents are calcium channel blockers (CCBs). Because of lack of pediatric data, choice is often dependent on adult studies, pediatric licensing of agents, frequency of dosing, and local availability of preparations. Long-acting agents with less frequent dosing are attractive in children. Younger children may not be able to swallow tablets and this may impact on choice of agent. Amlodipine is given once daily and some preparations can be dissolved. Nifedipine is available as a suspension in some countries and liquid can be extracted from capsules although this can be difficult for families. Modified-release preparations can be crushed but this may alter the slow-release properties of the drug.

A retrospective study from a pediatric rheumatology center analyzed the use of therapeutic agents in children with RP. It was underpowered to detect differences between drugs in terms of effectiveness and tolerability [47]. However, it did show that agents commonly used included amlodipine, nifedipine, and topical glyceryl trinitrate patches. The study included 42 patients of whom 76 % were diagnosed with primary RP; 23 % of patients failed first-line treatment and required a second agent although it is unclear whether this is due to poor response or intolerance.

Small case series and reports have suggested a beneficial response to certain vasodilators including nifedipine [48], phenoxybenzamine (an alpha-adrenergic antagonist), intravenous nitroprusside [49], and a transdermal prostaglandin E2 analogue [50].

Iloprost has been reported to be safe and effective in treatment of ischemic digits in children with JSSc and other connective tissue diseases, including children under 2 years of age [9, 51].

Iloprost can also be used for severe RP without critical ischemia in children who are not responding adequately to CCB and in whom there is concern regarding future tissue damage.

Bosentan does not have a pediatric license for treatment of digital ulcers. However, pediatric dosing and safety data exists from trials of pulmonary hypertension [52]. A case report suggested a response in Raynaud's symptoms as assessed by cold challenge thermography in a child with JSSc and pulmonary hypertension [53]. There is also a case report of healing of a chronic leg ulcer in a patient with JSSc [54] and a child with polyarteritis nodosa with refractory digital ischemia who responded to 5 days of iloprost and 12 weeks of bosentan treatment [55]. Similarly to bosentan, clinical trials of sildenafil for digital ulceration and treatment of refractory RP did not include children but pediatric trials in pulmonary hypertension again provide dosing and safety data [52]. The use of sildenafil in a child with marked digital ischemia and necrosis secondary to polyarteritis nodosa is reported [56].

Digital sympathectomy is indicated only in the management of gangrene or intractable pain in the digits refractory to medical management. Again, pediatric experience is limited [57].

Expert Opinion

RP can be the presenting feature of connective tissue disease among patients seen in pediatric clinics and should be carefully evaluated, as exemplified in Figs. 7.1 and 7.2. Large prospective follow-up studies of children with RP are needed to fully evaluate prognosis and risk factors for development of CTD. However, pediatric evidence suggests that abnormal NFC, in particular scleroderma pattern appearance and positive autoantibodies, are important risk factors for progression to a CTD in children as in adults. We therefore recommend that all children with RP have NFC examination and ANA testing as a minimum. Children with abnormal NFC and ANA positivity should be carefully and regularly evaluated with the aim to detect CTD early. Early diagnosis allows for prompt and aggressive management with the aim to improve outcomes.

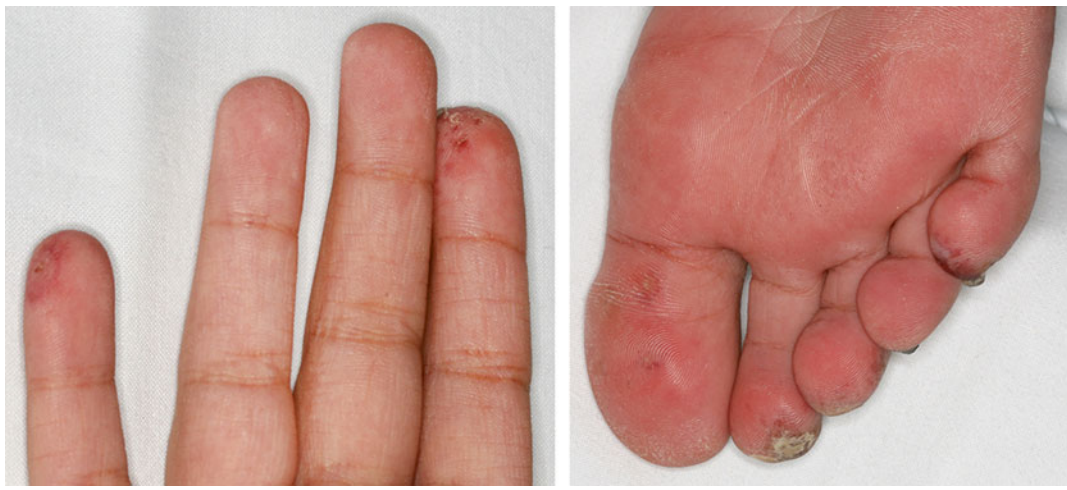

Fig. 7.1 Vasculitis lesions on hands/toes: A 12-year-old girl presented with rash on her hands, feet, and ear lobes associated with recent-onset cold extremities and biphasic color change. She had an 8-week history of fatigue, fever, and weight loss. She had normal nailfold capillaries but with vasculitic purpuric rash on nearly all of her fingers with dusky appearance, sluggish capillary refill, and a vasculitic discoloration under the nail beds with normal peripheral pulses. Investigations confirmed a diagnosis of C1q deficiency and JSLE associated with systemic vasculitis (see section "Case 1")

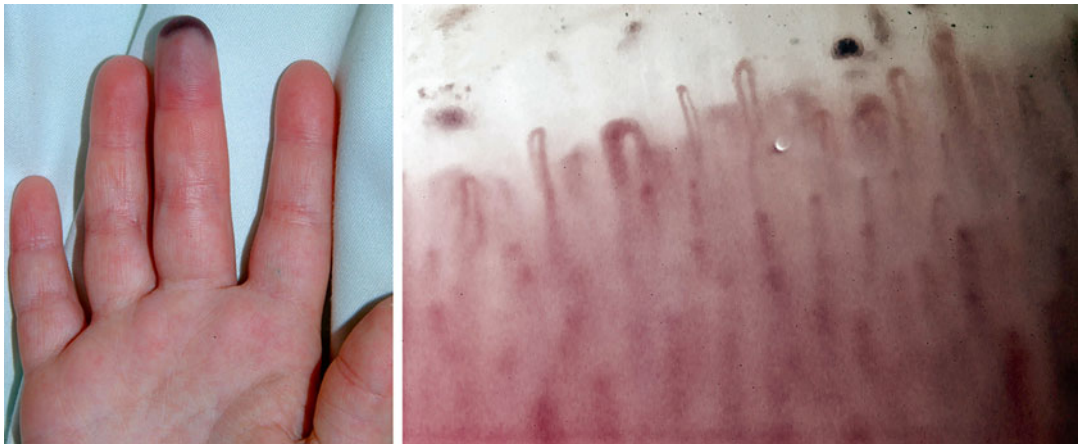

Fig. 7.2 Ischemic fingers and abnormal NFC: A 5-year-old girl presented acutely with digital ischemia affecting her finger (*left-hand panel*) with a background history of 2 months of Raynaud's symptoms, lethargy, and weakness. She responded well to 5-day intravenous iloprost, analgesia, and antibiotics with no tissue loss. She was ANA positive (titer 1:640, nucleolar pattern) with negative ENA and dsDNA panel. NFC (*right-hand panel*) showed some dilated capillaries and areas of hemorrhage. A diagnosis of systemic sclerosis with myositis overlap was made based on skin thickening, abnormal capillaroscopy, raised muscle enzymes, and MRI findings in keeping with myositis

Patients with primary RP benefit from education and non-pharmacological control measures while those with secondary RP more often require drug therapy. Long-acting CCBs are the most commonly used first-line drugs for RP in children. Severe or critical digital ischemia requires immediate evaluation to identify reversible vascular and coagulation defects and aggressive intervention with vasodilatory therapies to restore blood flow. As for adult patients, consideration should be given to pain control and treatment of secondary infection.

The complexity involved in conducting clinical trials in pediatric patients and the lack of standard outcome measures for RP remain a challenge to investigators. However, advances in the understanding of the pathogenesis of RP and the recent clinical trials in adults continue to improve outcomes, particularly for those with severe disease. The lack of pediatric data for newer drugs limits the availability of these therapies in clinical practice because of lack of pediatric licensing. Extrapolation from adult studies is not a substitute for robust pediatric clinical trials which are much needed in both primary and secondary RP.

Case 1

A 13-year-old girl presented with triphasic color change in her hands associated with pain and stiffness. Exacerbations were triggered by cold, wind, or changes in temperature. This was affecting her function, in particular her writing ability at school and her performance as a dinghy sailor. She had felt a little more fatigued recently and apart from some mild periungual erythema, there were no other features suggestive of an underlying CTD on history or examination. Full blood count, ESR, and thyroid function tests were normal and ANA was positive 1:160. ENA screen and anti-dsDNA were all negative. NFC was normal and she had some delayed re-warming on cold challenge thermography (Fig. 7.3). A diagnosis of primary RP (but with positive ANA) was made. The patient and family were educated about RP and non-pharmacological measures were introduced. However, her symptoms continued to impact on her function and she was started on oral amlodipine with good result, allowing her to continue to compete in her sport. Over several years of follow-up she remained otherwise well with no change in either NFC or autoantibody profile.

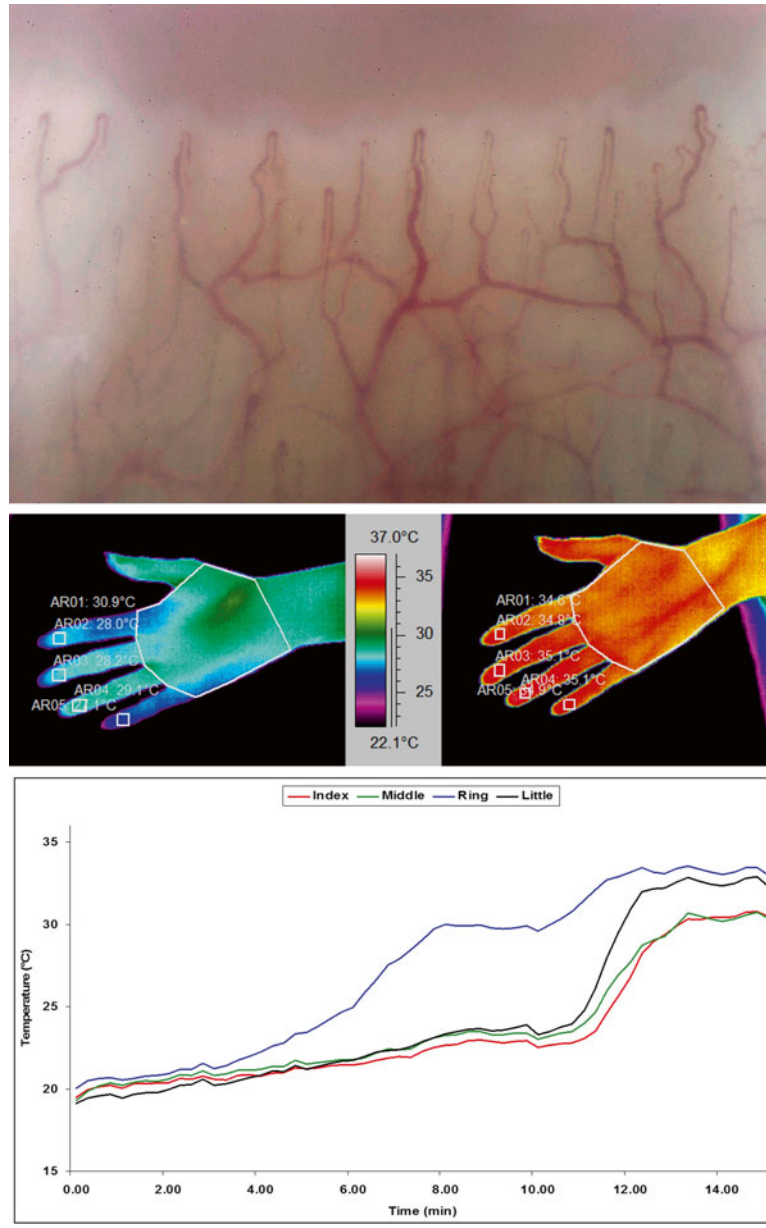

Fig. 7.3 Normal nailfold capillaroscopy (*upper panel*), thermograms showing cold fingers at 23 °C (*middle left*) but which warmed at 30 °C (*middle right*), and re-warming curves after a cold challenge, showing delayed but complete re-warming (*lower panel*). These capillaroscopy and thermography findings are consistent with a diagnosis of primary RP

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Secondary Raynaud's Phenomenon

8

Voon H. Ong and Christopher P. Denton

Abbreviations

ACE	Angiotensin-converting enzyme
APS	Anti-phospholipid syndrome
ARB	Angiotensin II receptor blocker
CCB	Calcium channel blocker
CTD	Connective Tissue Disease
EM	Erythromelalgia
IIM	Idiopathic inflammatory myopathy
MCTD	Mixed connective tissue disease
PM	Polymyositis
RP	Raynaud's phenomenon
SLE	Systemic Lupus Erythematosus
SS	Sjögren's syndrome
SSc	Scleroderma
TAO	Thromboangiitis obliterans
UCTD	Undifferentiated connective tissue disease
VEDOSS	Very early diagnosis of systemic sclerosis

Key Points

1. The Raynaud's phenomenon (RP) that occurs in the context of autoimmune rheumatic or connective tissue disease (CTD) is generally more severe than in cases with primary Raynaud's and it is more likely to be associated with more severe complications of vascular insufficiency.
2. Autoantibody testing [see Chap. 15] and examination of the nailfold capillaries {see Chap. 12} are central to the investigation of patients with a suspected diagnosis of secondary RP.
3. Scleroderma (SSc) is the most frequent CTD associated with RP, present in more than 90 % of patients.
4. Systemic Lupus Eythematosus (SLE) is much more common CTD than SSc but RP is less common in SLE affecting about 10–45 % of these patients.
5. Some of the most troublesome cases of secondary RP in association with connective tissue disease are associated with Idiopathic Inflammatory Myopathy (IIM) and specifically with polymyositis.
6. There is a high prevalence of RP in patients with Mixed Connective Tissue disease (MCTD) of up to 90 %, which is similar to that observed in SSc.
7. RP is reported to occur in about 13–33 % of patients with primary Sjögren's syndrome (SS) but the true prevalence of RP in this disease is not known.

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8. The frequency of RP in Rheumatoid arthritis is not well established in part due to the lack of consistent methods in reported studies.
9. Several studies showed that about 60 % of patients with Undifferentiated Connective Tissue Disease (UCTD) will remain clinically stable with a mild disease course; RP is seen in 45–60 % of these patients
10. Vasculitis is an especially important disease process that may overshadow RP

Introduction

The medical importance of Raynaud's phenomenon (RP) is to a large extent determined by whether it is a reflection of a disease such as an underlying autoimmune rheumatic disease. The Raynaud's phenomenon that occurs in the context of autoimmune rheumatic or connective tissue disease (CTD) is generally more severe than in cases with primary Raynaud's and it is more likely to be associated with more severe complications of vascular insufficiency. In addition, RP is important because it is often an early clinical feature of the associated disease and often it is the presenting feature that prompts investigation into the underlying diagnosis. One of the medical priorities for cases of secondary RP is to make the diagnosis of an associated disease as promptly as possible in order to begin appropriate management. This chapter will review some aspects that are relevant to the investigation, diagnosis and individual features of RP associated with specific connective tissue diseases. The characteristics of RP may point towards the underlying disorder and provide direction to the evaluation needed. It is important to identify cases who present with RP that are at risk of evolution into a defined connective tissue disease [see also Chap. 6]. Greater focus on the earlier diagnosis of some diseases, notably systemic sclerosis (SSc), has led to inclusion of RP and some key associated features into the 2013 ACR/EULAR classification criteria for SSc. It is also included in the separate research agenda to identify specific and sensitive features for the very early diagnosis of SSc (VEDOSS) [1, 2]. It is important to note that not all forms of CTD have Raynaud's as a first symptom; in fact, some severe cases have RP developing after onset. This is notably the case in patients who present with anti RNA polymerase III autoantibody reactivity [3]. Some cases with RP have autoantibodies and clinical features of an autoimmune disease but do not progress. These cases are best termed undifferentiated connective tissue disease (UCTD). Finally, some cases of RP occur in the context of overlap syndromes including cases that have clinical features of more than one rheumatic disease that is also considered as mixed connective tissue disease (MCTD). Other forms of associated or secondary Raynaud's occur in association with haematological disorders or other medical conditions [see Chap. 10]. Systemic diseases with vasculitis can either have associated RP or they can present with vasospasm that mimics RP.

Prevalence—The epidemiology of Raynaud's phenomenon is discussed in greater detail elsewhere in this textbook [see Chap. 3] but will be reviewed briefly as it is relevant to the investigation and differential diagnosis of secondary RP. It is important to remember that primary RP is by far the commonest form of the condition and by definition occurs in otherwise entirely healthy individuals. Of course these individuals may be affected coincidentally by unrelated medical disorders and this leads to the potential spurious associations with common diseases. Approximately 1 in 10 patients with RP reported in most series have some features of an associated medical condition, most often there will be features of an autoimmune rheumatic disease. Around 10 % of cases with some features of such a disorder will be diagnosed as a defined disease and the commonest associated diagnosis is SLE or MCTD. SSc is noteworthy because of the severity of RP and the specific complications that frequently occur as consequence of the underlying digital vasculopathy. It is important to differentiate those cases that present with vasospasm with or without typical RP due to complications that reflect fixed vascular insufficiency such as thrombosis, embolism, vasculitis and an occlusive vasculopathy. These vascular disorders are important as their occurrence differ between the autoimmune rheumatic diseases (Table 8.1).

Table 8.1 Classification of Raynaud's phenomenon and associated key features for primary and secondary Raynaud's phenomenon

Classification of Raynaud's phenomenon	Key characteristics
Primary Raynaud's	Familiar predisposition, young age of onset, lack of digital ulceration, absence of ANA
Secondary Raynaud's	
Connective tissue diseases	Features of SSc, SLE, Inflammatory myopathies, MCTD, UCTD
Vasculitis	Distinctive vasculitic rash with gangrene
Antiphospholipid antibody syndrome	History of thrombosis with positive serology
Thromboangiitis obliterans	Male preponderance, smoking history, lower limb extremities distally with typical arteriographic findings on distal vessels with cork-screw collaterals
Thromboembolic disease	Causes include infective endocarditis, atrial myxoma, proximal vessel disease
Cryoglobulinaemia	Palpable purpura, chronic ulcers with renal and neurological involvement. Serum cryoglobulins and low C4
Paraproteinaemia	
Other causes	Cold agglutinin disease with haemolysis, positive Coombs. Association with lupus and rheumatoid arthritis and female preponderance
	Thoracic outlet syndrome
	Iatrogenic including drugs (chemotherapeutic agents, non-selective beta blockers, ergotamine and bromocriptine)
	Hand arm vibration syndrome

Diagnosis—The diagnosis of secondary RP is dependent on a comprehensive history, careful physical examination and specific laboratory investigations. These features are discussed in general terms below and in more specific detail in relation to the individual associated conditions later in the chapter.

History of RP depends on first confirming that there is indeed a clear history of episodic vascular insufficiency affecting the extremities that is triggered by specific factors such as cold exposure, emotional stress, exercise and on occasion an aggravating medication. An important consideration is the age and gender of the patient. Secondary RP more often occurs in older individuals. It is much more likely when there is no clear history of RP or cold sensitivity prior to the age of 30. In particular it is important to carefully assess whether RP symptoms might in fact have been present for longer than first suggested by the patient who may ignore mild symptoms for many years. Associated symptoms may reflect an underlying connective tissue disease. The presence dermatitis, dry eyes or mouth (sicca symptoms), finger swelling, muscle weakness, fatigue and arthralgia or arthritis are especially important. Symptoms of upper gastrointestinal dysmotility such as dysphagia or heart burn in a patient with RP may indicate a secondary connective tissue disease like SSc. These symptoms of gastrointestinal reflux disease are an important sensitive indicator of disease but very non-specific as these symptoms are very prevalent in the general population that often become more severe or prominent in middle age; the same time that a CTD might be suspected. Finger swelling or puffiness can be the first sign of a CTD and warrants detailed investigation and serial observations. It is, however, not uncommon to have this in primary RP when it likely reflects transient increase in digital vascular permeability. The need to have rings enlarged is an important but again non-specific feature that may suggest an underlying CTD. A history of digital infarction or ulceration or other major trophic change or skin does not occur in primary RP. In addition digital nail abnormalities such as nail dystrophy or onycholysis should be sought, although nail changes are also common in primary RP [4].

On examination it is important to elicit any signs of CTD including those of SLE, SSc or dermatomyositis. There are some specific signs that may point to an associated vasculitis—such as purpura or skin infarcts. Ordering a laboratory test to detect a haematological disorder such as cold agglutinin disease or cryoglobulinaemia is appropriate in cases with typical skin lesions. These are discussed in more details below. It is especially important to identify any internal organ complications as it may be that these develop early and before a defined diagnosis is

made. This is evidenced by the relatively high frequency of RP in clinics assessing lung fibrosis, chronic liver disease or pulmonary hypertension as these may all occur in the context of mild CTD in which RP is an important clue to the presence of an associated autoimmune or inflammatory disease. When confronted with an organ based disease and RP, it is important to do further investigations to make a specific diagnosis, as it will not only define therapy for the associated disease by also the approach to management of RP. One of the most important investigations to highlight likelihood of secondary RP are nail fold capillaroscopy defined microvascular structural abnormalities [5, 6] [see Chap. 12]. There are specific patterns seen in particular with SSc and other CTDs including SLE, idiopathic inflammatory myopathies (IIM) that can help in diagnosis. Cases of undifferentiated CTD are typically associated with altered nail fold capillaries. The presence of enlarged and giant capillaries with haemorrhages for example suggests early morphological evidence of altered microcirculation in SSc (see Chap. 12). The typical SSc-NVC patterns occur in minority (2–15 %) of patients with SLE particularly those with RP, anticardiolipin antibodies and anti-U1RNP antibodies [7–9]; these cases likely to represent a cohort of patients with subclinical overlap syndrome. A greater variety of capillary abnormalities on the other hand are described for SLE. The most common NVC in SLE are capillary tortuosities with enlargement (2–88 %) but these changes may also occur in other connective tissue diseases [10–12]. The SSc-specific NVC pattern with microhaemorrhages and giant capillaries is on the other hand common among patients with IMM in particular dermatomyositis, and less so in polymyositis [13]. In contrast, there is a growing support that normal capillaroscopy should be incorporated into the diagnostic requirements for RP but it is noteworthy that there is a wide range of nailfold patterns seen in healthy individuals. Other forms of vascular imaging can be used to confirm the presence of RP—such as infrared thermography or laser Doppler flowmetry [14, 15] [see Chap. 13].

Autoantibody testing [see Chap. 15] is also central to the investigation of patients with a suspected diagnosis of secondary RP. In cases with a CTD, the serology testing will usually show a positive ANA pattern. The ANA may be secondary to an uncharacterized auto antigen or it may define a specific reactivity such as anticentromere staining. It is sensible to test any patient with significant RP symptoms as part of baseline investigation and subsequently if there are any new clinical features suggesting the development of an associated connective tissue disease. A negative ANA or low titre ANA (e.g. 1:40 by indirect immunofluorescence) on the other hand would support the diagnosis of primary RP. In the context of secondary RP, there may be disease-specific ANA reactivities that help with diagnosis. Indeed, specific autoantibodies are associated with disease and now are included in the classification criteria for SLE, SSc and IIM [1, 16]. The prognostic significance of altered nail fold capillaroscopy findings and a positive ANA reactivity in patients with isolated RP is discussed in more detail elsewhere (see Chaps. 12 and 15). It should be remembered that some of these cases will fulfil criteria for very early diagnosis of systemic sclerosis (VEDOSS).

In addition, changes in biomechanical properties of the proximal vascular arterial system have been evaluated in distinguishing secondary from primary RP [17]. For example, increased carotid stiffness and elasticity or reduced carotid compliance as determined by ultrasound measurement using a Doppler scanner was found among SSc patients but not among those with primary RP [17]. Interestingly, this difference in vascular stiffness between SSc and primary RP was not observed for muscular femoral arteries.

Risk stratification—refers to the specific features that are present in a patient at diagnosis or early in the clinical course that predict specific progression, likelihood of progression or risk of developing a specific complication of the disease. The concept of risk stratification is borrowed from other medical fields but has particular resonance to the investigation and management of cases with suspected secondary RP.

The most robust markers of progression in a case of true isolated RP are the presence of abnormal nail fold capillary pattern and positive

ANA. The specific pattern of ANA is important because a disease-associated antibody is more predictive of an underlying autoimmune disease. For example, a nucleolar pattern of ANA is more likely to be associated with progression from RP alone to definite SSc. It has been determined in a number of large series that the risk of developing CTD is around 15 % within 5 years of the onset of RP. The risk increases with length of follow-up and is much higher if a specific disease related ANA reactivity is present [9, 18]. Making a precise diagnosis of a CTD diagnosis is challenging as this is often a reflection of experience, expertise and clinical suspicion and the interpretation of the presence of a number of clinical features. It is complex in that many features such as skin changes or symptoms of gastrointestinal reflux disease (GERD) in themselves are not specific. Of more importance is the negative predictive value of normal capillaroscopy and negative ANA. It is very rare to develop a defined CTD if these tests are negative on two occasions separated by a minimum of 12 months of follow-up. The most robust evidence for this concept is the long term follow-up reported in a series published by Koenig et al., a prospective study that is congruent with earlier individual series and a meta-analysis [19, 20].

Thermography characteristics of secondary RP have now been evaluated and may eventually provide additional information for risk stratification. This approach together with other non-invasive methods of assessing vascular reactivity to cold challenges may help define a secondary process causing RP [see Chap. 13]. The sensitivity and specificity of these features is currently under investigation and will be important together with other practical considerations in introducing this into routine clinical practice.

Individual Conditions Associated with Secondary RP

Systemic Sclerosis (Scleroderma; SSc)

SSc is the most frequent CTD associated with RP in more than 90 % of patients. Raynaud's phenomenon is an important early symptom of SSc and often precedes the onset of other signs and symptoms. Moreover, presence of SSc specific antibody (anti-centromere, anti-topoisomerase or anti-RNA polymerase) and/or capillaroscopic findings have been shown to be the best predictors of Raynaud's progression to SSc [19]. Therefore, the early recognition of patients with RP at particular risk to develop SSc is of key importance. The presence of RP is now part of the preliminary criteria for very early diagnosis of SSc (VEDOSS) proposed by the EULAR Scleroderma Trials and Research group (EUSTAR) [2]. These criteria include digital puffiness with sclerodactyly, abnormal capillaroscopy with SSc pattern and positive ACA and anti-Scl70 antibodies (Fig. 8.1). Similarly, RP is now incorporated as one of the classification criteria recently updated by an ACR-EULAR committee [1]. The length of time from onset of RP is important as there are clear differences in the duration of RP

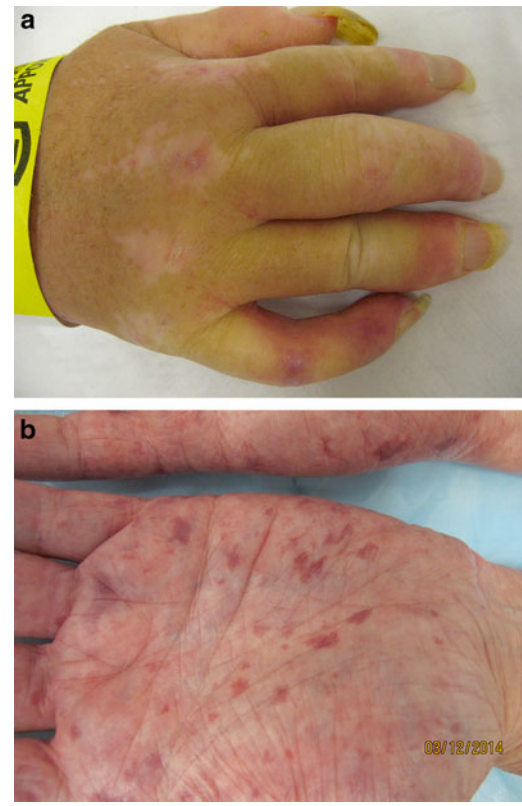

Fig. 8.1 (**a**) The early phase of scleroderma with oedema and thickened skin on hand and fingers; (**b**) Telangiectasia on the palm of the hand in a patient with scleroderma

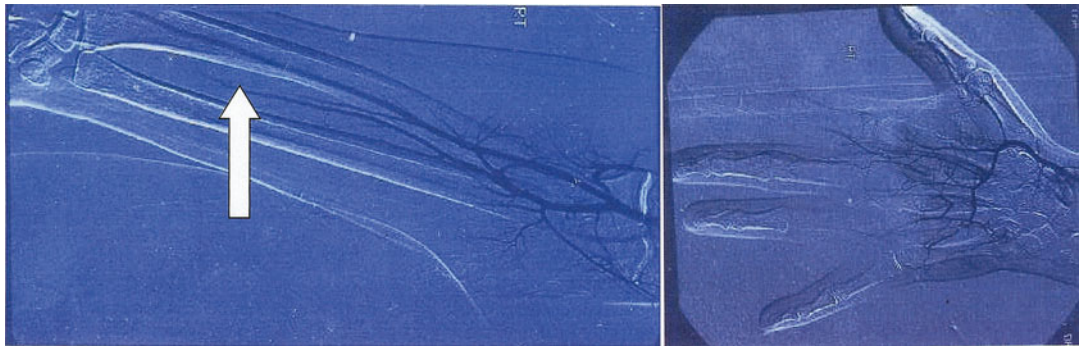

Fig. 8.2 Ulnar artery occlusion in a case of secondary Raynaud's phenomenon. Digital subtraction angiogram in a 36-year-old female with limited cutaneous SSc and severe Raynaud's phenomenon. In these images the ulnar artery tapers out in the distal forearm (*arrow*). The palmar arch is incomplete, and there is poor runoff to the digital arteries

according to both disease subset and ANA subtype. The different disease course of SSc subtypes makes the determination of the true onset date of SSc very challenging. In practice both the onset date for RP and for the first non RP manifestation of SSc are used to define disease onset. Most now agree that the new onset RP should be regarded as a first manifestation of SSc. This is only clear once an alternative diagnosis does not emerge or if there is disease progression with clinical signs to fulfil the criteria for SSc or VEDOSS. In clinical research the common practice is to use the first non RP manifestation of the disease to provide a more easily defined time on disease onset. This standardisation is used across all subtypes because it can be regarded as a time when internal organ manifestations of SSc are likely to occur. The interval between RP onset and the first non-RP sign in SSc will also predict the prognosis. A short interval is usually indicative of a more aggressive disease course. Differences in the length of time between RP onset and the development of SSc features have been shown to differ for different specific SSc related autoantibodies. The shortest interval is seen in those patients with anti-RNA polymerase III specificity compared to the other two hallmark SSc antibodies (ACA and anti-Scl70) [3, 21].

The definite pathogenesis of SSc is still not fully understood (see Chap. 5), but there is loss of normal control of vascular reactivity in SSc-associated RP. There are structural obliterative vascular abnormalities of both microvasculature and peripheral arteries including digital artery. Although the latter are involved, the vascular process predominantly affect the microcirculation and arterioles. Macrovascular disease has been reported in particular in association with ACA [22]. Presence of macrovascular disease with involvement of ulnar artery in particular in those with ACA has been shown to have a worse outcome with increased risk of digital amputation (Fig. 8.2) [22–25]. It is noteworthy that the thumb is more likely to be involved in secondary RP than in primary RP [26]. Thumb involvement in addition to late onset RP (>40 years of age) and those with worsening RP attacks are key clinical indicators that should alert the clinician to the possibility of an underlying connective tissue disease/disorder [27].

Patients with SSc often experience intense attacks that are painful and usually asymmetrical. Digital ulcerations as a consequence of severe digital vasculopathy with finger pulp loss as well as pitting scars are considered important features that have been incorporated into the new classification criteria of SSc [1].

Progressive acral skin ulcerations may either resolve leaving small scars, digital pits or evolve to tissue necrosis or gangrene. Bone resorption may occur over the digits and even self-amputation at the phalanges can occur. Several studies have reported the complications of severe digital vasculopathy [28–30]. In our cohort of over 1,100 patients follow-up over an 18-month period for frequency of complications of digital vasculopathy

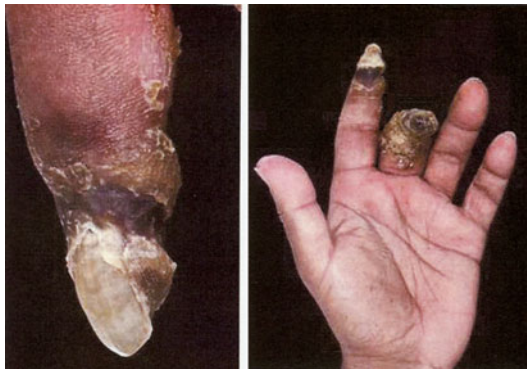

Fig. 8.3 Severe gangrene with autoamputation in a patient with limited SSc and Raynaud's phenomenon

including digital ulceration, critical digital ischaemia or gangrene, nearly 18 % of these patients developed these complications in particular those with diffuse subset (Fig. 8.3) [28]. Twelve percent required at least hospitalisation during the follow-up period requiring intravenous prostacyclin. Various groups reported that 11–15 % of patients underwent either digital amputation or gangrene [31, 32]. A study comparing bosentan to placebo in the prevention of digital ulcers (RAPIDS-2) reported digital amputation in 1–2 % of patients per year [33]. These results suggest that digital vasculopathy associated with RP in SSc contributes to significant morbidity with a negative effect on quality of life with significantly more impairment in work and daily activities. These patients require more support from others [34]. Digital ulcerations are also associated with worse non-vascular disease manifestations in particular severe skin and interstitial lung disease [35].

Management centres specialise upon specific management of RP as well as the overall management of the non-vascular manifestations of SSc. The specific approach to managing RP is reviewed in Chaps. 20 and 23. All patients should be educated as to importance of non-drug therapy as reviewed in Chap. 19. It is remarkable that despite the underlying severe vascular changes that cutaneous and digital blood flow can approach normal in a warm environment. In fact, avoiding cold temperatures is the most important intervention for managing RP in patients with SSc. Smoking cessation is also recommended [36]. The relationship of smoking and digital vasculopathy is perhaps less clear although there is sufficient evidence to indicate that smokers are at risk of persistent ulcer disease and thus, require more hospitalisations [22, 32, 37]. A calcium channel blocker is generally the drug of first choice. However, if this is not well tolerated or ineffective, then there are several other alternatives exist. However, the evidence base to support the use of other vasodilators is not strong. These agents include angiotensin II receptor antagonist, an angiotensin-converting enzyme (ACE) blocker, a selective serotonin reuptake antagonist or phosphodiesterase V inhibitor. Various combinations of the above vasodilators may be tried for those who failed to achieve a satisfactory response to single agent alone but again this approach has not been formally evaluated in clinical trials. Parenteral treatment such as prostacyclin (epoprostenol or iloprost) may also be considered although this is generally reserved for most severe cases that are refractory to simpler measures.

Specifically for digital ulceration (see also Chap. 21), the endothelin-1 receptor antagonist bosentan has been shown to prevent SSc-related digital ulcers in two randomised, double-blind controlled clinical trials [33, 38]. Bosentan reduces the number of new digital ulcers by 30–48 % and the effect was most marked in those with severe digital ulcer burden (more than three ulcers at baseline). However, bosentan did not have an effect on healing rate of existing ulcers.

Systemic Lupus Erythematosus (SLE)

SLE is much more common CTD (Fig. 8.4) than SSc but RP is less common in SLE affecting about 10–45 % of these patients. RP is reported to be more prevalent among female patients and less prevalent among those with late-onset SLE [39–41].

On the other hand, RP is reported to be more common among patients with lupus associated with pulmonary arterial hypertension (PAH) as compared to those without PAH (62–80 % of patients with SLE-PAH) [42, 43]. This may reflect that a generalised vascular disease is present in these patients and suggest that a there is the potential role of pulmonary arterial vasospasm in pathogenesis of PAH in SLE. It is also noteworthy that

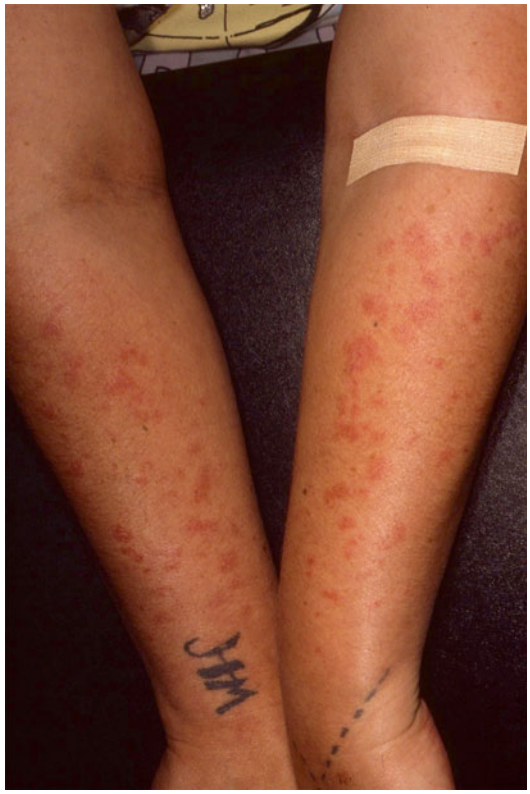

Fig. 8.4 Cutaneous lupus in a young woman with SLE and RP

RP may precede the onset of SLE in about half of patients with SLE. Therefore, in cases presenting with RP defining specific features that permit a robust diagnosis of SLE are important. The severity of RP symptoms vary but are often not the most troublesome feature for patients. A change in severity should prompt assessment for associated complication especially thromboembolic disease in the presence of an anti-phospholipid antibody or an associated vasculitis. It is important to distinguish typical uncomplicated RP from vasospasm related to a secondary complication caused by a necrotizing inflammatory vessel process or a thrombotic event. These events mimic RP but are different in presentation and consequences. Critical ischemic from a lupus related vascular disease usually presents with asymmetrical vasospasm or involvement of a single or few digits with evidence of tissue ischemia (ulcerations) and associated other signs of active lupus. It is also important to consider the presence of coexistent macrovascular disease as SLE patients have a substantially increased risk of atherosclerosis compared to the healthy population [44]. It is noteworthy that other important complications such as small vessel vasculitis, acrocyanosis and cryoglobulinaemia may coexist with RP in SLE [45, 46]. Conflicting results have been reported on association of RP and the presence of antiphospholipid antibodies in SLE. Although RP may not be directly associated with an anti-phospholipid syndrome (APS) is important to recognise its presence in lupus patients for specific management is warranted; a hypercoagulable state would require anti-platelet therapy or anti-coagulation [47]. There appears to be autoantibody clustering and clinical subsets exist in SLE patients but this may be subject to geographical variation. For example, RP was reported to be more common among those with anti-nRNP antibodies compared to other antibodies associated with SLE (including anti-Sm, SSA and SSB antibodies) but this association is less robust when anti-nRNP antibody is clustered with anti-Sm antibody. This was not replicated in recent studies [48, 49].

The significance of RP in predicting the development of SLE is unclear. There is some evidence to suggest that the presence of RP may associate with specific disease manifestations of SLE. Central nervous system complications including epilepsy and psychosis and peripheral neuropathy may be more common in SLE patients with RP while secondary Sjögren's syndrome may be more common in SLE patients without RP [50]. Some studies also suggest that skin and joint involvement, oral ulcers, thrombotic events and myopathy may associate with SLE but these associations are variable across different studies [50, 51]. These studies indicate that RP may be prognostically relevant in SLE.

Although no specific or pathognomonic capillaroscopic change is observed in SLE, enlarged capillaries, haemorrhages with avascular areas may be more prominent in patients with SLE and RP compared to patients with SLE without RP [10, 52]. Whilst it is unclear if RP in SLE is associated with more severe course of disease, it is important to note that those individuals with SLE and RP with typical SSc-NVC changes should be

closely monitored for development of major internal organ involvement.

Treatment of RP in SLE reflects that of other connective tissue diseases with first line approaches centred on vasodilators. Specific requirement for additional therapy such as anti-platelet, anticoagulation and statins will need to be considered in the context of the thrombotic risk and macrovascular disease in SLE. Related to SLE, chilblain lupus erythematosus (see Chap. 11) should be considered in patients with cold-induced purpuric rash and it is important to note that a minority of these cases may progress to develop SLE. This may be diagnosed on its clinical presentation and histopathological assessment.

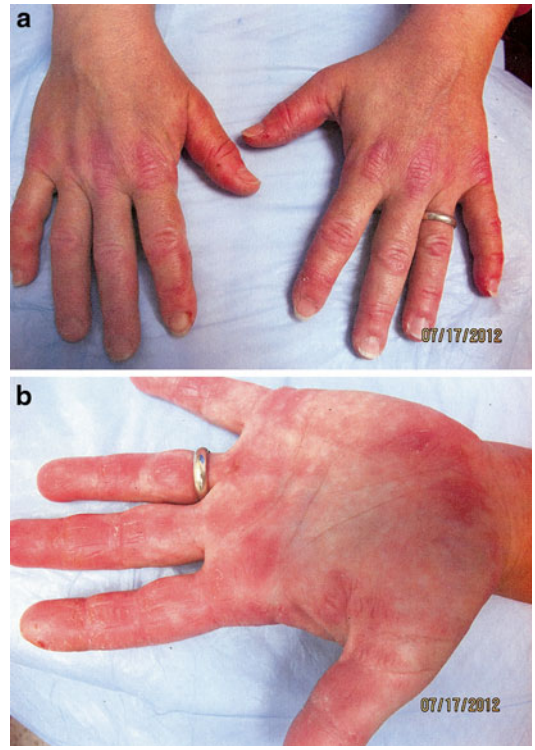

Fig. 8.5 (**a**) Mechanic hands with erythema, and (**b**) scaling on palms and papules of Grotton's sign on dorsum

Idiopathic Inflammatory Myopathy (IIM)

Along with SSc, some of the most troublesome cases of secondary RP in association with connective tissue disease are associated with IIM and specifically with polymyositis (PM). This may in part reflect a systemic vasculopathy that is a hallmark of the disease; there may also be an associated vasculitis. RP develops in about 40 % of patients with IIM and in half of cases with anti-Jo-1 antibody associated antisynthetase syndrome [53].

It is important to recognise that many of the early features of IIM and PM are quite nonspecific. The presence of the typical rash of DM makes earlier diagnosis more likely (Fig. 8.5a, b). A constellation of signs that are suggestive of the systemic features of IIM associated with antisynthetase antibodies include fever, proximal muscle weakness, interstitial lung disease, "mechanic's hands" and a nonerosive symmetrical polyarthritis of small joints. RP may be present at disease onset or appear later as the disease progresses. In IIM, persistent or severe digital ischemia leading to digital ulceration or infarction is uncommon [54]. Several case series have evaluated clinical risk factors that predispose to malignancy in dermatomyositis [55–57]. Interestingly the absence of Raynaud's was reported to be associated with increased risk of malignancy; this remains to be confirmed [58]. Among the myositis autoantibodies that define the clinical phenotypes of IIM patients, RP appears to be common among patients with anti-signal recognition particle (SRP) and anti-synthetase autoantibodies [59]. Patients with anti-SRP associated myositis (5–8 % of cases with IIM) have severe refractory myositis [60].

In the appropriate clinical setting, the diagnosis is confirmed by one or more investigations with serology (including anti-Jo-1 antibody), muscle enzymes (creatine kinase, LDH, aldolase), electromyography, muscle biopsy and imaging. Some patients may have nailfold capillary abnormalities but these changes are not specific to IIM [61]. The severity of interstitial lung disease largely determines the long term outcome and therefore treatment is often governed by the extent and severity of lung disease. Most of these therapies for the systemic features of IIM do not have a direct impact on RP. RP directed treatment strategies follow those of other types of secondary RP.

Mixed Connective Tissue Disease (MCTD)

Although the concept of mixed connective tissue disease is somewhat controversial it is clear that a reasonably homogeneous group of patients can be identified that fulfil one of more of the established criteria for classification of MCTD [62, 63]. Compared to the other autoimmune rheumatic diseases, there is a high prevalence of RP in patients with MCTD of up to 90 %, which is similar to that observed in SSc. It is also commonly the initial symptom of the disease with no other features of MCTD at initial presentation. Although the existence of MCTD as a unique entity is debatable, RP is a major feature in this cohort of patients. There are important and characteristic clues that may help to identify the subset of patients with RP who may progress to develop MCTD. These include nailfold capillary changes, autoantibody specificity and clinical features in particular features of SSc, lupus, myositis, Sjögren's and arthritis. However, there may be an operational distinction between those that have more features of SSc that can be at substantially greater risk of some complications such as scleroderma renal crisis, lung fibrosis. Pulmonary arterial hypertension occurs in MCTD and outcomes seem to be determined by coexistent features—patients with features of SLE have a much better long-term outcome than MCTD cases with prominent features of SSc. Together the features of RP, nailfold changes and associated PAH confirm that vasculopathy is a frequent feature of MCTD and also challenges the concept that this is often a mild disease. There are characteristic capillary nailfold changes in patient with MCTD particularly when compared with those with SLE. Only few patients with SLE demonstrate an SSc-NVC pattern; in contrast, up to 56 % of patients with MCTD would exhibit an SSc-NVC in particular the slow SSc pattern with giant or megacapillaries and nailfold haemorrhages [64, 65]. For this reason, a diagnosis of MCTD should be considered when s slow SSc-NVC pattern with irregularly enlarged or giant loops with minimal capillary loss is observed. Presence of anti-U1-RNP antibody also assists to identify a cohort of patients with RP that are at risk of developing visceral complications in particular pulmonary hypertension. Anti-U1-RNP antibody may be detected across a spectrum of connective diseases other than MCTD including SLE, SSc and undifferentiated connective tissue disease [66].

In terms of the RP, there is often a very florid cyanotic phase in cases of RP with anti U1-RNP but overall the RP tends to be less severe than in patients with SSc. This suggests that the process is a little different from SSc, and points to AV shunt closure with the preservation of nutritional arterial flow and venous stagnation suggesting less structural vascular disease in MCTD. It may be that this is the reason there is less severe complications of vascular insufficiency such as ischaemia and ulceration in these cases. While there are no reliable predictors that may identify patients who have MCTD who are at risk for developing severe complications from RP, those patients that do show these vascular complications secondary to RP often have an overall SSc clinical phenotype.

Sjögren's Syndrome

RP is reported to occur in about 13–33 % of patients with primary Sjögren's syndrome (SS) but the true prevalence of RP in this disease is not known due to variable definition of SS and different methods used to assess RP [67, 68]. It is reported that RP often precedes the onset of sicca symptoms in 37–50 % of SS patients [68, 69] and may be an early feature of SS. However, given that both RP and SS are common, it is probable that some patients with RP may develop SS and the two processes are indeed independent of each other. Compared with the other CTDs discussed the severity of RP is often less in Sjögren's and indeed a substantial number of cases that fulfil classification criteria do not manifest clinical RP. When RP occurs the symptoms and features are similar to those in patients with MCTD and it may be that these

cases are indeed a form of overlap connective tissue disease.

Analysis of the clinical features of this subset of patients with RP showed a higher frequency of systemic involvement with extraglandular features of cutaneous and articular involvement [68, 69]. Similar to other CTDs, RP was noted significantly more frequently in SS patients with PAH, again suggesting a common biological link in the pathogenesis of RP and the vasculopathy of PAH. In support of this observation, RP is also reported to be more common in those with cutaneous vasculitis in Sjögren's compared to those without vasculitis [70]. Some studies also reported that sensorimotor neuropathy and mononeuritis multiplex in Sjögren's are associated with RP, cutaneous vasculitis, and renal involvement, suggesting an immunovascular injury. It is possible that patients with SS and RP represent a subset with a homogeneous clinical phenotype. It is of interest to speculate that this may be related to its genetic background in that some studies have described an association with HLA-DR3 and DR4 of RP in SS [71, 72].

Most studies indicate that the clinical course of RP is generally benign in patients with SSc compared to those with other CTDs; in particular SSc [68, 73]. In one series of 40 patients, no vascular complications were observed and pharmacological treatment with vasodilators was required in only 40 % of patients [69].

Rheumatoid Arthritis

The frequency of RP in RA is not well established in that early studies suggest that RP is rare among patients with RA [74]. However, recent studies suggest that it may occur in up to 63 % of patients with RA. [75] However, both these studies are of small scale perhaps accounting for the heterogeneous results. Climate conditions, time trend, exact definition, and objective diagnostic criteria of the prevalence of RP in patients with RA may also explain the sources of heterogeneity. Finally, the differences in prevalence were also due to the lack of a precise definition for RP. This points out that an important factor which affects determining the prevalence of RP is an exact definition and objective diagnostic criteria (see Chap. 3).

A recent meta-analysis of 28 studies with over 3,700 patients reported that 12.3 % of patients suffering from RA also suffer from RP but there was significant heterogeneity among the included studies in its prevalence. It is possible that some of the patients included in these studies may have overlap syndrome with associated conditions, in particular SSc, in which the incidence of RP is frequent. In contrast to earlier studies that suggest females are commonly affected than males [76, 77] with both RA and RP, more recent studies suggest the opposite [78, 79] and the reasons for this are unclear.

RA has been reported to occur in 8–32 % of patients with overlap connective tissue diseases in particular with SSc and SS [80, 81]. The possible development of associated connective disease in patients with RP and RA was evaluated in a prospective study ($n = 71$). The authors reported that RP was associated with sclerodactyly and that higher rheumatoid factor titres were associated with longer RP duration [82]. Contemporaneous onset of RP with RA did not affect the erosive nature of the joint disease whereas late onset of RP after onset of RA may have a deleterious effect on joint disease. In majority of cases, SSc RA overlap patients predominantly were affected with limited cutaneous SSc. Apart from RP, patients with overlap SSc RA may develop digital ulcers, lung fibrosis, oesophageal dysmotility and cardiac involvement [83]. Serological examination for anti-CCP antibody and rheumatoid factor may help to identify this subset of patients. Moreover, anti-CCP antibody correlates with arthritis and erosive disease [83]. Specific SSc antibodies (ACA and anti-Scl70 antibodies) have also been reported in these cases [81]. It is therefore important to consider coexisting connective tissue diseases among patients with RP and RA in particular those with early features of SSc.

Undifferentiated Connective Tissue Disease (UCTD)

In contrast to cases of overlap connective tissue diseases that fulfil classification criteria for at least one of the autoimmune rheumatic diseases, but also manifest some features of another, undifferentiated connective tissue disease (UCTD) is a less defined group. Operationally it includes patients that have features suggesting SLE or one of the other diseases discussed above but not fulfilling classification criteria. In some cases over time other clinical or laboratory features may develop and these cases may later fulfil criteria and become better labelled as a defined CTD or overlap CTD. However many patients remain undifferentiated.

Several studies showed that about 60 % of patients with UCTD will remain stable undifferentiated during the disease course and most have a mild clinical course including RP in 45–60 % of patients [84]. In the remaining subset of UCTD, evolution to defined CTDs often occurs within the first 5 years of disease and these includes SLE, SSc, SS, MCTD, RA, vasculitis and inflammatory myopathies. In cases that include ANA for the definition of UCTD, a majority either harbour anti-Ro/SSA or anti-RNP antibodies. For the subset with anti-RNP antibody associated UCTD, RP tends to be mild without digital ischaemia [85, 86], and this is often managed along the lines of secondary RP. Similarly, for the specific treatment of the systemic features of UCTD, these patients often only require low dose steroids and antimalarial; the use of immunosuppressive therapies are rare.

A recent study examined outcome of 83 patients with UCTD and a majority (64 %) remains as stable undifferentiated at a mean followup of 181 months [84]. RP was a common feature for all patients and ANA was positive for all patients. Of the remaining patients who developed a defined CTD, most progressed to develop SLE (26 %) with the remaining patients were affected with SS, RA, SSc and MCTD. Overall these studies support that although an incremental number of patients with an initial diagnosis of UCTD will develop a defined CTD, a majority will maintain an undifferentiated phenotype over time.

This population comprises a substantial number of attendees of any rheumatology clinic and management needs to be individualised according to the severity and degree of manifestations and likelihood of progression. After several years of follow-up without change then they may be more stable. Raynaud's is almost universal in this group although the severity varies [86]. It is likely to reflect referral bias as RP is more likely to lead to rheumatological referral. Treatment of RP is very much along the lines of that discussed elsewhere in the textbook and in this chapter below.

Other Causes of Secondary RP: Vasculitis, Haematological Associations and Erythromelalgia (See Also Chaps. 11 and 10)

This is a very important group or cases of secondary RP although they do not receive very much attention as the features of RP are generally overshadowed by other manifestations or complications. Vasculitis is an especially important group as the complications of this may overshadow RP and need different approaches to therapy.

The presentation of digital infarction and critical ischaemia in vasculitis resembles that of secondary RP. In most cases, patients present with acutely painful, swollen fingers in a symmetrical distribution, but there is often a marked disparity between involvement of the upper and lower extremities. The affected digits are often exquisitely tender and the searing pain often extends into the deep tissues of the affected limb. Patients lie awake with pain and may hang the affected limb down to improve circulation. The pallor phase is often not noticed by patients and they often experience the rapid onset of cyanosis following onset of the pain and unless prompt treatment is instituted, these may progress to gangrene. Physical examination may reveal supportive evidence of cutaneous vasculitis including splinter haemorrhages and palpable purpura that do not blanch on applied

pressure, Notably, loss of digital pulp from previous episodes of digital ischaemia is not specific to vasculitis. Extra-cutaneous involvement of vasculitis in particular arthritis, renal and gastrointestinal involvement should be carefully assessed.

It is important to consider that overlap vasculitis occurs in the context of other autoimmune rheumatic diseases and this has recently been reported in SSc. One particular subset of vasculitis, thromboangiitis obliterans (TAO) or Winiwarter Buerger disease in particular has been recognised to be associated with RP. Originally described in 1908, it is a primary systemic vasculitis of unknown aetiology that affects medium-sized arteries and veins predominantly in the lower and upper extremities, with multiple segmental inflammatory obliterative diseases especially in young male smokers. The reported prevalence of RS in patients with TAO is variable [87, 88] but a recent meta-analysis suggests despite some heterogeneity in the clinical studies that 28.1 % of patients with TAO also have RP [89]. Although smoking is not directly thought to be relevant in the aetiopathogenesis of RP, it is likely that the distal vascular occlusion in TAO predisposes the extremities to cold hypersensitivity and this is supported by observations that clinical features of TAO are more prominent in cold weathers. Abnormal platelet aggregation and contractile force in clotting was reported in TAO and these shared mechanisms in particular with platelet aggregation may underline RP in TAO [90]. Digital infarction and critical ischaemia together with vasculitic ulceration can occur and this may require specific treatment in addition to management of vasospasm (Fig. 8.6).

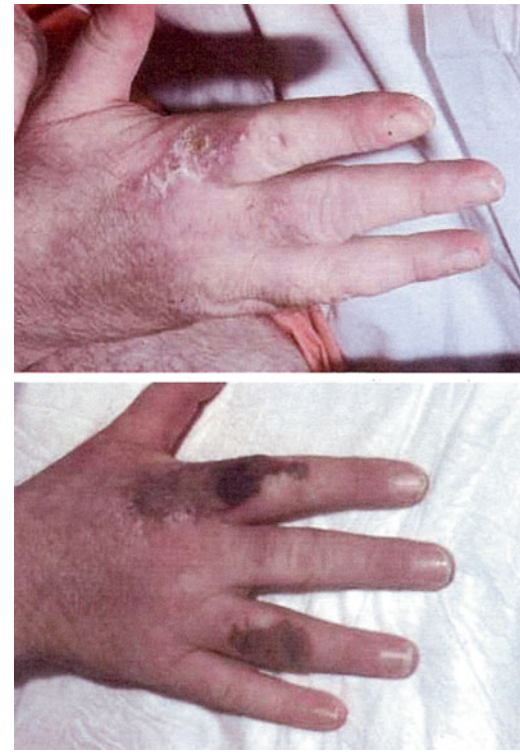

Fig. 8.6 Digital infarction with vasculitic ulceration in a gentleman with small vessel vasculitis. These lesions gradually healed over 6-month follow-up with combination of regular intravenous Iloprost treatment and immunosuppressive therapies

As the underlying pathophysiological processes in vasculitidies are vascular occlusion complicated by vasoconstriction, treatment is largely aimed at vasodilatory approaches in addition to treatment of the underlying vasculitis in particular if it is not limited to skin. Therapy must therefore be individualised and appropriate management of systemic vasculitis should be considered. For example, immunosuppressive agents such as intravenous cyclophosphamide, mycophenolate mofetil or rituximab may be required in patients with glomerulonephritis or pulmonary complications. These approaches often lead to improvement of the digital ischaemia as well.

Whether primary antiphospholipid syndrome or the antiphospholipid antibodies is associated with RP is unclear. The results so far reported on the association between aPL and RP have been contradictory. In an early study, Vayssairat reported a higher prevalence of aCL in patients with RP especially in those with CTD compared to healthy controls [91]. This is not unexpected given that aPL or RP occurs more frequently among patients with CTD than in general population. Interestingly, other groups have subsequently suggested that secondary RP is not associated with aPL in patients with SLE; the same group also reported that IgG aCL is negatively associated with RP [47, 92–94].

However, in patients with APS the direct association between macrovascular disease and arterial thrombosis may be more relevant than the link between RP and venous thrombosis. Recently, another group showed the risk of thrombosis is increased among patients with RP and secondary APS and SLE [95]. However, RP does not appear to be associated with arterial thrombosis in primary APS [96]. It is important to appreciate that the two pathological processes of vasospasm of small arterioles and thrombotic process may coexist and in these cases and therefore long term anticoagulation may be necessary in addition to vasodilator treatment.

Erythromelalgia (EM) (see Chap. 11) is intense blushing of the skin secondary to vasodilation of the cutaneous circulation usually in the hands and feet [97]. It can mimic RP because it is triggered by environmental temperature changes and can be seen at in patients who also have typical cold induced RP. It is important to differentiate primary EM from secondary in that treatment of the underlying secondary disease may greatly improve the EM. Pathogenesis is complex and likely to reflect micro-circulatory and neural dysfunction as well as possibly altered platelet biology. The latter is much more of an issue in those cases associated with an underlying haematological abnormality, most typically thrombocytosis. Management needs to be multifaceted and is often very challenging. Avoidance of warm temperature is the mainstay of therapy. Secondary trophic changes and ulceration can occur and this is especially difficult to treat. The association with RP comes from those cases where there is also evidence if cold induced vasospasm and this may occur at the early stages of an attack of symptoms. In these cases it may be that EM is in part an exaggerated suffusion phase of RP and on this basis some benefit has been reported for treatments that try to improve or reduce the severity of vasospasm. Thus vasodilators or even in some cases parenteral prostanoids have been used successfully in some patients. Overall this remains a complex and challenging group of patients probably because it is a heterogeneous group and as a consequence of the severe symptoms that occur and secondary consequence that may overlap with regional pain syndromes and require expert input from pain teams. In addition there is the risk that some strategies for treatments might actually worsen or aggravate some of the EM components especially for those treatments that are directed towards vasospasm that could lead to vasodilatation.

Management Principles

The management of RP is described in detail elsewhere [see Chaps. 20 and 23] in this volume but there are specific aspects that reflect the underlying disease in secondary RP and these are discussed below. As for all cases of RP the management can be considered under the following headings:

Supportive Measures

Supportive measures include lifestyle changes and specific non-prescription therapies that can be helpful. It is often beneficial to have a patient education programme formalised and linked to an outpatient service. This may be paper based, online or face to face with a specialist nurse. Patent support organisations also provide some excellent supporting material for education and advice and telephone advice lines are also available and valued by some patients. The most important lifestyle change is to avoid smoking. This seems to be especially detrimental in secondary RP. For example, in studies for treatments for digital vasculopathy in SSc only non-smokers derived benefit for example in the number of new digital ulcers developing on bosentan [38].

Avoiding cold exposure to help maintain normal core body temperature is key. Adjustments to in the work environment to keep warm and allowing automobile parking close to work during winter months can be helpful. For some occupations there may be specific issues arising from RP and since this is generally more severe when associated with SSc or some other diseases this is an important consideration.

Non-pharmacological treatments including antioxidants supplements and other pharmaco-

nutrients are often recommended but the evidence that they are helpful is insufficient to give specific recommendations.

Combination Vasodilator Therapy

As for other forms of RP, including primary RP, prescription vasodilators offer a first line medical approach to try and reduce attack frequency and severity as well as the impact of symptoms on function. In general cases of secondary RP are more refractory to these treatments than the primary form of this condition. This may require an individual approach to assess treatment benefit and side effects in a systematic and objective way. It is often necessary to combine two agents of different class such as a calcium channel blocker (CCB) and angiotensin II receptor blocker (ARB). Our practice is to use CCB and ARB in RP associated with CTD.

Selective Serotonin Reuptake Inhibitors

There has been one small controlled trial of fluoxetine for RP that pointed to benefit compared with CCB control are and this drug was well tolerated [98]. The mechanism likely reflects reduction in levels of serotonin in platelets that are dependent on exogenous uptake using a specific transporter channel that is blocked by SSRI. Interestingly subgroup analysis suggests women and PRP are more likely to benefit from fluoxetine that SSc associated RP but the basis for this is not clear.

Anti-platelet and Anti-thrombotic Strategies

Although no formal clinical trial data are available that support the use of antiplatelet approaches for secondary RP they are widely used. It may be more logical to use these strategies for SSc and SLE or other CTD associated RP where there is known EC dysfunction and potential for micro thrombosis in damaged or structurally altered vessels. This is the rationale for using clopidogrel in severe RP and this is often used in cases associated with digital infarcts or critical ischemia. Duration of therapy is unclear but this approach is well tolerated generally. Studies of low dose aspirin are not positive but the additional health benefits of this drug make it a logical treatment. Recent data suggests that combination aspirin and dipyridamole did not improve digital microvascular perfusion or recovery from local cold challenge in patients with primary RP and SSc [99].

Hydroxychloroquine on the other has been recognised to reduce thromboembolic events for over two decades In addition it may inhibit platelet aggregation and potentially reduce levels of anti-phospholipid antibodies [100]. Thus, HCQ may be useful in selected cases of CTD-associated digital vasculopathy with dyslipidaemia and thromboembolic manifestations [101].

Prostacyclin and its analogues form the main current treatment for severe and complicated RP in the context of CTD in UK and many European countries. There is clinical trial evidence supporting this and in some countries the agent iloprost is licensed for the treatment of severe RP. Some benefit for digital ulcers and other skin manifestations has been inferred from relatively limited controlled trial data. There is a wealth of experience of this approach and most patients receive 3–5 days infusion in a hospital setting with appropriate monitoring.

PDE5 Inhibitors and NO Pathway Agonists

Nitric oxide is a critical endogenous vasodilator and endothelial NO levels may be reduced in cases of RP. This pathway may be augmented in several ways and these have been tried in RP [102]. First, nitrates can be used in a transdermal patch that can increase skin blood flow. Patients report some benefit but side effects of headache may be severe and limit use. In addition there may be advantages in using these patches only for a few hours each day to prevent tachyphylaxis. Breakdown of the secondary messaging GMP can he reduced by

selective phosphodiesterase inhibitors such as sildenafil or tadalafil [103, 104]. Emerging data support this approach come from a small number of clinical trials. One of these using a slow release formulation of sildenafil suggested a reduction in attack frequency and severity in cases of SSc associated secondary RP [105]. Finally, the new guanylate cyclase agonist riociguat could have potential applicability although no studies have yet been performed.

Statin Therapy for Secondary RP

The potential beneficial role of statin therapy in SSc associated RP is supported by one clinical trial and by data from studies that suggest that the number of circulating endothelial progenitor cells may be increased after treatment with atorvastatin at standard doses [106]. In addition there are potential benefits for macrovascular disease. However there benefit reported is not observed consistently in clinical practice and further studies are necessary to better define the risk and side effect benefit balance before the place of statin therapy in cases of secondary RP except for those with clear other cardiovascular risk factors.

Role for Surgical Intervention (See Chap. 22)

Surgical approaches for secondary RP are potentially valuable in selected cases, especially in the context of SSc or where there is demonstrable macrovascular disease that may be amenable to revascularisation. Percutaneous techniques with sympathetic blockade with bupivacaine have been reported to improve ulcer healing in refractory RP in selected cases [107].

Digital sympathectomy (surgical adventectomy) can be very helpful—surgically performed as an adventectomy. There is most experience in SSc and this can be a valuable approach although it requires careful case selection as it cannot be repeated and has impact in hand function and healing may be a consideration. Occasionally more proximal approaches can be useful such as radial or ulnar arterial adventectomy.

Local infiltration of botulinum toxin around the digital arteries has recently been performed and has some potential benefit bit effects may be temporary and the procedure painful [108]. Other novel approaches include autologous fat grafting to affected extremities have been used in SSc patients but further studies are required to determine efficacy [109]. Ongoing strategies to improve the outcome, case selection and feasibility of these surgical interventions are awaited.

Benefits from Disease Modifying Strategies

In connective tissue disease with associated vasculitis the symptoms of secondary RP may be substantially improved when appropriate antivasculitis treatments are given. Likewise systemic treatment for antiphospholipid syndrome may be beneficial for RP. Finally, in cases where systolic cardiac dysfunction occurs there can be worsening of Raynaud's symptoms and this may improve once there is treatment of cardiac disease [110, 111]. Likewise RP may worsen in the context of other vascular manifestations such as SRC and the treatments are likely to benefit RP.

Conclusions

Although only a minority of cases of RP are associated with an underlying connective tissue disease (CTD) there are much more likely to be significant complications in this group. Severe RP is particularly common among patients with SSc and MCTD and less so with SLE, RA, vasculitis, myositis and Sjögren's Syndrome. There are distinctive differences in the clinical presentation of secondary RP associated with CTD and the outcome of secondary RP depends on the underlying condition and it is generally associated with a greater burden of vascular complications. There is a central role for nailfold capillaroscopy and serological assessment in the investigation of patients with suspected CTD. Early identification

alerts the clinician to the possibility of the patient's RP progressing to complications. Management of Raynaud's phenomenon depends upon avoiding precipitants, smoking cessation and good patient education. A variety of supplements and vitamins are reported by patients to be helpful although formal evidence of benefit is sparse. The most severe cases may benefit from prescription vasodilator drugs. Calcium channel blockers are often tried first but other agents that have been found to be helpful include angiotensin II receptor blockers and in some cases selective serotonin reuptake antagonists, which appear to reduce vasospasm and may act through depletion of platelet serotonin levels. Management of the underlying systemic disease would complement the specific treatment of the vascular aspects of RP.

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Traumatic Vasospastic Disease

9

Ami A. Shah

Abbreviation

HAVS Hand-arm vibration syndrome

Key Points

1. Traumatic vasospastic disease most commonly results from repetitive trauma but can also be caused by mechanical percussion injury to the hands or palmar trauma.
2. Traumatic vasospastic disease is a common cause of Raynaud's phenomenon in men.
3. Prevalence varies across geographic regions reflecting different climate and occupational exposures.
4. A careful history of occupational and environmental exposures is a key part of the assessment of the patient presenting with Raynaud's phenomenon.
5. Elimination of the exposure and cold avoidance may prevent further vasospastic episodes and more serious morbidity.
6. When occupational traumatic vasospastic disease is suspected, referral to an occupational health physician should be considered.

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In 1918, Alice Hamilton described complaints from stonecutters in Indiana who had "attacks of numbness and blanching in the fingers, particularly of the chisel hand, coming on suddenly under the influence of cold, and then disappearing" [1, 2]. While the vast majority of cases of Raynaud's phenomenon are primary in nature or secondary to an underlying connective tissue disease, traumatic and occupational etiologies continue to remain a significant concern and potential trigger of Raynaud's phenomenon, particularly in men. Repetitive vibration exposure is the most common cause of trauma-induced vasospasm, and this has been referred to by many terms, including vibration Raynaud's syndrome, vibration white finger, vibration-induced white finger, Raynaud's phenomenon of occupational origin, and the hand-arm vibration syndrome (HAVS) [3, 4]. Common occupations and exposures that may result in repetitive vibration induced trauma are detailed in Table 9.1. In addition to vibration injury, individuals with repetitive mechanical percussion injury to the hands, significant cold exposure, or electric shock injury are also at risk of developing traumatic vasospastic disease. Some professions may result in multiple concomitant exposures (e.g., vibration and cold). As many of these patients may present to their community physicians rather than occupational health specialists, it is important for physicians to familiarize themselves with these potential etiologies.

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Table 9.1 Causes of traumatic vasospastic disease and commonly associated occupations and exposures[a]

Exposure	Prevalence (%)	Additional information	References
Vibration			
Pneumatic drillers, knives, hammers, rock breakers, grinders, chippers	30.2–45	Commonly used in quarries, by stone cutters	[72–77]
		Halving the years of exposure allows a doubling of the energy equivalent vibration	
		Vibration exposure level correlates with severity of vasospastic disease	
		Symptoms of vasospasm and abnormalities after cold provocation persist despite removal of exposure	
		Higher frequency of vasospasm among current smokers	
Surgical instruments (a type of vibration exposure)		Reported in five patients using pneumatically powered surgical instruments to harvest bone for bone banks	[78]
		Developed after 7–32 months of use	
	3.70	Study of orthopedists	[11]
Dental instruments	4.8–6.1	Studies of dental technicians and dentists	[11, 79]
Chain saw operators	5–53	Extensive data in lumberjacks	[11, 13, 17, 18, 80]
		Risk increases with higher vibration magnitudes and exposure durations	
		Risk substantially higher in smokers than nonsmokers	
Road drilling/ breaking	24 % with blanching	Risk of blanching rose with lifetime hours used and dose of vibrating tools	[81]
Chiseling			[28]
Impact wrench use	5.5–26.3	Risk increased exponentially after 12 years of use in one study	[82, 83]
Riveting machines/ hammers	25.30	340 riveters in aircraft industry studied; 86 with Raynaud's	[84]
		Among the subgroup exposed for >10 years, 50 % had Raynaud's even though mean daily exposure was ~1 minute/day	
Pounding and lasting machines			[28]
Brush saws		Japanese longitudinal study from 1961–1980	[85]
		12 % prevalence in cohort starting in 1961–1962; 0 % in cohort beginning in 1969–1970	
		Prevalence increases with exposure time	
		Often used during warmer season for grass trimming and limbing; may account for lower prevalence rate than reported with chain saws	
Sewing machines	4.30		[11, 86]
Grinding or polishing machines	3.7–23	Lower body weight was a risk factor in a study of Swedish aircraft employees	[11, 75, 87]
Single axle tractors	10	If used 8 h/day in full load, high risk of white finger after only 3–4 years	[88]
Car mechanics	15	Increased to 25 % after 20 years	[89]
High pressure hose use			[90]
Mechanical percussion and palmar trauma			
Carpenters			[68]
Masons			[68]
Metal workers			[68]
Factory workers			[68]
Typists			[28]

(continued)

Table 9.1 (continued)

Exposure	Prevalence (%)	Additional information	References
Pianists			[28]
Recreational exposure through martial arts or other sports			[68]
Cold			
Meat cutters and wrappers	9 % of women/2 % of men	Risk higher if >5 years of working in poultry slaughterhouse, <4 rest breaks, taking breaks in nonheated room, exertion of the hand or arm, and performing continual repetition of the same series of operations	[91]
Fishing company employees		Risk of Raynaud's was higher in workers exposed to alternating heat and cold compared to workers with long term cold exposure	[92]
Acute thermal injury such as frostbite		In a study of 1,095 reindeer herders, frostbite was more common in patients with vibration-induced vasospasm (27 %) than in patients without vasospasm (5 %)	[93]
Electric shock injury			[94]

[a]Prevalence estimates and additional information are provided where epidemiologic data are available

Prevalence and Risk Factors

The reported prevalence of Raynaud's phenomenon of traumatic and occupational origin varies significantly across geographic region of study, in part due to differing climate and occupational exposures. Most prevalence estimates in the literature focus on a particular profession (see Table 9.1 for details) rather than a large regional or national workforce. In addition, many estimates in the literature predate the use of antivibration devices on tools and are now outdated.

Roquelaure and colleagues performed a cross-sectional study in the Loire Valley area of West-Central France between 2002 and 2005 [5]. In this area, an occupational physician examines all French workers annually. The study population consisted of 2,161 men and 1,549 women, and 31 men (1.4 %) and 56 women (3.6 %) were diagnosed with Raynaud's phenomenon. Risk factors for the development of Raynaud's phenomenon included female gender, older age, lower body mass index, exposure to a cold environment or object for >4 h/day, and performance of highly repetitive tasks. High psychological demands at work and low support from supervisors were also noted to be risk factors in women.

In Great Britain, investigators mailed a questionnaire to a random sample of 22,194 working age adults to ascertain the prevalence of Raynaud's phenomenon [6]. Responses were obtained from 6,913 men and 5,994 women; 14.2 % endorsed a history of finger blanching, 11.8 % noted blanching was cold induced, and 4.6 % noted there was clear border of demarcation between pallor and normal color in their finger. Smoking was a risk factor for Raynaud's phenomenon in men. It was estimated that approximately one-third of Raynaud's phenomenon cases among men in Britain were attributable to hand vibration exposure. The authors estimated that, at the time this study was conducted, 222,000 men nationally had extensive blanching (affecting 8+ digits or 15+ phalanges) attributable to hand transmitted vibration.

In a Japanese population, Harada and colleagues studied 1,875 men and 1,998 women to determine the local prevalence of Raynaud's phenomenon [7]. A physician interviewed all individuals, and it was estimated that 3.3 % of males and 2.5 % of females had Raynaud's phenomenon. For men, the prevalence rate of Raynaud's phenomenon was seven times higher in manual laborers than in desk workers; Raynaud's phenomenon cases were attributed to vibration

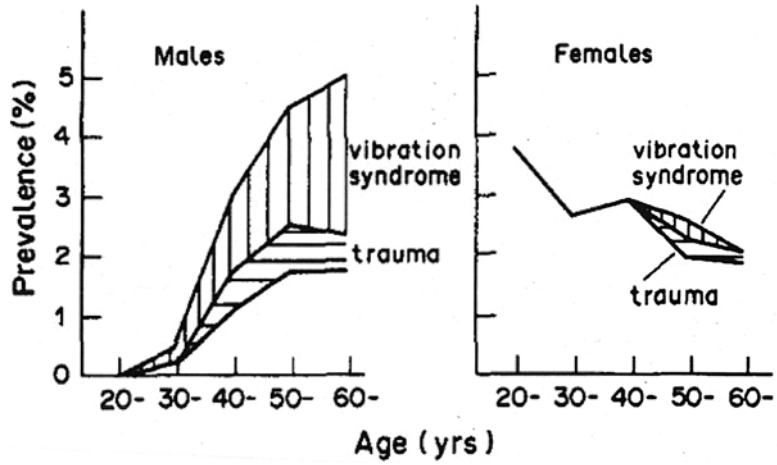

Fig. 9.1 Prevalence rate of Raynaud's phenomenon divided into three parts according to presumed causes (*upper*: vibration syndrome; *middle*: trauma to the fingers; and *lower*: other causes). Reprinted with permissions from SAGE Publications

exposure in 49 % of male cases, to trauma in 15 %, and to collagen vascular disease in 3 %. In comparison, only 4 %, 6 %, and 4 % of female cases were attributed to vibration, trauma and collagen vascular disease, respectively. Interestingly, the prevalence rate of Raynaud's phenomenon increased with age among men and decreased with age among women (Fig. 9.1).

In one US investigation, authors examined the incidence and natural history of Raynaud's phenomenon in the community-based Framingham cohort study [8]. Approximately 11 % of women and 7.8 % of men had baseline prevalent Raynaud's phenomenon; over the study follow-up period, incident Raynaud's phenomenon developed in 2.2 % of women and 1.5 % of men. Subjects were followed for an average of 7.1 years. Raynaud's phenomenon symptoms persisted over the study period in ~36 % of men and women, and remitted in the remainder. Among men, 11.3 % of those without Raynaud's phenomenon had a history of occupational vibratory tool use compared to 22.2 % of men with incident Raynaud's and 27.8 % of men with persistent Raynaud's.

Lastly, one study examined the geographic variation in Raynaud's phenomenon prevalence across five regions, one in South Carolina, USA and four in France [9]. Climate was clearly a major driver of the development of Raynaud's phenomenon, and the majority of Raynaud's cases had lived their entire lives in a cold climate. Patients with Raynaud's in warmer climates had previously lived in colder climates. In the multivariable model, the relative odds of Raynaud's phenomenon was 1.93 (95 % CI 1.07, 3.49) times higher in individuals using vibrating tools than in those who do not use such tools. Older age, lower BMI, frequent outings lasting more than 1 day in duration, cardiovascular disease and a family history of Raynaud's were also predictors for the development of Raynaud's.

Features Unique to Vibration Exposure

The United States National Institute of Occupational Safety and Health has estimated that approximately two million workers in the USA and UK have clinically significant hand-arm vibration [3]. The cumulative vibration dose, which is a function of vibration magnitude/acceleration and exposure duration, is strongly predictive of the development and the severity of traumatic vasospastic disease [3, 10–15]. In one study, the prevalence of vasospastic disease was 0–4.8 % among workers exposed to hand-transmitted vibration levels of 1.1–2.5 m/s^2 and reached 9.6 % among workers exposed to

levels of 2.7–5.1 m/s^2 [11]. The prevalence of vasospastic disease at these lower vibration doses may not differ significantly from the expected prevalence of Raynaud's phenomenon in the general population, although the safe vibration threshold may vary by ethnicity or geography [16]. In another survey, full time pneumatic grinders working in a shipyard had a significantly higher prevalence of vibration induced vasospastic disease compared to workers with part time vibration exposure (71 % vs. 33 %) [12]. Lastly, a third longitudinal study examined changes in the prevalence of vibration induced vasospastic disease among professional forestry workers in Finland from 1972 to 1990 [13]. Over this follow-up time, the weighted vibration acceleration of chain saws decreased significantly from ~14 to 2 m/s^2 [13]. The prevalence of vasospastic disease correspondingly decreased from 40 to 5 % [13]. In addition to vibration magnitude, exposure duration is a significant risk factor for the development of vasospastic disease. In a study of 447 Japanese chain saw operators, the prevalence of vasospastic disease increased with exposure duration: 2.5 % with ≤14 years of use, 5 % with 15–19 years of use, 11.7 % with 20–24 years of use, 13.1 % with 25–29 years of use, and 20.9 % with ≥30 years of use [17].

As detailed above, smoking, a family history of Raynaud's phenomenon, prior arm injury, and exposure to a cold climate are also risk factors for developing vibration induced vasospastic disease [18]. Smokers have more advanced vasospastic disease based on symptoms and increased vasoreactivity on cold provocation testing [19, 20]. Concomitant cold and vibration exposure significantly increases the risk of Raynaud's phenomenon. In a study of 134,757 Swedish male construction workers, the relative odds of developing white fingers was 1.7 times higher in vibration exposed workers in a colder climate than exposed workers in a warmer climate [21]. Similarly, a Chinese study detected a higher prevalence of vibration induced vasospastic disease in riveters, chippers and grinders from cooler regions (19.2–19.4 %) compared to those from warmer regions (7.3–9.1 %) [22].

Clinical Characteristics

Pallor and numbness characterize vasospastic episodes of a traumatic origin, and it is reported that cyanosis and pain are less common [23]. These episodes are often asymmetric with the hand that has been traumatized being more severely affected [1, 24]. In one study, it was noted that men with vibration induced Raynaud's phenomenon had fewer involved fingers but more frequent attacks than men with primary Raynaud's disease [7]. Most cases of digital trauma-induced Raynaud's phenomenon are localized to the traumatized digit or just a few fingers [7, 25, 26]. However, it has been reported that the contralateral hand may be more frequently or severely affected than the exposed hand [27]. The feet are generally spared [28].

Vasospastic attacks can be precipitated by ongoing use of vibratory tools or cold exposure. Symptoms may persist years after removal from the exposure, however [29]. In a longitudinal study of 204 symptomatic, former users of pneumatic tools, skin temperature recovery after cold challenge remained impaired for years after eliminating the exposure [29]. Interestingly in one study, lumberjacks with Raynaud's phenomenon had vasospastic episodes triggered by chain-saw noise alone [30].

Medium sized arterial thrombosis and digital necrosis can develop in severe cases [25, 31]. While palmar trauma is a major cause of hypothenar hammer syndrome (see details below), vibration has also been reported to cause hypothenar hammer syndrome in a subset of patients [32, 33].

Patients with vibration exposure may also have hearing loss, digital polyneuropathy, and carpal tunnel syndrome [34–36]. Vibrotactile senses are often impaired resulting in impaired grip force with a tendency to drop items, numbness, and difficulty with finger dexterity including tasks such as buttoning and pouring from a jug [37, 38].

Diagnostic Approach

Correctly diagnosing Raynaud's phenomenon of traumatic or occupational origin is critical as this

Table 9.2 Suggested screening questionnaire for hand arm vibration syndrome [41]

Sensorineural questions
Do you suffer from numbness in response to the cold?
Do you suffer from tingling in response to the cold?
Do you suffer from tingling (for longer than 20 min) after using vibratory tools?
Do you suffer from numbness (for longer than 20 min) after using vibratory tools?
Vascular questions
Have you ever suffered with your fingers going white on exposure to cold?
Do you suffer from numbness during attack of whiteness?

often affects workman's compensation claims. Subjective history alone is often unreliable. In one study of 36 workers with a history of occupational hand-arm vibration exposure and a diagnosis of Raynaud's phenomenon, only 57 % of individuals were able to demonstrate photographic evidence consistent with Raynaud's phenomenon [39]. In another study, 83.5 % of compensation claimants reported Raynaud's symptoms, but only 46.8 % had evidence of vasospasm after provocative testing using a severe cooling protocol [40]. Elms and colleagues have suggested a highly sensitive 6-item screening questionnaire to assess for hand arm vibration syndrome (Table 9.2) [41], and severity of disease is staged according to the Stockholm Workshop scale [42]. Nailfold capillary abnormalities may be present in patients with vibration induced vasospastic disease. In one small study, ten patients with vibration induced vasospastic disease were compared to ten age matched controls [43]. Seventy percent of patients had capillary dropout, and 30 % had tortuous, elongated capillary loops; these abnormalities were not present in the controls [43]. In another investigation, lumberjacks with Raynaud's phenomenon were compared to a control population and similarly demonstrated a reduction in the number of nailfold capillaries [44].

Tools to improve accuracy in diagnosis, such as infrared thermometry or assessment of finger systolic blood pressure after cold challenge, are an active area of research in the occupational health literature. Studies have demonstrated that patients with vibration induced Raynaud's have an altered digital cutaneous temperature [45], a long rewarming time after cold water immersion [45, 46], and abnormal finger systolic blood pressure measurements [47–49]. Further validation studies are needed to determine whether these tools are sensitive and specific for the diagnosis of trauma induced vasospastic disease. If traumatic vasospastic disease is suspected, referral to an occupational health specialist is recommended.

Pathophysiology and Pathology

The exact mechanism causing abnormal vascular reactivity following vibration or traumatic injury is not fully defined. Vibration may result in direct vascular damage and neural dysfunction, both of which may contribute to vasospasm and Raynaud's phenomenon [50]. Dysautonomia due to sympathetic hyperactivity or parasympathetic depression may result in vasoconstriction [50–54]. Data also support the presence of peripheral neural dysfunction that may result in peripheral vasoconstriction, increased vibration and thermal perception thresholds, and slowed digital sensory and motor nerve conduction velocities [50]. In one study, 21 patients with vibration white finger and 17 controls underwent cold water immersion of their right hand for 10 min, and power spectral analysis of heart rate variability was performed to assess autonomic nervous function [34]. The patients with vibration white finger had evidence of increased sympathetic activity with cold water immersion, and they had significantly lower cutaneous temperature after 5 min of cold water immersion and in the recovery period [34]. Vascular manifestations may reflect a combination of microangiopathy, vasospasm and arterial thrombosis [55]. Vascular biomarker studies suggest that there is endothelial damage and dysfunction, impairment in smooth muscle responses to nitric oxide, and an increase in adhesion molecules that may contribute to microvascular damage in patients with vibration-induced Raynaud's [50, 56, 57]. Additional data about the pathophysiology of cutaneous vasospastic diseases are covered in Chap. 11.

Pathologic abnormalities have been detected in blood vessels, surrounding nerves and connective tissue in patients with vibration induced vasospastic disease [58]. Hypertrophy of muscle cells of arteries and medial thickening, periarterial fibrosis, a marked loss of peripheral nerve fibers, severe loss of myelin sheath, regenerated smaller axons without myelin, and collagen deposition in perivascular and perineural lesions with destruction of elastic fibers have been observed [58].

Treatment and Prevention

Affected patients need to change their occupational exposure to minimize recurrent attacks, and if this is not feasible, modifications in the work routine may be required to reduce vibration exposure time and cold work environments [59]. In addition, patients should be advised to grip their tools lightly to reduce vibration transmission [59]. Smoking cessation is also critical. In a cross-sectional study of former users of pneumatic tools, smokers had more severe vasospasm, as assessed by cold challenge plethysmography, than nonsmokers [60]. Subjects who quit smoking had comparable test results with those of nonsmokers, with physiologic benefits persisting 1 year after smoking cessation [60]. Standard vasodilator therapy including calcium channel blockers may also be beneficial [59, 61].

Anti-vibration devices on tools have increased the latent interval between vibration exposure and the development of Raynaud's syndrome, and there has been significant progress in the modification and design of new tools in high risk groups [3]. Device modifications include using isolation and damping techniques to reduce vibration transmission, properly servicing and maintaining older tools, and ensuring hand tools are ergonomically designed to minimize strain on the user [59, 62]. The use of vibration proof tools has dramatically reduced the risk of vibration induced Raynaud's phenomenon [63]. Patients at risk should wear gloves to maintain warmth and attenuate vibration exposure [59]. In developed countries, regulations to minimize exposure and to monitor individuals at risk with robust occupational health care systems have also led to significant decreases in the prevalence of hand-arm vibration syndrome [3, 64]. Workers paid by the hour may be incentivized to have greater exposure and therefore risk of complications [3, 62], and job rotation or adequate rest periods between use are encouraged [59, 65].

Features Characteristic of Mechanical Percussive Injury, Palmar Trauma, and the Hypothenar Hammer Syndrome

The hypothenar hammer syndrome may result in vascular insufficiency due to trauma of the ulnar artery as it passes over the hamate bone, resulting in thrombosis or aneurysm formation [66]. This may develop in the context of repetitive palmar trauma, and in a subset of patients this may be associated with Raynaud's phenomenon.

In a French cross-sectional survey, ~10 % of men in the general population had evidence of ulnar artery occlusion, most commonly affecting the dominant hand [67]. Older age, male gender, and occupational exposure to repetitive palmar trauma, examined as both frequency of impacts and duration of exposure, were significant risk factors for ulnar artery occlusion. Thirty six percent of men with ulnar artery occlusion had associated Raynaud's phenomenon, and one patient had evidence of permanent digital ischemia.

In another French study, 47 (1.13 %) of 4,148 patients referred for evaluation of Raynaud's phenomenon had evidence of hypothenar hammer syndrome, and 43 (91.5 %) of these patients had occupational exposure to repeated palmar trauma [68]. Of these 47 patients with hypothenar hammer syndrome, 21.3 % were factory workers, 12.8 % were masons, 10.6 % were carpenters, 10.6 % were metal workers, and one individual (2.1 %) had recreational exposure to trauma through aikido training. Interestingly, three patients developed the syndrome due to a single direct hypothenar injury. Clinical manifestations were typically unilateral (87.2 % of cases), and a striking 42.6 % of patients developed digital necrosis.

While the hypothenar hammer syndrome is often related to occupational exposure, there are reports of this syndrome developing in drummers, those kneading bread, and in a variety of sports including tennis, golf, baseball, volleyball, softball, karate, weightlifting, and hockey [66]. A careful history of leisure activities is required when the diagnosis is suspected.

Clinical Features and Diagnostic Approach

In patients with hypothenar hammer syndrome associated Raynaud's phenomenon, pallor and cyanosis are often seen, but a hyperemic phase is absent [66]. Patients may have tenderness of the hypothenar eminence, isolated Raynaud's in the last fingers, and a hypothenar mass or callus [66]. A modified Allen test may be a useful bedside screening tool. To perform this test, a practitioner should use his thumbs to compress the radial and ulnar arteries supplying the hand of interest [69]. The patient should then clench his fist repeatedly and finally open the hand. When the practitioner releases compression of the ulnar artery, the palm of the hand should promptly return to a pink color [69]. If there is persistent pallor or slow reperfusion of the hand, further testing for ulnar artery occlusion should be pursued [69]. A false negative modified Allen test is possible, and in a patient with a suggestive history, further imaging should be pursued. Noninvasive Doppler examination may suggest thrombosis or aneurysm of the ulnar artery [70]. Angiography (Fig. 9.2) is the gold standard test, and is warranted to evaluate for ulnar artery occlusion and/or aneurysm and for digital arterial occlusions [66, 68]. In one series of 67 patients who required surgical treatment for hypothenar hammer syndrome, angiography demonstrated ulnar artery occlusion (89 %), irregularity (56 %), tortuosity (46 %), and digital emboli (89 %) [71].

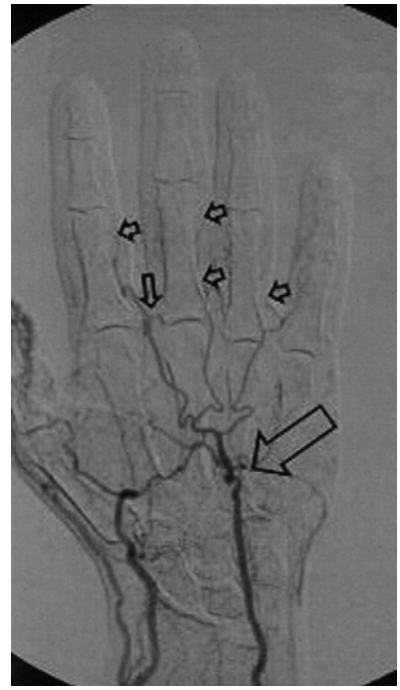

Fig. 9.2 Left hand angiography demonstrating characteristic terminal ulnar artery tortuosity and a corkscrew appearance (*large arrow*). Proper digital artery occlusions are noted in digits 2–4 (*small arrows*)

Pathology

Pathologic findings in hypothenar hammer syndrome are often secondary changes consistent with repetitive trauma [71]. In a study of 67 cases of hypothenar hammer syndrome requiring surgical management, common histologic features included luminal thrombosis (87 %), intimal thickening (60 %), intimal fibrosis (57 %), internal elastic membrane disruption (95 %), medial fibrosis (96 %), hypertrophy (43 %), neovascularization (49 %), dilatation (29 %), disruption (25 %), and adventitial neovascularization (53 %) [71].

Treatment and Prevention

Avoiding occupational exposure is especially critical in patients with the hypothenar hammer syndrome given the risk of necrosis. Prior therapies utilized for the hypothenar hammer syndrome include cold avoidance, calcium channel blockers, platelet aggregation inhibitors or anticoagulants, smoking cessation, cholesterol management, and therapy for arterial hypertension [68, 70]. Conservative measures are often successful, but vascular reconstructive surgery and more

potent vasodilatory therapy with prostacyclin analogs may be required in some patients [68]. Clinical recurrences are common in patients with the hypothenar hammer syndrome, and close longitudinal follow-up is recommended [68].

Expert Opinion

Identifying traumatic vasospastic disease requires a careful history of occupational and environmental exposures. Elimination of the exposure and cold avoidance may prevent further vasospastic episodes and more serious morbidity. If an occupational etiology is suspected, it is advised that an occupational health specialist participate in the patient's care to ensure that appropriate changes are made in the workplace and mechanisms are in place to monitor workers' safety.

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Other Secondary Causes

10

Marina Anderson and Michael Hughes

Abbreviations

ADHD	Attention deficit hyperactivity disorder
CsA	Cyclosporine A
ET	Endothelin
IFN-α	Interferon-alpha
IFN-β	Interferon-beta
IFN-γ	Interferon-gamma
MS	Multiple sclerosis
OR	Odds ratio
RP	Raynaud's phenomenon
SSc	Systemic sclerosis
VCM	Vinyl chloride monomer

Key Points

1. RP can be secondary to a wide range of conditions which includes not only connective tissue disease and trauma, but also drugs and toxins, metabolic and haematological conditions, and malignancy.
2. The evidence base for some of the traditionally acclaimed causes of secondary RP is weak, based on case reports and small series.
3. A detailed history, examination and investigation plan is essential in identifying causes of secondary RP.
4. Carpal tunnel syndrome is associated with RP, but whether there is a causal relationship remains unclear.
5. Several drugs and toxins can cause RP: always take a careful drug history and social history.
6. Metabolic causes of RP include hypothyroidism, carcinoid syndrome and phaeochromocytoma.
7. Haematological diseases which can cause RP include polycythaemia, thrombocythaemia, leukaemia, paraproteinaemias, cryoglobulinaemias and coagulopathies. Many are malignancy-associated.
8. RP has been reported in association with a wide range of malignancies (as well as with chemotherapeutic drugs).
9. Many of the "other" secondary causes of RP can result in very severe digital ischaemia with ulceration and gangrene.

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Introduction

Raynaud's phenomenon (RP) in the majority of patients is idiopathic (primary RP; PRP), however in approximately 10–20 % of patients there is an underlying driving aetiology (secondary

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Table 10.1 The "other" secondary causes of Raynaud's phenomenon

Carpal tunnel syndrome	Associated with primary Raynaud's phenomenon	
	Associated with systemic sclerosis (in particular early, rapidly progressive diffuse cutaneous disease)	
Drugs and toxins	Immunosuppressive agents	
	Chemotherapeutic agents	
	Drugs used in the treatment of hypertension	
	Drug used in the treatment of anxiety and headache syndromes	
	Toxins (including occupational exposure)	
Metabolic	Hypothyroidism	
	Carcinoid syndrome	
	Phaeochromocytoma	
	POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) syndrome	
Haematological	*Abnormal cellular constituents*	Leukaemia and lymphoma
		Polycythaemia
		Thrombocythaemia
	Abnormal blood components	Paraproteinaemia
		Cryoglobulins
		Cryofibrinogenaemia
		Cold agglutinin disease
	Coagulopathy	Inherited thrombophilias
Malignancy	Solid tumours	
	Leukaemia, lymphoma and others	
	Paraneoplastic Raynaud's phenomenon and digital ischaemia	
	Raynaud's phenomenon secondary to localised radiotherapy	

RP; SRP). Recognition of SRP (unlike PRP) is of utmost importance as it may progress to irreversible tissue damage and alert the physician to the presence of an underlying serious disease process. RP secondary to connective tissue disease and to trauma has been discussed in the previous two chapters. The purpose of this chapter is to explore the evidence base for the "other" widely recognised causes of SRP (Table 10.1), namely, carpal tunnel syndrome, drugs and toxins, metabolic and haematological abnormalities and malignancy-related.

Carpal Tunnel

Introduction

Carpal tunnel syndrome (Fig. 10.1) may be primary (idiopathic) or secondary to a number of recognised causes, including SSc. RP and idiopathic carpal tunnel syndrome are both common conditions in the general population and may also cause similar symptoms such as painful dysthesia of the extremities [1]. An association between the two conditions has long (as early as 1957) been suspected [2, 3]; however, proving a definitive causal relationship has remained elusive.

The Association Between Idiopathic Carpal Tunnel Syndrome and Raynaud's Phenomenon

There is a limited evidence base relating to the association between idiopathic carpal tunnel syndrome and RP. The prevalence of coexisting RP in patients with clinical and neurophysiologically proven carpal tunnel syndrome has been reported to be as high as 60 % [4]. In a recent meta-analysis of eight studies conducted between 1957 and 2006 (with a total of 675 patients), the prevalence of coexisting RP in patients with carpal tunnel syndrome, using a random effects model was 0.155 (95 % CI 0.043, 0.318); that is 15.5 %

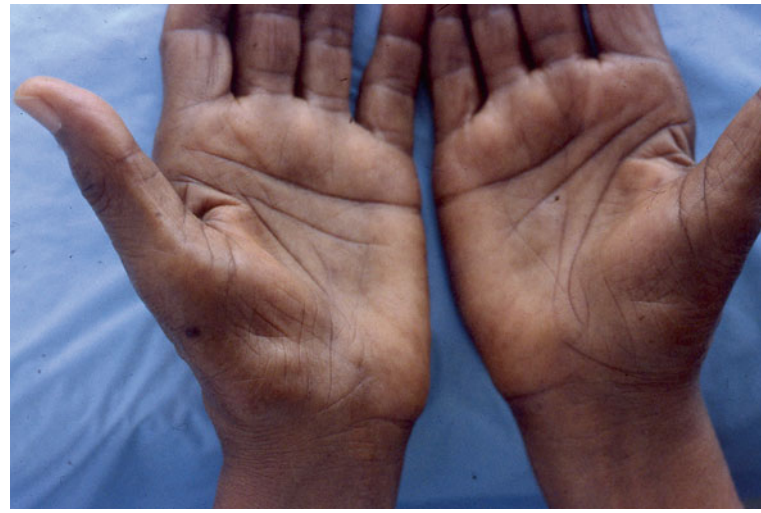

Fig. 10.1 Note the thenar atrophy due to chronic carpal tunnel syndrome

of patients with carpal tunnel syndrome also suffer with RP [5]. Of note there was a significant publication bias present and the prevalence of coexisting carpal tunnel syndrome and RP increased over time; for example, the odds ratio (of both carpal tunnel syndrome and RP coexisting) increased over the decade 1957–1967 from 1 (95 % CI 1.065, 1.112) to 2.340 (95 % CI 1.886, 2.903). The authors suggest that the increased prevalence (of both conditions coexisting) with year of publication may be due to the different characteristics of the included studies, namely, the varying climate conditions, time trend and the exact definition/diagnostic criteria of RP.

In a study of 93 patients with objectively proven idiopathic carpal tunnel syndrome and 57 control subjects, RP was observed (using a validated patient questionnaire) in 36 % of patients with idiopathic carpal tunnel syndrome and only 12 % of control subjects ($P=0.002$) [1]. Chung et al. reported objective evidence of cold sensitivity as assessed by a cold provocation test with photoplethysmography in 60 % (18 out of 30) of patients with clinically and electromyographically proven idiopathic carpal tunnel syndrome [4]. The authors conducted a subsequent study on the same cohort of patients to evaluate the effect of open carpal tunnel decompression on their RP. A good improvement (improvement in both RP symptoms and normal pulse amplitude after exposure to cold) was observed in ten patients (56 %) and fair (pulse amplitude recovery by two thirds of that before cold exposure) in four patients (22 %); with a mean recovery time of 4.2 months (6 weeks to 1 year) [6].

A neuroanatomical difference in the localisation of the conduction delay between patients with idiopathic and SSc-related RP has been reported [7]. In a prospective study, nerve conduction velocity was examined in 39 patients with idiopathic RP and 18 patients with SSc-related RP, all with no symptoms of carpal tunnel syndrome [7]. Isolated conduction delay was localised in the patients with PRP to the carpal tunnel, whereas patients with SSc-related RP had slowing of both the median and ulnar nerves; the authors postulate that it is due to subclinical peripheral neuropathy.

Carpal Tunnel Syndrome Secondary to Systemic Sclerosis

Carpal tunnel syndrome is a well-recognised early complication in the disease course of patients with systemic sclerosis (SSc) [8, 9], in particular progressive disease [10] and the diffuse cutaneous subtype. During the oedematous

phase, there may be compression of the median nerve in the carpal tunnel, which may regress as the fibrotic phase progresses. Often surgical decompression of the carpal tunnel syndrome can be avoided and symptoms may improve spontaneously as the oedema resolves.

Expert Opinion

Many clinicians have long suspected an association between carpal tunnel syndrome and RP. Both conditions are common in the general population and may present with similar symptomology; however, a causal relationship has yet to be established. In early SSc (in particular rapidly progressive, diffuse cutaneous SSc), carpal tunnel syndrome commonly occurs, but may spontaneously improve as the oedematous phase resolves with the onset of skin fibrosis. Lack of validated measures of RP in studies of patients with carpal tunnel syndrome makes it difficult to tease out whether some symptoms are related to carpal tunnel syndrome or to RP. Of clinical relevance to the rheumatologist, only one small study has suggested that the (surgical) treatment of carpal tunnel syndrome may significantly improve patients' symptoms of RP,

Drug and Toxins

Introduction

A considerable list of drugs and toxins (Table 10.2) can alter peripheral blood flow: some of these agents may cause vasoconstriction that can either aggravate existing RP or precipitate acute vasospasm mimicking RP.

When assessing the patient with RP a thorough drug, occupational and social history is essential to ascertain if there are any putative agents causing peripheral vasospasm. If potential causative agents are identified, these drugs/toxins should be stopped or avoided if at all possible. For example, the patient presenting with RP after starting a beta-blocker for hypertension should be changed to another class of suitable antihypertensive. However, there will be instances when the drug causing or worsening RP cannot be stopped, in which case appropriate management of the resultant RP will need to be instituted.

Table 10.2 The secondary drug and toxin causes of Raynaud's phenomenon

Immunosuppressive agents	Cyclosporine A
	Interferons
Chemotherapeutic agents	Bleomycin
	Vinblastine
	Cisplatin
	Other agents, e.g. tegafur, gemcitabine/S-1
Drugs used in the treatment of hypertension	Beta-blockers
	Clonidine
Drug used in the treatment of anxiety and headache syndromes, and amphetamines	Ergots
	Methysergide
	Amphetamines
Toxins (including occupational exposure)	Cocaine
	Cannabis
	Vinyl chloride

It is also important to be aware that the drugs and toxins presented in this section may cause SRP, and this should be considered on regular review of medication after initiation of the therapy.

Immunosuppressive Agents

Cyclosporine A

Since approval in the early 1980s, cyclosporine A (CsA) has become a widely used immunosuppressive agent, preventing rejection of organs following transplantation surgery and treating a range of autoimmune diseases. Amongst potential side effects, case reports since the earliest years of its use have suggested that CsA can precipitate RP [11–14]. In vitro study suggests that the mechanism of this drug-induced peripheral vasospasm may be endothelial cell synthesis and release of endothelin (ET) on CsA exposure [15]. However, interrogation of clinical, therapeutic and hormonal characteristics of organ transplant patients in clinical study by Piquard et al. questions the link between CsA and high levels of ET in this patient group [16] and non-invasive

measures of finger blood flow fail to exhibit vasoconstriction on low maintenance CsA following heart transplant [17]. Indeed it has been suggested that CsA may even augment skin vasodilation [18].

Interestingly, CsA has been proposed and investigated as a potential therapy for patients with SSc, most of whom experience severe RP. Whereas there has been suggestion of the potential therapeutic benefits of CsA for non-Raynaud's aspects of disease in small open-label studies of SSc [19, 20], there have been concerns about other side effects, particularly renal toxicity [21].

Interferons

Interferon-alpha (IFN-α), with its broad range of effects on various biological pathways, is an attractive therapeutic option for a number of clinical indications: IFN-α induced RP, usually with associated catastrophic digital ischaemia resulting in peripheral tissue infarction, has subsequently been described in patients treated for hepatitis B [22], hepatitis C [23] and several malignancies, such as chronic myeloid leukaemia [24–26] and melanoma [27].

Less commonly, RP has been linked with interferon-beta (IFN-β) therapy. Induction of RP has been reported in a patient with multiple sclerosis (MS) treated with IFN-β [28]. SSc (almost invariably associated with significant RP) has developed in some IFN-β treated cases of MS [29, 30].

Data on interferon-gamma (IFN-γ) is limited and conflicting, with report of treatment exacerbating RP in patients with SSc [31], whilst an in vitro study has suggested that a population of CD4+ T cells produces high levels of IFN-γ, which may be protective in RP [32]. IFN-γ and IFN-α have been studied in SSc patients by a numbers of investigators, but initial promise [33] has not translated to a useful therapy.

Mohokum et al. [34] conducted a meta-analysis assessing the prevalence of RP in patients treated with interferons in published data. Their conclusion was that, despite heterogeneity, there was a possible association between RP and IFN therapy, but the caveat was that there were only six eligible studies for inclusion.

Chemotherapeutic Agents

Bleomycin, Vinblastine, Cisplatin and Other Agents

The development of RP on chemotherapy has been well documented, particularly for testicular neoplasms. A steady stream of reports, from the late 1970s onwards, links bleomycin alone or in combination with vinblastine and/or cisplatin with onset or significant worsening of RP in this group [35–40]. Vogelzang et al. [41] found 22 of 60 men (37 %) treated with bleomycin and vinblastine, with or without cisplatin, for testicular cancer developed RP. Even without RP there is evidence of exaggerated cold response on non-invasive testing of vascular function in patients treated with this chemotherapy regime [42, 43]. RP occurring following these three agents has been linked, potentially, to hypomagnesaemia [44] as well as being reported in combination with cryoglobulinaemia [45]. Bleomycin-induced RP has even been associated with acral sclerosis in one case report [46].

Precipitation of digital gangrene in a patient with coexisting RP treated for non-Hodgkin lymphoma with bleomycin and vincristine has also been described [47] as well as RP after a single dose of bleomycin in Hodgkin Disease [48].

Bleomycin for acquired immune deficiency syndrome-related Kaposi's sarcoma has also been linked to induction of RP and severe peripheral ischaemia in numerous cases, either alone [49–52] or in combination with vinblastine [53], vincristine/vinblastine [54] or vincristine and doxorubicin [55]. Decreased capillary density has been found on nailfold capillary microscopy on bleomycin treatment in this group of patients [51]. Local intradermal bleomycin treatment for warts can also initiate RP [56–58].

The various contributions of the individual agents to peripheral vasospasm in chemotherapy regimens are not clear. Hladunewich et al.[53] found that bleomycin or vinblastine alone was not associated with RP but sequential vinblastine followed by bleomycin was. McGuire et al. [59] found a 2-year-old treated for a vaginal tumour developed RP after bleomycin, with resolution of her vasospasm despite continued vinblastine.

Mohokum et al. [60] conducted a meta-analysis to tease out the prevalence of RP in patients receiving cisplatin-based therapy and found some indication of an association in the 24 eligible studies, although results were confounded by heterogeneity of studies.

Other chemotherapy agents have been linked with RP and RP-associated disorders. RP, severe digital ischaemia and SSc have been triggered by tegafur, the pro-drug of 5-fluorouracil, [61] as well as with gemcitabine/S-1 for pancreatic metastatic pancreatic cancer [62] and gemcitabine/carboplatin in an SSc patient treated for lung cancer [63].

Drugs Used in the Treatment of Hypertension

Beta-Blockers

Beta-adrenergic blockade is an established treatment for the extremely common problem of essential hypertension, and is proven to prevent many of the damaging sequelae of uncontrolled high blood pressure. Beta-blockers have a number of other therapeutic indications, such as treatment of cardiac failure, protection of the myocardium post-myocardial infarction, arrhythmia control and reduction of tremor/anxiety. A recent meta-analysis interrogated the published evidence behind the generally accepted paradigm of beta-blocker association with RP [64]. Of 13 eligible, but heterogeneous, studies and 1,012 individuals, the pooled prevalence of RP in patients receiving beta-blockers was 14.7 %, indicating only a possible association between RP and beta-blocker therapy.

Clonidine

Clonidine is a preferential alpha-2 adrenergic agonist (see Chaps. 4 and 5). It can be used to treat essential hypertension, although it is infrequently used for this indication currently. Clonidine may also be used for attention deficit hyperactivity disorder (ADHD) or anxiety. In a double-blind study of 60 forest workers with hand-arm vibration syndrome, clonidine was studied, with the hypothesis that it would attenuate peripheral sympathetic activity and alleviate RP. However, clonidine showed no difference to placebo in length or frequency of RP attacks, and indeed two subjects had apparent clonidine-provoked RP [65]. Coffman and Cohen [66, 67] confirmed that both alpha-1 and alpha-2 adrenoreceptor subtypes were present in the digital vasculature, with the alpha-2 receptors being the more important in sympathetic neural vasoconstriction at this site (see Chaps. 4 and 5). In PRP subjects, Freedman et al. [68] found increased peripheral vascular adrenergic receptor sensitivity compared to controls, with clonidine, like phenylephrine, resulting in greater digital blood flow reduction in the PRP group (see Chaps. 4 and 5). The same group then established that cooling augmented the alpha-2 adrenergic vasoconstriction produced by clonidine in controls [69], and subsequently that cooling increased the alpha-2 adrenergic vasoconstriction produced by clonidine in PRP [70] and SSc-related RP [71] but not in the control group on this occasion.

Phenylephrine is commonly used in over-the-counter decongestants. Although it can cause powerful vasoconstriction of digital arteries (see Chaps. 4 and 5), it is extensively but variably metabolised in the gut and it is unclear if it can attain sufficient blood levels to cause clinically significant vasoconstriction (see Chap. 18).

Drugs Used in the Treatment of Anxiety and Headache Syndromes, and Amphetamines

Ergots

Ergot alkaloids are used in the management of migrainous headache. They can initiate vasoconstriction through multiple mechanisms including activation of alpha-adrenergic and serotonergic receptors. In migraine, they are assumed to function by vasoconstriction of cranial blood vessels [72]. The first published description of the use of "ergot of rye" was in the British Medical Journal in 1868 [73]. Vascular toxicity from ergots is well- and long-recognised, with descriptions of peripheral gangrene being recorded in the medical literature through the decades, back to 1930,

although historical references to ergotism predate even this [74].

Bromocriptine is also an ergoline but is used for its dopamine agonist effects to treat pituitary tumours, hyperprolactinaemia, Parkinson's disease and type II diabetes mellitus, rather than headaches. Via the same sympatholytic, vasoconstrictor mechanisms it can also precipitate RP.

Methysergide

Methysergide is a serotonin (5-HT) inhibitor initially synthesised from lysergic acid. It was developed to treat migraine but it has been limited therapeutically because it causes retroperitoneal fibrosis with chronic use. It is a proven vasoconstrictor with effects on peripheral vasculature [72, 73].

Amphetamines

Amphetamines are central nervous system stimulants, affecting dopaminergic and noradrenergic systems. They result in the release of catecholamines from synapses, and theoretically can cause peripheral vasospasm. The main clinical use for the amphetamine class is treatment of ADHD. Goldman et al. [75] set out to investigate whether RP was associated with use of these amphetamine-based medications in children with ADHD, and found a significant association in their case–control study of 64 patients.

Toxins (Including Occupational Exposure)

Cocaine and Cannabis

Both vasoconstriction, via blocking of presynaptic uptake of norepinephrine and dopamine, and thrombosis contribute to cocaine-induced arterial compromise in a number of vascular beds. Although ischaemic myocardial events are well described in cocaine users, RP is surprisingly rarely reported in association with cocaine consumption [76]. Short duration of cocaine use is postulated as a possible reason behind the lack of RP reports in cocaine abuse [77]. There have been a number of reported cases of RP associated with SSc developing in individuals abusing cocaine [78].

Concomitant tobacco use is the norm in these reports [76, 78], with similarities to thromboangiitis obliterans (Buerger's disease). In addition, some comparable clinical cases are described in cannabis use, and a link with arsenic poisoning has been suggested [79].

Vinyl Chloride

Vinyl chloride monomer (VCM) is an aliphatic hydrocarbon, used as the base material in the synthesis of the commonly used synthetic resin polyvinyl chloride (commonly referred to as the abbreviation "PVC") [80]. Although working with PVC is completely harmless, exposure to VCM, e.g. during the manual descaling of autoclaves, is potentially hazardous [80]. Occupational exposure to VCM has been associated with a scleroderma-like syndrome, including extensive skin [81] and lung fibrosis [81], acro-osteolysis [82, 83] and RP [80, 84, 85]. A similar genetic susceptibility to both SSc and the scleroderma-like syndrome associated with VCM exposure has been reported [86]. SSc-like nailfold capillary changes have been described in patients with previous VCM exposure [80, 84, 85, 87, 88]. However from the published literature, a causal relationship between microvascular abnormalities (as assessed by capillaroscopy) and the development of RP in this patient group is far from certain [80, 85]. In a recent study that included 21 patients exposed to VCM (and 40 controls), capillaroscopic abnormalities were still present on average 15 years after retirement [80]. Although, the patients who were exposed to VCM had a statistically significantly higher reported prevalence of RP (19 % vs. 0 % respectively), this was not associated with the presence of capillaroscopic abnormalities [80].

Expert Statement

A number of prescription, non-prescription drugs and toxins (including occupation related) may precipitate or exacerbate RP. When these agents are initiated, care should be exercised in individuals with pre-existing RP, and, if possible, alternative therapies, which do not compromise peripheral blood flow, should be used instead.

Patients started on therapies, which can trigger RP, should have medication review at appropriate intervals to ensure that medication does not have to be stopped or treatment added for associated RP. In the patient presenting with RP, particularly of "late onset", a careful drug and social history is imperative to identify any potential causative agents.

Metabolic

Introduction

There is interplay of endocrine control with vasomotor tone. Disturbance of endocrine systems may result in RP. This is most commonly recognised in hypothyroidism, and, when taking a clinical history, examining and ordering laboratory investigations in the person presenting with RP, this possibility should be considered.

Thyroid Disorders

Both primary and central hypothyroidisms are commonly associated with a number of general symptoms including feeling cold, and hypothermia is a feature of myxoedema coma. Therefore, as thyroid disease results in impaired thermoregulation, in routine clinical practice, hypothyroidism might be a potential cause of or exacerbating factor for RP.

However, there is limited hard evidence in the literature for a link between hypothyroidism and isolated RP. In 1976, Shagan and Friedman presented two cases of patients with RP who were found to be hypothyroid, and whose symptoms abated with thyroid replacement therapy [89]. They postulated that altered autonomic function in hypothyroidism resulted in RP. The same authors published a case report of a patient with panhypopituitarism whose only clinical symptom was RP, advocating that the diagnosis of hypothyroidism should be considered in the individual presenting with RP [90]. A later case report suggested the same consideration should be made in paediatric populations [91]. Nielsen et al. reported that 15 of 17 untreated patients with hypothyroidism had cold hands, with 4 having true RP, and confirmed digital artery closure on local finger cooling in the 4 RP sufferers [92]. Treatment with L-thyroxine significantly attenuated the cold sensitivity [92] and a further case report has described resolution of severe RP on adequate L-thyroxine treatment of hypothyroidism [93]. One case report of a 29-year-old woman linked her hypothyroidism presenting with acute myocardial infarction to her background history of several years of antecedent RP, suggesting that vasospasm of the peripheral and coronary arteries may both be linked to thyroid inactivity [94]. However, there have been no further suggestions of such an association in the subsequent 30 years.

Thyroid disorders are well described in autoimmune diseases that have an association with RP [95]. In particular, SSc, which is associated with severe RP in most cases, has been associated with subclinical/clinical hypothyroidism and hyperthyroidism in a large number of case reports and series [96–108]. Antonelli et al. set out to evaluate the prevalence of thyroid disorders by studying 202 consecutive SSc patients and comparing to a matched control group of 404 subjects: the odds ratio (OR) for female SSc versus controls was 14.5 for clinical hypothyroidism, and there were three cases of Grave's disease and two cases of papillary thyroid cancer in the SSc group compared to zero cases in the control group [109].

Neuroendocrine Tumours: Carcinoid and Phaeochromocytoma

Carcinoid syndrome occurs in less than 10 % of patients with the rare neuroendocrine tumour, carcinoid. Circulating neuroendocrine mediators (serotonin) result in vasomotor disturbance, most commonly resulting in facial flushing and peripheral oedema, with RP being less frequently reported. However, even in 1963, in a clinicopathological conference of carcinoid occurring in a woman with a background of RP, the discussants question the association of the RP with carcinoid and describe clinical and pathological features suggestive of concurrent SSc [110].

A number of cases have been published of SSc occurring in carcinoid: in some cases the carcinoid occurs in patients with established SSc and associated RP, and in other cases sclerodermatous skin involvement alone develops in advanced carcinoid [111–113].

Phaeochromocytoma is a neuroendocrine tumour of the adrenal medulla that secretes catecholamines, and is associated with symptoms of sympathetic overactivity: hence, RP has been associated with the list of possible symptoms [114]. The finding of phaeochromocytoma has also been reported in patients with RP and SSc [115].

POEMS Syndrome

RP has been associated with the rare multisystem disorder POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) [116, 117], which is a paraneoplastic syndrome associated with plasma cell dyscrasia [117]. The skin changes in POEMS syndrome may mimic SSc [118] and (reversible) pulmonary hypertension has been described [119, 120], that has been reported to be steroid responsive [121]. There are several case reports [122–124] in the published literature reporting an association between RP and POEMS syndrome. In a single centre review of patients with confirmed POEMS syndrome, 20 % of patients had coexisting RP [118]. Of interest, in a study that included 9 patients with POEMS syndrome (4 had RP) who received an autologous haematopoietic stem cell transplant, three patients' RP improved and the other patient stabilised [125].

Expert Statement

When there is endocrine imbalance, disturbance of vasomotor tone may occur. Hypothyroidism is common and may present as or exacerbate existing RP. On assessing the patient with RP, one should consider thyroid or other endocrine disease. Treatment of hypothyroidism may also treat associated RP.

Haematological

The physician must perform a comprehensive clinical assessment and maintain a high index of suspicion to identify those patients with SRP due to an underlying haematological abnormality. In general, these may be considered within three groups (Fig. 10.2), that may overlap: (1) abnormal cellular components, (2) abnormal blood components and (3) a pro-thrombotic tendency (coagulopathy).

Abnormal Cellular Components

Both quantitative (e.g. an increased cellular count and haematocrit) and functional abnormalities (including a propensity towards intravascular thrombosis) are recognised causes of RP and also erythomelalagia. Malignant transformation of myeloid lineage cells (polycythaemia and essential thrombocythaemia) is considered here, whereas leukaemia, lymphoma and related conditions are discussed in section "Malignancy".

Polycythaemia and Thrombocythaemia

Although polycythaemia and thrombocythaemia are generally considered by many to be recognised causes of SRP, there is a lack of a robust evidence base to support this. Polycythaemia (or more accurately speaking "erythrocytosis") may be defined as an increase in the circulating red blood cells with a persistently elevated haematocrit [126]. It may be primary (polycythaemia vera) or secondary to hypoxemia (chronic lung disease, smoking, right to left cardiopulmonary vascular shunts and hypoventilation syndromes), renal disease (polycystic kidney disease and hypernephroma) and miscellaneous causes (including raised oxygen affinity haemoglobin, hepatoma and cerebellar haemangioma) [126, 127]. Thrombocythaemia (thrombocytosis) is usually a reactive process (e.g. to an underlying infection, chronic inflammation, cancer or major trauma); however, in a small number of patients it may be due to a clonal proliferation of hematopoietic stem cells (essential thrombocythaemia) [128].

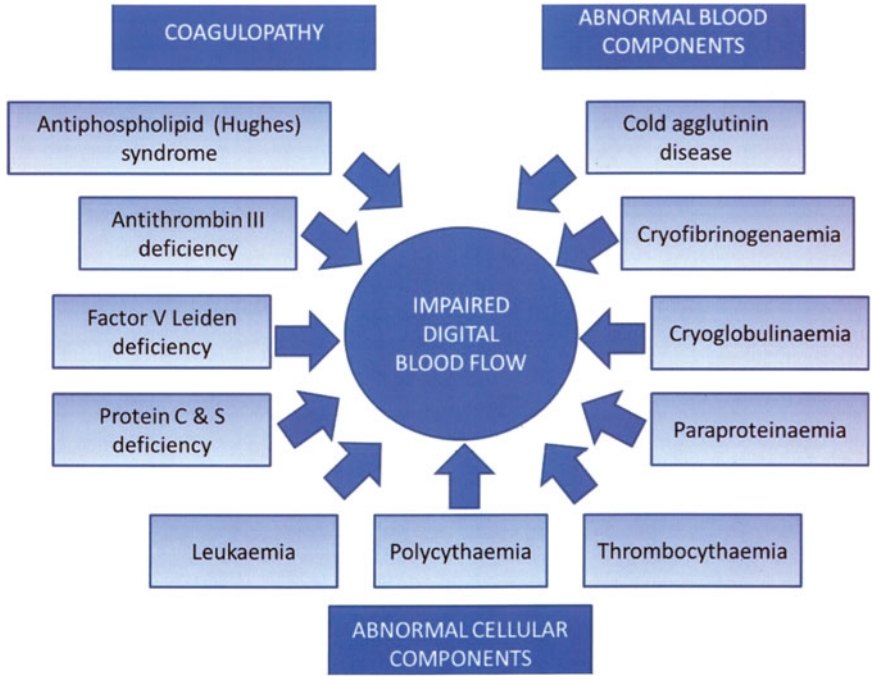

Fig. 10.2 The haematological causes of Raynaud's phenomenon

Polycythaemia and Thrombocythaemia Due to Myeloproliferative Neoplasms, Including a Propensity Toward Thrombotic Disease and Erythromelalgia

The myeloproliferative neoplasms are a group of related clonal disorders that arise from haematopoietic progenitor cells, including polycythaemia vera and essential thrombocythaemia [129]. An activating mutation in the tyrosine kinase JAK2 has been well described in both of these conditions [129]. In both polycythaemia vera and essential thrombocytaemia, an increased propensity towards thrombosis has been observed. Large vessel (arterial) thrombosis occurs most frequently, however microcirculatory occlusive disease is also seen, manifesting as (but not limited to) Raynaud's-like phenomenon [130, 131], which may result in critical digital ischaemia [132]. Myeloproliferative neoplasms are also a secondary cause of erythromelalgia; that may mimic RP [130, 131, 133]. Erythomelalgia is characterised by severe burning pain and skin erythema (akin to the hyperaemic phase in a Raynaud's attack), but is quite dissimilar through a notable improvement in cold ambient environments; again, stressing the paramount importance of eliciting a comprehensive history of cold sensitivity [134] (Chap. 11).

Abnormal Blood Components

RP and digital ischaemia have been associated with various abnormal blood constituents. This may occur due to the physical obstruction of the microcirculation or as an immunologically mediated phenomenon.

Paraproteinaemia

A paraprotein is the protein product (monoclonal immunoglobulin or immunoglobulin light chain [Bence Jones protein]) of the clonal proliferation of mature B-lymphocyte lineage cells (including plasma cells) that may be detected in the blood and urine [135]. Paraproteinaemia and cryoglobulins (a type of paraprotein with unique physical properties) have been associated with RP [136] and in particular cryoglobulins with digital ischaemia.

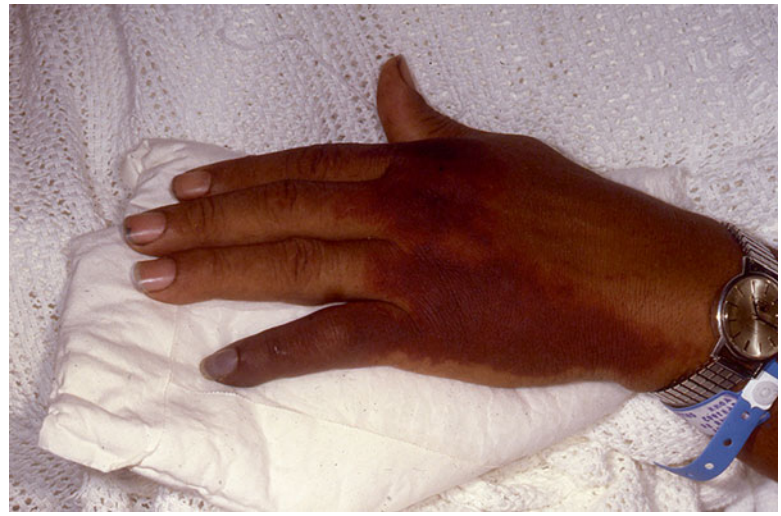

Fig. 10.3 Cryoglobulinaemia: Cutaneous infarction on hand due to type 1 cryoglobulins

Cryoglobulins

Cryoglobulins (cryoglobulinaemia) (Fig. 10.3) denotes the presence in the serum of single or mixed immunoglobulin chains [137] that precipitate at temperatures below 37 °C and dissolve upon rewarming [138]. Type 1 cryoglobulins are single monoclonal immunoglobulin (usually IgM) and account for approximately 10 % of patients with cryoglobulinaemia [137]. Mixed cryoglobulins are immune complexes that contain either monoclonal (type 2) or polyclonal (type 3) immunoglobulins [139]. Essential cryoglobulinaemia is a rare systemic vasculitis due to immune complex deposition in the wall of small and medium blood vessels [138]. In a small case series of three patients with essential cryoglobulinaemia, disease was characterised by RP, arthralgia-arthritis and skin lesions [140]. Monoclonal cryoglobulins are often associated with haematological conditions (including lymphoproliferative disorders and B-cell dysplasias) [137–140], whereas mixed cryoglobulins are associated with a number of systemic conditions (including autoimmune diseases, e.g. Sjögren's syndrome and systemic lupus erythematous [SLE]) [141] and infections (classically hepatitis C infection) [138, 141].

In a multi-centre retrospective study of 891 patients with cryoglobulinaemia, at the time of diagnosis, overall 19.5 % of patients reported symptoms of RP; however, this was almost twice as frequent in patients with cryoglobulinaemias secondary to an underlying connective tissue disease [142]. Ferri et al. reported RP in patients with mixed cryoglobuinaemia in 36 % (79/220 patients) at baseline and 48 % (91/190) at the end of follow-up between 1972 and 2001 (mean duration of follow-up 6.7 years) [143].

Considering the SSc population, in a study of 246 patients with SSc, circulating cryoglobulins were detected in 7 (2.8 %); 2 patients had trace amounts, whereas 5 (4 limited cutaneous SSc: 1 diffuse cutaneous SSc) had mixed cryoglobulins [144]. All five patients were positive for hepatitis C infection and four developed a clinically apparent cryoglobulinaemic vasculitis. These patients had a severe vascular syndrome (including necrotic skin ulcers and one patient required bilateral below knee amputation). The authors propose the severe vascular disease observed in these patients may be due the additive effect of their underlying SSc-related microvascular disease and cryoglobulinaemic vasculitis [144]. There is no evidence available to suggest that

treating a patient's cryoglobulinaemia improves their coexisting RP.

Cryofibrinogenaemia

Cryofibrinogenemia is a much rarer condition that cryoglobulinaemia. Cryoprecipitate (formed of fibrinogen, fibrin, fibronectin and other smaller proteins) is formed as the plasma (note, not the serum as in cryoglobulinaemia) is cooled at 4 °C, and becomes resoluble again as the temperature of the sample is rewarmed towards 37 °C [145]. Similar to cryoglobulinaemia, it may be primary (essential) or secondary to a range of conditions, including systemic autoimmune conditions, infections and malignancy [146]. The frequency of RP in the literature in essential cryofibrinogenemia ranges between 16.6 % [147] and 53.7 % [145] and secondary cryofibrinogenaemia between 0 % [148] and 24 % [145]. Again, there is no evidence available to suggest that treating a patient's cryofibrinogaemia improves coexisting RP.

Cold Agglutinin Disease

Cold agglutinin disease is a cold-induced autoimmune haemolytic anaemia due to pathological reactive antibodies that are directed towards antigens present on the surface of red blood cells [149, 150]. In cold agglutinin disease, the antibodies are usually of the IgM class (monoclonal IgM kappa paraproteins) [151] and exhibit reactivity at body temperature (37 °C), with maximal biological activity at 4 °C [149]. Cold agglutinin disease may occur as a primary or secondary phenomenon to a range of infections, including bacterial (*Mycoplasma pneumonia* and *Chlamydia psittaci*) [151] and various viruses (*Cytomegalovirus, Epstein–Barr, Parvovirus B19, Rubella and Varicella zoster*) [151]. In the few published case reports [151, 152], cold agglutinin disease is associated with severe RP that often occurs bilaterally and involves all the digits and not uncommonly progresses to critical digital ischaemia [151, 152]. Kröger et al. found in their study of 306 patients with RP, that the detection of low titres of cold agglutinins in 49 patients was not associated with significant symptoms, or definite abnormalities on nailfold capillaroscopy after 3 years of follow-up [153]. In one case report, treatment of the patient's cold agglutinin disease (monoclonal IgM band) with chemotherapy was not associated with an improvement in their RP (with digital ischaemia and ulceration); subsequently requiring intra-arterial reserpine [152].

Coagulopathy

Inherited Thrombophilias (Antiphospholipid Syndrome and Protein C, Protein S, Antithrombin III, Factor V Leiden Deficiencies)

The antiphospholipid (Hughes) syndrome is characterised by recurrent (and potentially catastrophic) thrombosis (arterial or venous) and obstetric morbidity, in the presence of characteristic antiphospholipid autoantibodies (anticardiolipin antibody, the lupus anticoagulant and antibodies toward β2-glycoprotein I) [154, 155].

Despite a strong theoretical rationale (thrombotic occlusion of the microcirculation) for the digital microcirculation to be compromised in the inherited thrombophilias (Protein C, protein S, antithrombin III and factor V Leiden deficiencies), there is a lack of a robust evidence base to support this. In a study of 200 patients with PRP and 200 healthy controls, the prevalence of thrombosis associated alleles (including the factor V Leiden mutation) did not differ significantly between the two groups [156].

The evidence for an association between anticardiolipin antibodies and RP is conflicting, with some studies reporting a positive association [157, 158] and others reporting no association [159–161]. Lupus anticoagulant positivity has been associated with RP in patients with SLE [157]. However, paradoxically in a study of 93 patients with SLE (40 with and 53 without RP), the prevalence of all antiphospholipid antibodies (including anticardiolipin and β2-glycoprotein I) was higher in those patients *without* RP, and a negative association between RP and the IgG subtype of anticardiolipin autoantibody was reported [161]. An association between IgG anticardiolipin antibody and digital necrosis has been described [158].

Antiphospholipid antibodies are not uncommonly seen in patients with SSc; although characteristic thrombotic complications are uncommon [162]. While an association between

antiphospholipid antibodies and macrovascular disease (including pulmonary hypertension) in patients with SSc has been described [163, 164]; the association with RP and in particular, critical digital ischaemia is conflicting. Several studies have reported an association between antiphospholipid antibodies and digital infarcts [163, 164], whereas one study has found no association between anticardiolipin antibodies and severe digital ischaemia [165]. Antiphospholipid antibodies have also been described with internal malignancy, including in the context of coexistent digital ischaemia [166]; however, it is not clear if they play a pathological role in thrombosis or are an epiphenomenon [167].

Expert Opinion

A wide range of haematological abnormalities has been associated with RP, although the evidence base for some haematological causes is equivocal or contradictory. Mechanistically there is a strong theoretical rational for how the haematological causes may compromise digital vascular blood flow. The association with RP is more likely caused by occlusive vascular disease or hypoperfusion due to RP attacks, rather than isolated vascular compromise. Haematological causes of RP may broadly be considered under the following three headings: abnormal cellular and blood components as well as a propensity towards intravascular thrombosis. All may be malignancy driven. The identification of the haematological causes of RP requires a high index of clinical suspicion to ensure optimal management. Firstly, many of the haematological causes may well be treatable and secondly, they are not uncommonly associated with severe digital vascular disease, e.g. gangrene.

Malignancy

The association between RP and (often) critical digital ischaemia with internal malignancy has been informed by a limited number of case reports and series in the published literature. Digital ischaemia may occur as a direct result of the neoplastic process, e.g. occlusion of the microcirculation through malignant cells or as a true paraneoplastic effect independent of the direct effect of the underlying neoplasm. Of caution to the clinician, this may predate the diagnosis of the underlying malignancy and inform the diagnostic process, through the course of investigation to exclude a secondary cause for the patient's RP. Malignancy may also drive the production of cryoproteins (cryofibrinogen and cryoglobulins) and antiphospholipid antibodies. The association between radiotherapy and the development of RP including digital ischaemia is also discussed here, whereas therapeutics used in the treatment of malignancy have been discussed earlier in this chapter. Of note to the clinician in the assessment of patients with RP, ANA positivity (often in very high titre) may long predate the diagnosis of the malignancy [168, 169].

Solid Tumours

Most solid tumours have been associated with RP and, in case reports, with critical digital ischaemia, often as a paraneoplastic phenomenon. These include (in alphabetical order): bowel [170–172] (Fig. 10.4), breast [170, 173], cervical [170, 173], lung [173–179], kidney [170, 180], melanoma [170, 181], oesophagus [170, 182], ovary [170, 183–186], pancreas [170], prostate [170], stomach [170] and uterus [170, 187, 188]. Rarer solid tumours, e.g. carcinoid tumours and phaeochromocytoma, have been described elsewhere in this chapter. Figure 10.4 illustrates a case of paraneoplastic digital ulceration secondary to underlying progressive metastatic adenocarcinoma.

Leukaemia, Lymphoma and Others

Both the acute and chronic forms of myeloid [170, 189] and lymphocytic leukaemias [170, 190] have been associated with RP and digital ulceration/critical ischaemia. An association with different forms of lymphoma: angiocentric [191], Burkitt's [192], classical Hodgkins [193, 194], gastric [195] and T-cell [196, 197], as well as multiple myeloma have [198] also been described. Figure 10.5 illustrates a case of paraneoplastic RP with digital ulceration secondary to lymphoma.

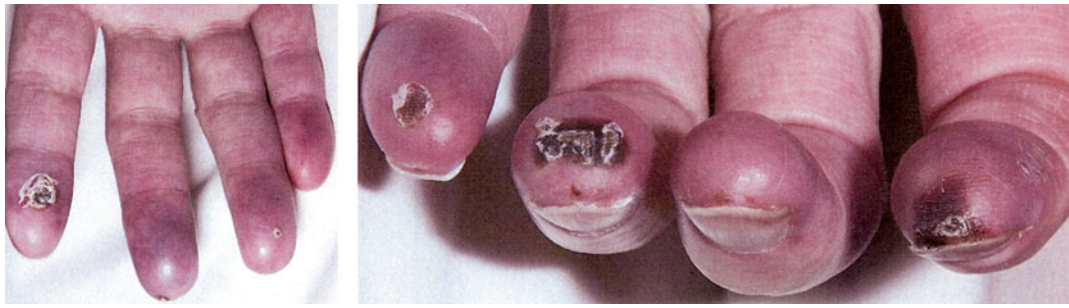

Fig. 10.4 A 73-year-old male was referred to our specialist centre with digital ischaemia for further assessment. He presented with a 6-week history of new discolorisation of the tips of the fingers and a 3-week history of ischaemic digital lesions, aggravated by cold ambient environments (no previous history of RP). In warm environments his fingers resumed an almost normal colour. He has an underlying progressive metastatic adenocarcinoma of the bowel, for which he had received both surgical (hemicolectomy) and chemotherapeutic (including capectiabine) treatment. A diagnosis of paraneoplastic digital ischaemia was made. *Copyright Salford Royal NHS Foundation Trust*

Paraneoplastic Raynaud's Phenomenon and Digital Ischaemia

In a review of acral paraneoplastic syndromes (two case reports with a literature review of 68 previously published cases), 12 patients had RP, 16 had acrocyanosis and 40 patients had gangrene [170]. There was a male predominance (89 % male) and the median age was 59 years. The fingers only were involved in the majority (94 %) of patients, in combination with the toes in 30 % and the toes only were involved in three patients. Adenocarcinomas were the most frequently observed (28 patients [41 %]), with equal numbers of epidermoid or anaplastic carcinomas and haematological malignancies [both 12 patients [18 %]). The remainder of the malignancies consisted of a variety of histological types, including two patients in which the primary site of origin could not be established.

The most common solid tumour sites were lung (nine patients), ovary (seven patients), stomach (five patients) and breast/uterus (both four patients). Of the available outcomes of the paraneoplastic vascular symptoms for 54 patients, 26 (48 %) patients experienced regression of their digital ischaemia after treatment of the underlying neoplasm. Six patients' acral vascular syndromes responded to prostacyclin infusions. The authors highlight in their review that acute digital gangrene was in the vast majority an isolated clinical event that never recurred. However of note, in one patient, the recurrence of digital ischaemia (6 months after tumour treatment) occurred simultaneously with the development of widespread metastatic disease. Trousseau's syndrome relates to acute arterial thrombosis in the presence of a malignancy-related hypercoagulable state [199] (note that Trousseau's sign [migratory thrombophlebitis] is also often, though not exclusively, associated with internal malignancy).

Raynaud's Phenomenon Secondary to Localised Radiotherapy

Westbury et al. present two patients who developed late (13 and 22 months) onset inducible cold sensitivity at the site of previous radical radiotherapy (posterior tongue and the lip respectively) [200]. Both patients had quite distinct longstanding primary RP, which was not worsened post-radiotherapy. Vascular injury (including to endothelial cells), vascular dysfunction and detrimental vascular remodelling [200] have all been proposed to contribute to the development of post-radiotherapy fibrosis and the same pathophysiological mechanisms could explain

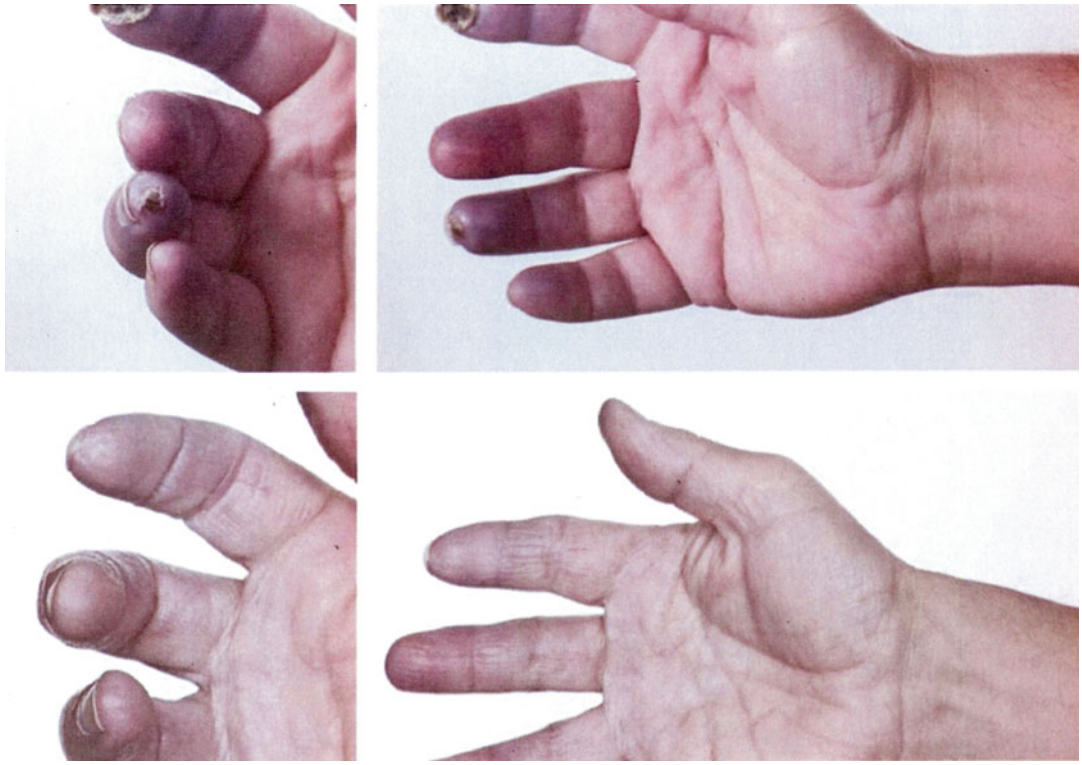

Fig. 10.5 A 67-year-old male was referred to the rheumatology clinic with a 6 month history of new onset RP, which had rapidly deteriorated progressing to ulceration of his fingertips (*top row left* and *right*). Intravenous prostacyclin and subsequent digital sympathectomy of the left hand was not significantly beneficial. At this time, through the investigation of his mild anaemia, he was diagnosed with lymphoma of the nasal sinuses and completed a course of chemotherapy and radiotherapy. A diagnosis of paraneoplastic RP was made. Upon completion of his lymphoma treatment, his digital ulceration (*bottom row left* and *right*) and RP have both spontaneously improved. *Copyright Salford Royal NHS Foundation Trust*

the development of temporally and anatomically distinct RP in this patient group.

Expert Opinion

Although many clinicians recognise malignancy (both solid and haematological) as a cause of RP, there is a limited base to support this association, which is mainly based upon case reports or series. RP may also occur as a result of the chemotherapeutic drugs used to treat malignancy, as a paraneoplastic phenomenon (that may predate and inform the diagnosis of the underlying malignancy) and in relation to local radiotherapy. As a generalisation, RP in malignancy is severe and not uncommonly associated with digital ischaemia with arterial thrombosis a likely culprit.

Conclusion

In conclusion, the clinician must perform a comprehensive clinical assessment and maintain a high index of suspicion as to the presence of the "other" causes of SRP, namely, carpal tunnel syndrome, drugs and toxins, metabolic and haematological abnormalities and malignancy-related. The other causes of RP are a heterogeneous group of conditions, with in general, a limited evidence base to support a definitive association. Severe digital vascular disease, e.g. digital ulcer-

ation and/or the development of critical digital ischaemia, is not uncommon in many of the causes of SRP. Several of the causes of SRP may be malignancy-related: therefore, development of RP may inform (or even predate) the diagnosis of an underlying malignancy. In most circumstances it is unclear whether treating the underlying cause of SRP will also improve the patient's RP.

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Raynaud's Mimics

11

Zsuzsanna H. McMahan and Julie J. Paik

Abbreviations

CRPS	Complex regional pain syndrome
FRRS	First rib resection and anterior scalenectomy
IASP	International Association for the Study of Pain
QSART	Quantitative sudomotor axon reflex tear
RSO	Resting sweat output
RST	Resting skin temperature
TOS	Thoracic outlet syndrome
TRVP	Transient receptor vanilloid channels

Key Points

1. Patients with Raynaud's are at an increased risk of frostbite and there is an increased risk of developing Raynaud's phenomenon after cold injury.
2. Chilblains presents with discrete palpable acral lesions rather than the more even discoloration seen in Raynaud's phenomenon.
3. Chilblain lupus presents with painful discolorations of the skin and palpable lesions after cold exposure.
4. Acrocyanosis is less common than Raynaud's and is characterized by nonparoxysmal painless bluish-red symmetrical discolorations of the hands, feet, and knees.
5. Livedo reticularis is usually a normal physiologic finding that resolves with warming while Livedo racemosa is thought to result from an underlying inflammatory and/or occlusive pathology.
6. Both Raynaud's and erythromelalgia are temperature sensitive conditions but erythromelalgia is a condition in which patients experience attacks of burning or piercing pain and erythema of the skin of the extremities upon exposure to mild warmth.
7. Thoracic outlet syndrome is in the differential for Raynaud's phenomenon because it is usually unilateral with paresthesias pain, and discoloration of the fingers.
8. Complex regional pain syndrome has autonomic and motor disturbances which mimics Raynaud's phenomenon when the patients present with pain and a cold bluish, or pale extremity.

There are several clinical situations that present with temperature sensitivity and cutaneous findings that can mimic Raynaud's phenomenon but are distinguished by associated cause, character of

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skin and tissue changes and course of the disease process. This chapter reviews the characteristics and a management approach to some of the most common clinical disorders that cause temperature sensitivity and tissue changes in the fingers and/or toes that can be mistaken for Raynaud's phenomenon.

Frostbite

Description

The most common cold-induced injury is frostbite [1]. In this condition, peripheral vasoconstriction results in ischemia after prolonged exposure to severe cold. Hands and feet are most commonly affected, but all acral areas are susceptible. Frostbite is categorized both in degrees of severity (four) and into superficial or deep subsets based on the severity of physical findings and complications (Fig. 11.1) (see Table 11.1) [1–3].

Etiology

The homeothermic response in humans is limited [4]. Peripheral vasoconstriction and increased metabolic rate contribute to the ability to maintain human core body temperatures in the cold [2]. However, these responses can become pathogenic when peripheral circulation is restricted for long periods of time and tissue injury occurs as a consequence of local hypoxemia. Risk factors for frostbite include environmental factors such as under-dressing for the weather, lack of access to shelter, and trauma [5]. Intoxication with alcohol and drugs, as well as physiologic factors like dehydration, hypoxia, and high altitude also are thought to play a role [4–7]. In addition, frostbite may occur at higher temperatures in patients with preexisting arterial disease, and people who previously experienced frostbite are more likely to develop it again in the same body part than an individual without this history [2]. Medical conditions, such as Raynaud's phenomenon and psychiatric conditions may also increase the risk of developing frostbite [5]. Mechanical factors such as tight clothing, exposure to high winds, and contact with conducting materials may be important as well [6, 7].

Evidence That It Presents as Raynaud's

Frostbite is considered to be in the differential diagnosis of Raynaud's. Both are temperature sensitive conditions that primarily affect the extremities. In cold temperatures, blood is shunted centrally from the periphery through peripheral vasoconstriction and results in white and/or blue discoloration in the affected areas. This response is pathologic in both conditions and peripheral tissue injury and loss may result. Patients with Raynaud's are at an increased risk of frostbite and it is thought that frostbite injury may increase risk of developing Raynaud's [9].

Raynaud's, however, is more easily reversed with warming, and generally limited to white, blue, or red discoloration in mild to moderate cases. Cases of severe digital ischemia as a consequence of secondary Raynaud's may, however, be more easily confused with frostbite, as digital ulcers may look violaceous, mottled, and necrotic and will also often be associated with a history of prolonged cold exposure.

Diagnosis

The diagnosis of frostbite in patients is dependent on a history of prolonged exposure to cold. Findings on physical exam typically include pain in the affected tissue that may or may not be associated with numbness. Milder injuries are suggested by the presence of warmth, sensation, and normal color, whereas discoloration, with white, mottled, violaceous, pale yellow or waxy appearance suggests more severe tissue injury [2].

Potential complications of frostbite are variable. On exam patients may have evidence of neuropathies, while others notice decreased nail and hair growth, lymphedema, ulcerations, or persistent Raynaud's in the affected area.

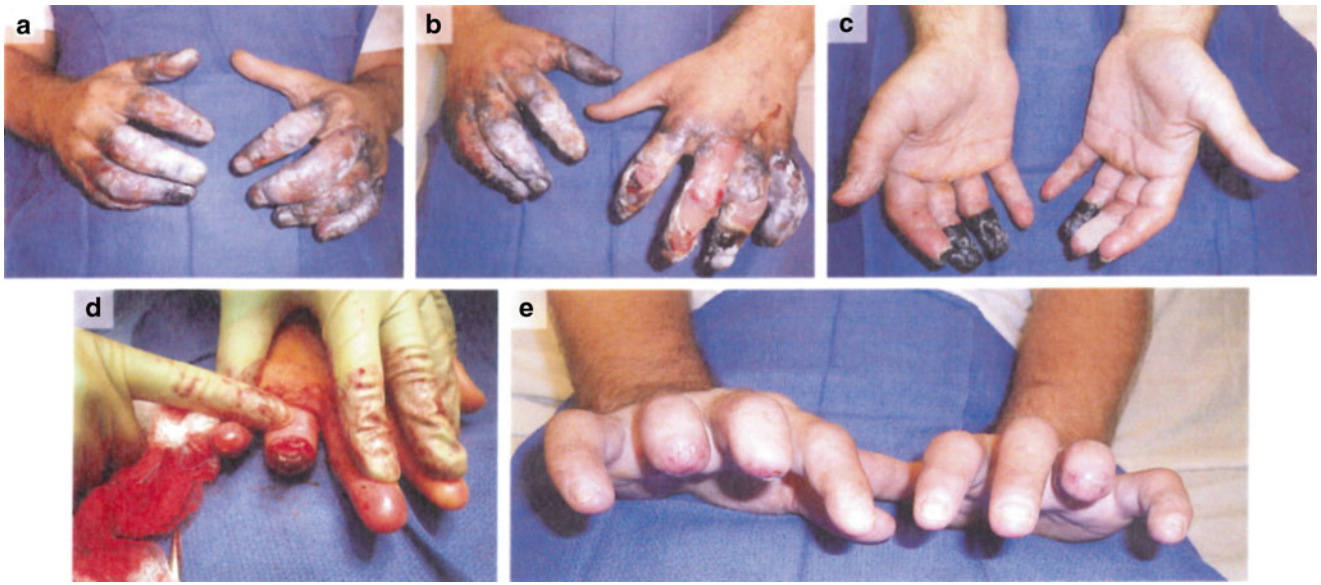

Fig. 11.1 Frostbite: These pictures show evidence of frostbite-related tissue injury following accidental prolonged cold exposure. After 36 h of outdoor exposure to freezing conditions, he was rescued and admitted to the local hospital, where he was treated with a hyperthermic bath, warm intravenous fluids, topical silver sulfadiazine, and physical therapy and was discharged home after 3 days. At follow-up, examination of his hands revealed edema, purple discoloration, and sloughing of the skin on all digits except his left thumb (panel **a**). Serial debridements were performed and stellate ganglion blocks were administered on an outpatient basis. The appearance of his fingers and right thumb improved over the next month (panel **b**). Demarcation of necrotic, mummified tissue on the distal left ring finger and right middle and ring fingers was noted 2 months after the initial injury (panel **c**). Amputation of the affected areas was subsequently performed; intraoperative findings included nonbleeding, necrotic bone (panel **d**). Postoperative healing was uneventful (panel **e**) [8]

Table 11.1 Type of frostbite based on extent of tissue injury

	Type of frostbite	Extent of skin injury	Complications
Superficial	First degree	Partial skin freezing; epidermal	Erythema, edema, hyperemia, desquamation, cold sensitivity
	Second degree	Full thickness skin injury	Edema, large clear blisters, eschar; paresthesia, hyperhidrosis, cold sensitivity, desquamation, black eschar
Deep	Third degree	Full thickness skin and subcutaneous injury	Smaller hemorrhagic blisters, cyanotic skin, deep burning pain with rewarming, blue-gray discoloration, severe cold sensitivity
	Fourth degree	Full thickness skin and subcutaneous injury; also involves muscle, bone, tendon involvement	Complete necrosis, gangrene, loss of the affected part; minimal edema

Permanent tissue loss, such as subcutaneous tissue atrophy, bony defects on X-ray examination, and abnormal epiphyseal growth, may also occur.

Management

The management of frostbite varies, depending on the timing of their presentation relative to the time of tissue injury. The initial priority in approaching acute frostbite is removing the patient from the cold environment. The rewarming process is critical and during this period it is important to avoid attempts at rewarming using approaches such as weight bearing activity or exercise, or rubbing the affected area because this may result in additional tissue injury. Early restoration of normal body temperature is a priority, using a water bath at 39–42 °C (102–108 °F) prior to additional therapeutic interventions [7].

Key aspects of the rewarming technique are listed in Table 11.2. The most important points to consider during this process are that (1) the rewarming should occur in a sterile environment to minimize risk of infection, (2) it should occur gradually, (3) pain control is important to minimize stress-induced vasoconstriction and to provide comfort the patient. Importantly, the injury should be monitored for several weeks prior to determining the degree of injury, as injury may progress in the time following the initial insult [3].

In patients who present days after the cold incident, the degree of injury may be more obvious. This group of patients does not require rewarming, and thus the focus is more on protection of the injured extremity and possibly anti-platelet therapy. Silvadene may be used on injured areas. As in the above group, these patients are then monitored for several weeks to determine the degree of injury before any surgical approaches are initiated. Aggressive revascularization is warranted in more severe cases to maximize healing. Surgical debridement is contraindicated unless the wounds are infected.

Table 11.2 Initial approach to frostbite

Approach to rewarming frostbite (30–45 min) [2, 4]	
1. Use strict aseptic technique	Mask, powder-free gloves, etc
2. Use a relatively large bath	The bath volume should be such that the injured tissue does not rapidly reduce the water temperature
3. Carefully monitor the bath temperature as it cools	
4. To warm the bath, first remove the extremity and then add hot water until 39–42 °C	Stir the bath and reevaluate the temperature prior to reintroducing the extremity
5. Continue rewarming until the frostbitten extremity appears flushed	This suggests reestablished peripheral circulation
6. Control the pain	Narcotics may be required
7. Once the extremity is warm, clean gently; debride non-hemorrhagic blisters if present	Use fine-pore sponge soaked in poloxamer 188 for debridement
8. The damaged part should be loosely bandaged	Use dry protective nonadherent dressings and padding, especially between digits

Prevention of secondary complications of the initial tissue injury is also important to consider. With severe cold-induced injury, such as frostbite, the integrity of the skin is broken down, thus increasing the risk of subsequent infections. Tetanus prophylaxis is important as frost-bitten areas are considered to be susceptible to tetanus infections [4]. Other bacterial infections may also complicate the situation; however it is treatment of specific complications which is generally recommended over prophylactic therapy.

Another consideration involves the prevention of progressive dermal ischemia at the site of injury. Prostaglandin and thromboxane production occur during tissue injury, and may result in local vasoconstriction. Inhibition of these mediators through the use of selective NSAIDs, prostaglandin inhibitors, and aloe vera is important to minimize the reduction in local perfusion [3, 10, 11]. A controlled trial recently evaluated aspirin + buflomedil versus aspirin + iloprost versus aspirin + iloprost and rt-PA. This trial supported the use of aspirin plus prostacyclins with and without rt-PA in stage 3 frostbite as the use of these medications significantly reduced digital amputations compared to the aspirin + buflomedil group [11]. An open-label trial also supported TPA use in frostbite [12]. Aloe may be applied directly to a wound following debridement or to intact hemorrhagic blisters and should be reapplied several times throughout the day. Local edema should be minimized by elevating the extremity. Vasoconstrictors, such as tobacco, should be avoided during wound healing. Use of the affected extremity should be minimized until partial or complete wound healing occurs and the swelling has largely resolved.

Rehabilitation programs may play an important role during wound healing and can include water treatments (e.g., whirlpool), and physical therapy to maintain joint flexibility and avoid contractures [7]. Surgical intervention may be required, but it is generally recommended to wait 60–90 days prior to amputating tissue, given that it can be challenging to clinically determine the depth of permanent tissue damage. Only in the setting of severe infection or sepsis should such an intervention be contemplated earlier.

Although data is limited, a variety of medications have been reported to have potential efficacy in frostbite including antithrombotic agents, such as heparin, thrombolytic agents, pentoxifylline, and hyperbaric oxygen [12–18]. Sympathectomy may also provide some benefit, but data is comprised of a non-randomized trial and case-series showing mixed results [9, 10, 19, 20].

Primary Pernio/Chilblains

Description

Primary pernio, also known as chilblains, is a cold-induced vasculopathy that is more commonly seen in damp climates and not associated with an underlying disease state [21, 22]. It primarily affects the hands and feet and is more commonly seen in young women in a bilateral, symmetric distribution [23]. Lesions may also affect the pinnae of the ear, nose, and thighs [22]. Inflammatory red to purple macules are characteristically seen on the distal ends of the affected area and usually appear within hours following cold exposure (Fig. 11.2) [22]. Lesions are often associated with burning, pain, and/or pruritis. Small joint enlargement may be seen in the involved areas, and ulceration of lesions is occasionally noted [24].

Etiology

Chilblains is idiopathic and not usually indicative of a more serious underlying condition [24]. The etiology is not well defined, but is thought to be related to abnormal vascular responses to cold exposure [25, 26].

Evidence That It Presents as Raynaud's

Chilblains may be confused with Raynaud's as both conditions occur after exposure to cold, affect acral areas, and may cause associated pain and red or purple discoloration of the skin.

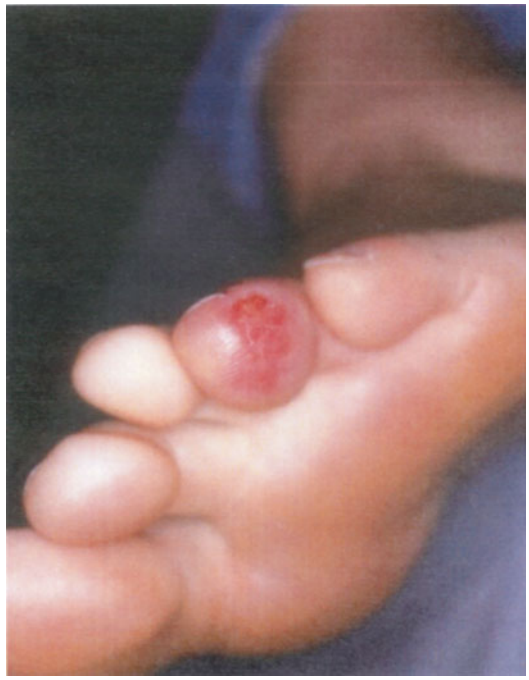

Fig. 11.2 The inflammatory violaceous macule shown on the distal end of the 4th toe is characteristic of primary chilblains and usually appears within hours following cold exposure

Chilblains tends to present with more discrete acral lesions rather than the more even discoloration seen in Raynaud's [27, 28].

Differences between chilblains and Raynaud's in the acute setting include an absence of the early pallor in chilblains, which is often present in Raynaud's. In addition, persistence of cold or purple hands despite rewarming is more commonly seen in chilblains than Raynaud's [28, 29]. As a result, symptoms of chilblains are less likely to recede in the summer months [30].

Diagnosis

Prompt recognition through a careful history and physical exam can avoid excessive investigation and anxiety, allowing appropriate simple advice and treatment [24]. Laboratory studies from patients with chilblains usually do not demonstrate evidence of cryoglobulins, cryofibrinogens, or cold agglutinins [23]. In an initial evaluation, however, these studies, in addition to complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, c-reactive protein, serum protein electrophoresis, complement, rheumatoid factor, antiphospholipid antibodies, and ANA should be evaluated to look for secondary causes, but are usually normal in primary chilblains [23, 26, 28]. Evaluation for cryoglobulins in the initial evaluation remains an area of debate [26, 31]. Biopsies are not routinely recommended, but when performed, are done to distinguish between chilblains and the skin lesions of SLE. The lesions are thought to be inflammatory with a variety of histopathological changes described. A mononuclear vascular infiltrate and variable papillary dermal edema are described but are not specific enough to be diagnostic of chilblains [24]. Findings that are not specific for lupus but that suggest chilblains lupus over primary chilblains include the combination of edema and reticular dermis infiltrate with a perieccrine reinforcement, differences in spongiosis, vacuolation of basal layer, edema of the dermis, and deep perieccrine inflammation [32].

Management

Chilblains is generally benign without systemic complications [24]. Most cases will resolve in 1–2 weeks, with modification of cold exposure and avoidance of acute temperature changes [23]. Early recognition can avoid excessive diagnostic testing, alleviate anxiety, and allow appropriate simple lifestyle modification and management as indicated [23]. Avoidance of extended cold exposure through proper attire and limiting the time of exposure to cold temperatures minimize risk of future attacks. In an Australian review, most patients improved with the warmer weather or responded to cold protection with all cases resolving by late spring [24]. However, most were also treated with nonsteroidal anti-inflammatory drugs, prednisone or calcium channel blockers and therefore distinguishing the effects of the drug from the effects of environmental changes is challenging [24].

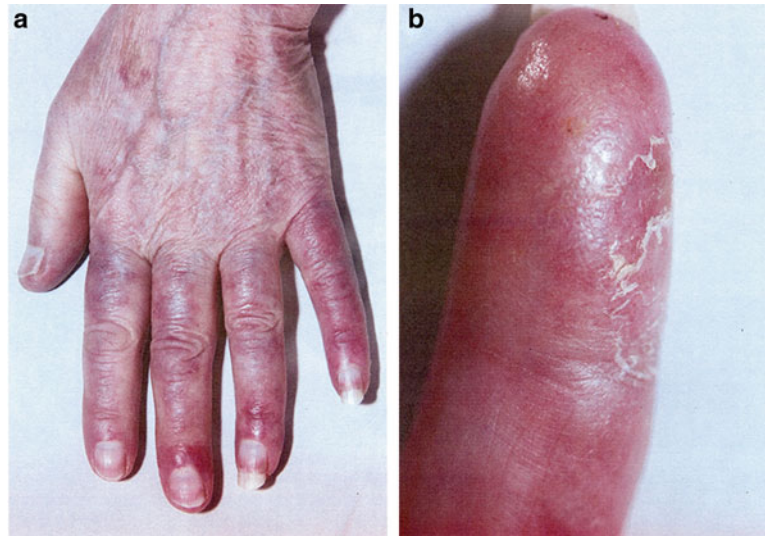

Fig. 11.3 (**a**) Erythematosus and violaceous skin lesions on the fingers of a patient with Chilblains lupus. (**b**) Typical Chilblains lupus lesion on distal finger

In situations where repeated cold exposure is likely and lesions are persistent or recurrent, we recommend a short course of pharmacologic therapy. While several treatment options exist, we recommend calcium channel blockers, as first line therapy in such cases. This class of medications has been studied in two small placebo-controlled trials in patients with chilblains [33, 34]. Both studies supported the use of this class of medications over placebo in the treatment of chilblains. Short courses of oral prednisone (3–5 days), topical steroids, prazosin, or NSAIDS prescribed for 1–2 weeks would be the alternative therapies to calcium channel blockers [21, 24, 35]. As data for using these drugs for treating chilblains is limited, we recommend selecting the therapeutic agent based on the risk–benefit ratio for the patient and their comorbidities.

Chilblain Lupus

Description

Chilblain lupus, or Hutchinson lupus, was first described in 1888 by Jonathan Hutchinson. It is a rare and chronic form of cutaneous LE characterized by erythematosus-purple plaques located in the distal extremities, often also affecting the nose and ears. These lesions are induced by exposure to cold or a drop in temperature. Lesions may be associated with mild pain, pruritis, or hyperhidrosis. In addition, pigmentary changes and atrophic scarring may also be seen (Fig. 11.3). Chilblain lupus and primary pernio/chilblains may be confused, but other coexisting features of systemic lupus suggest chilblain lupus over primary pernio/chilblains [36, 37]. At times, chilblains lupus may be associated with other forms of cutaneous lupus and may progress to systemic disease (Fig. 11.3).

Etiology

The etiology of chilblain lupus may be sporadic or familial. The pathogenesis of the sporadic variant remains unknown, but is thought to involve reduced digital perfusion resulting from reversible vasoconstriction or microvascular injury provoked by cold exposure [38]. Sporadic chilblain lupus usually presents in adulthood with symptoms occurring during cold or damp periods.

The familial form usually presents early in childhood and is attributed to autosomal dominant inheritance of missense mutations in TREX1 [38, 39]. TREX1 encodes the most abundant

exonuclease in mammals and functions to degrade single stranded DNA [40, 41]. It is hypothesized that the buildup of intracellular nucleic acids in the setting of decreased TREX1 initiates an IFN-mediated immune response resulting in inflammation and autoimmunity [38, 42].

Evidence That It Presents as Raynaud's

Chilblain lupus, like Raynaud's, predominantly affects acral areas that are more susceptible to the cold. They can present together or independently. Chilblain lupus presents with painful discolorations of the skin after cold exposure or with relative changes in temperature. Like patients with Raynaud's, secondary to an autoimmune disease, patients with chilblain lupus may have associated autoantibodies, including ANA, anti-DNA, and anti-nucleosome, but generally do not progress to systemic lupus.

Diagnosis

The history is the most critical factor in making the diagnosis of chilblain lupus. Although not widely used, the "Mayo Clinic Diagnostic Criteria" were proposed by one group of authors to standardize the diagnosis of chilblain lupus [43]. Two major and three minor criteria were proposed. The major criteria included (1) skin lesions in acral locations induced by exposure to cold or a drop in temperature, and (2) evidence of lupus erythematosus in the skin lesions by results of histopathologic examination or direct immunofluorescence study. The three minor criteria include (1) coexistence of systemic lupus erythematosus or other skin lesions of discoid lupus erythematosus, (2) response to anti-lupus erythematosus therapy, and (3) negative results of cryoglobulin and cold agglutinin studies. For diagnosis of chilblain lupus, both major criteria and one minor criterion must to be present [43].

Additional confirmatory studies may include findings on pathology, although biopsy is not necessary to confirm the diagnosis. Such findings include epidermal atrophy, basal layer degeneration, and periadnexal and perivascular inflammatory infiltrates. Additional, less common findings include dyskeratosis, dermal mucin deposition, deposition of granular Ig deposits and complement in the basement membrane [30].

Management

If uncomplicated, chilblain lupus should initially be managed with lifestyle modification, including minimizing cold exposure and enhancing protective clothing when cold exposure is necessary. Topical or oral antibiotics may be used if secondary wound infection is suspected. If lifestyle modification is inadequate as manifested by recurrence of the lesions, systemic corticosteroids and/or mycophenolate may be used [44, 45].

Acrocyanosis

Description

First described by Crocq in 1896, acrocyanosis is a persistent, symmetric, painless, cyanotic discoloration of the digits and face that is characterized by persistent color changes and exacerbated by exposure to cold temperatures [46]. It is often associated with local hyperhidrosis of hands and feet. Acrocyanosis can present as a primary or idiopathic condition or as a secondary manifestation of another disease.

Etiology

The etiology of primary acrocyanosis is not well understood, and it has been suggested that pathologically different mechanisms may underlie this condition [46]. Primary acrocyanosis is usually a benign condition that predominantly affects young women in the second and third decades of

life that may spontaneously resolve [46]. Secondary acrocyanosis, on the other hand, is seen in association with a variety of conditions including but not limited to malignant and hematologic disorders, drug and toxin exposures, infections, and others [47–54]. Secondary acrocyanosis often correlates with disease severity and may resolve with treatment or removal of the underlying cause and thus may be a clue to the underlying diagnosis [47–54].

Evidence That It Presents as Raynaud's

Acrocyanosis and Raynaud's are similar conditions and may be confused in the clinical setting. Both conditions are cold-sensitive and may result in a cyanotic discoloration of the affected areas, with most prominent manifestations occurring in the hands and feet. Acrocyanosis differs from Raynaud's in that it involves persistent digital discoloration while Raynaud's is reversible. In addition, acrocyanosis lacks the initial phase of pallor that often precedes the bluish discoloration in Raynaud's. Finally, Raynaud's may be associated with pain whereas acrocyanosis is typically painless.

Acrocyanosis is less common than Raynaud's, and contrary to the latter, is characterized by nonparoxysmal, in most cases persistent, painless bluish-red symmetrical discolorations of the hands, feet, and knees. Like Raynaud's, it is more frequent in women than in men. With both Raynaud's and acrocyanosis, a distinction is made between primary and secondary forms [55].

Diagnosis

Diagnosis of acrocyanosis depends largely on the history and physical examination. The diagnostic value of pathology is limited as the tissue findings are often nonspecific. Findings generally include local edema and fibrosis with superficial capillary dilation with or without evidence of new vessel formation. Mild perivascular lymphocytic infiltrates may also be seen [46].

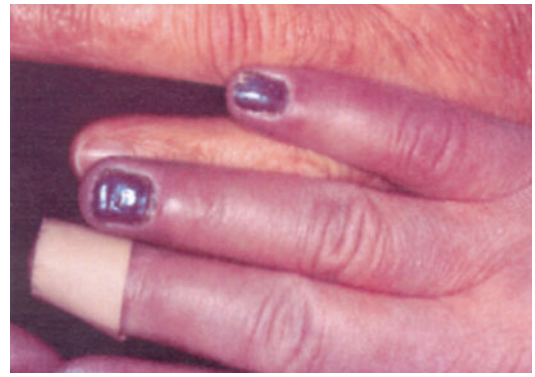

Fig. 11.4 The photograph illustrates the contrast between the digital cyanosis in a hand of a patient with acrocyanosis (*left*), and a normal hand (*right*)

Management

The management of acrocyanosis involves avoidance of environmental triggers, such as cold exposure, and enhancing local circulation [46]. Data regarding the efficacy of medications for the treatment of acrocyanosis lacking as definitions of acrocyanosis vary widely across the literature (Fig. 11.4) [46].

Livedo Reticularis and Racemosa

Description

Livedo reticularis was first described in 1860 by Ferdinand von Hebra, an Austrian dermatologist who was describing the skin discoloration as "pale blue" or *lividus* in Latin [56]. It is an erythematous to violaceous netlike vascular pattern on the skin that blanches with applied pressure [57, 58]. It predominantly affects young women and is most frequently observed in the lower extremities [58]. Livedo reticularis is usually a normal physiologic finding that resolves with warming, but it can also be suggestive of an underlying hypercoagulable state [57–59].

Livedo racemosa, or "broken pattern livedo," is distinguishable from livedo reticularis [57]. There is a widespread form which can sometimes be confused with livedo reticularis, but it is generally distinguishable by its asymmetry, lack of

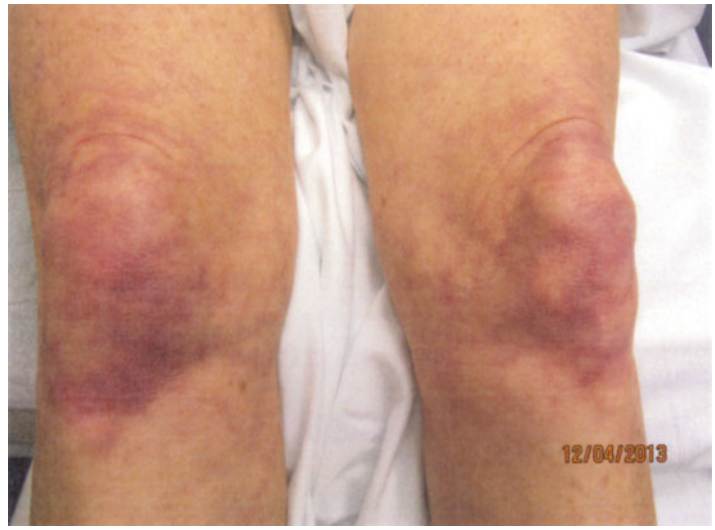

Fig. 11.5 This photograph illustrates the violaceous netlike vascular pattern on the skin in a patient with livedo reticularis

blanching, and irreversibility with warming [60]. It is important to make a distinction between the two conditions because livedo racemosa is usually associated with underlying vascular disease (e.g., anti-phospholipid syndrome), while this is only sometimes true for livedo reticularis (Fig. 11.5) [58]. In addition, the long term cutaneous complications of livedo racemosa may be more severe, as the clinical course can result in retiform pigmentation and ulceration [56].

Etiology

The cutaneous vascular anatomy contributes to the pattern seen clinically in livedo reticularis [59]. Central blanching at the center of arterial hexagons and/or a blanchable cyanotic venous congestion along the venous rims are the typical cutaneous patterns seen in livedo reticularis [56]. As blood flow through these vessels is impaired (e.g., vasoconstriction from exposure to cold), cyanotic discoloration occurs in the anastamotic areas where blood flow is slowed and the characteristic net-like pattern is seen [58].

Livedo racemosa, or "broken pattern livedo," is thought to result from an underlying inflammatory and/or occlusive pathology leading to irregular and persistent impairments in blood flow and a branching pattern of blueish discoloration of the skin [60]. There are many causes of livedo racemosa and they include a variety of connective tissue disorders (e.g., polyarteritis nodosa, systemic lupus erythematosus with or without APS), infections (e.g., syphilis, tuberculosis), drugs, hematological disorders (e.g., APS, polycythemia rubra vera, essential thrombocythemia, cryoglobulinemia, cold agglutinins), and cholesterol embolization syndrome [56, 58, 59]. Antiphospholipid syndrome is a particularly strong concern as the association with livedo is strong and it may be the only clue to an early diagnosis [57, 61–67].

Evidence That It Presents as Raynaud's

Raynaud's and both forms of livedo are associated with cyanotic color changes in the skin and can be associated with exposure to cold. Raynaud's and livedo reticularis, however, may completely reverse with warming, whereas livedo racemosa does not (Fig. 11.6) [59]. The distribution of the two conditions is quite different with Raynaud's predominantly affecting acral areas and livedoid vasculopathy predominantly affecting skin in a more proximal distribution (e.g., skin on the thighs and knees). Both Raynaud's and livedo racemosa may be associated with some cutaneous ulceration resulting from ischemia of the affected area.

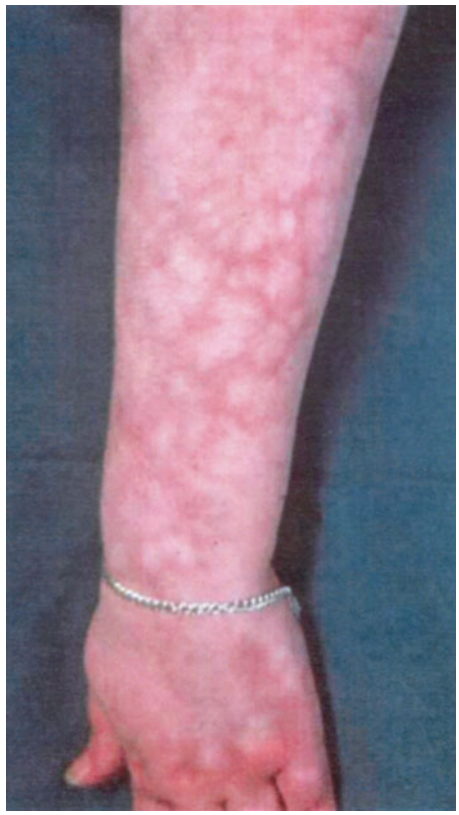

Fig. 11.6 Livedo racemosa is shown on the arm of this woman, and the characteristic violaceous skin discoloration appears in irregular broken circles

Diagnosis

The diagnosis of livedo reticularis and livedo racemosa is based on clinical context and findings on physical examination [59]. As both forms of livedo may be associated with other systemic diseases, a careful and thorough history should be taken to evaluate for relevant signs and symptoms [58]. Particular attention should be paid to personal or family history of autoimmunity and/or thrombosis. A detailed personal history of medications changes, recent vascular procedures, and history of relevant complicating factors such as renal failure or hepatitis C should also be acquired [59].

On physical examination, a thorough review of the patient, particularly evaluating the skin pattern, color, and distribution of the lesions is essential. While laboratory testing in patients with livedo reticularis should be guided by findings in the history and physical examination that cause suspicion for underlying systemic conditions, in livedo racemosa, extensive laboratory testing is required given its more frequent association with a variety of other systemic illnesses [58, 59]. Skin biopsies are generally low yield in patients with livedo reticularis although they may help distinguish vasculitis from vasculopathy and normal skin. When skin is obtained, several punch biopsies are recommended from varying locations, including from the central blanched area and peripheral blue areas [59]. If fixed purpuric areas or subcutaneous nodules are present, these should be biopsied as well. As the purpose of such biopsies is to obtain tissue from medium blood vessels which are present in the deep reticular dermis and subcutaneous fat, large punch biopsies or wedge biopsies are recommended [59].

Management

Other than cold avoidance, no treatment is indicated for primary livedo reticularis [59]. Treatment of the underlying cause in either livedo reticularis or livedo racemosa should be the aim of medical management of the underlying disease state.

Erythromelalgia

Description

Erythromelalgia was first described in 1878 by an American neurologist, Dr. Silas Weir Mitchell, and is thus also known as Weir Mitchell's disease [68]. In the literature, erythromelalgia is also referred to by a variety of other names, including acromelalgia, erythralgia, erythermalgia, erythermomelalgia, and erythroprosopalgia [69].

Erythromelalgia is a condition in which patients experience attacks of burning or piercing pain and erythema of the skin of the extremities upon exposure to mild warmth (32–36 °C) (Fig. 11.7). The attacks are generally alleviated by cooling [70]. In some patients symptoms are

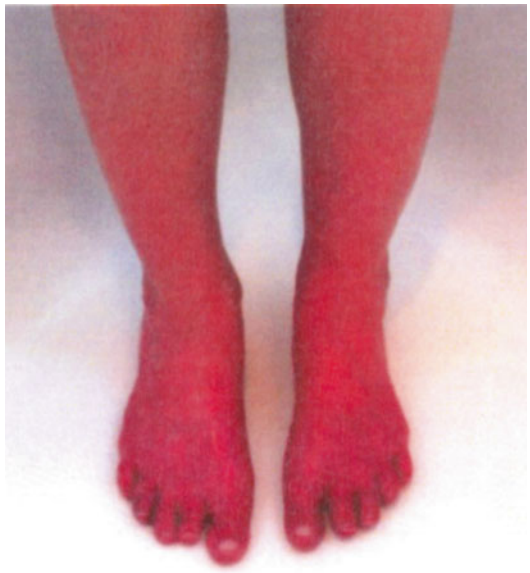

Fig. 11.7 Erythematous symmetrical skin discoloration is seen on the legs of this patient with erythromelalgia

constant, varying only in intensity, while in others they are episodic, sometimes occurring several times a day [69, 71]. It is most commonly reported in the lower extremities, but involvement of the hands, ears, and face has been described [71]. Symptoms are most common in the warm summer months and can be exacerbated by ambulation, physical activity, leg dependence, shoes, and gloves [68, 69, 72]. Immersion of the affected area in ice or cold water, exposure to air currents, or elevation have all been reported to provide some relief [69]. It is thought that women are more frequently affected than men [55, 73]. The average age of onset is reported as 40–55 years of age, but children and elderly persons may also be affected [55, 72, 74]. A patient's quality of life can be significantly impacted by the disease, with depression and even suicide reported as outcomes [71, 75].

Etiology

Erythromelalgia can be classified either as a primary (inherited) or secondary (sporadic) disorder. The primary form of erythromelalgia in some families, is inherited in an autosomal dominant pattern and is caused by a gain-of-function mutation in the *SCN9A* gene on chromosome 2q31-32 encoding the Na(v) 1.7 sodium channel while at other times it is sporadic, possibly caused by acquired mutations [68–70]. The Na(v) 1.7 sodium channel is mainly expressed in the sympathetic and nociceptive small-diameter sensory neurons of the dorsal root ganglion. This mutation causes a hyperpolarizing shift in activation and slow deactivation, resulting in hyperexcitability of the cells containing these channels [68, 69]. It is hypothesized that the connection between the pain and temperature related symptoms in erythromelalgia may be related to the co-expression of Na(v)1.7 channels in neurons with temperature sensitive transient receptor vanilloid channels (TRPV) although more data is needed [70].

Secondary erythromelalgia is not well understood, but some suggest that it is a consequence of neuropathic and microvascular complications related to one or more drugs or underlying disorders [70, 76]. Withdrawal of the precipitating medication or treatment of the underlying disorder usually results in eventual resolution of the symptoms.

Evidence That It Presents as Raynaud's

Both Raynaud's and erythromelalgia are temperature sensitive conditions. Pain is often experienced with relative changes in temperature, and in both conditions symptoms are primarily localized to the hands and feet. Both conditions may involve an erythematous flush of the skin during episodes and they may coexist [77].

Erythromelalgia and Raynaud's differ in several ways. First, the ischemic phase that defines Raynaud's is absent in erythromelalgia. Erythromelalgia also may improve with elevation of the extremity, while this is uncharacteristic of Raynaud's. Erythromelalgia also usually improves or resolves with cold exposure, and digital ulcers are not seen. Finally, in contrast to Raynaud's, erythromelalgia is more common in lower extremities than the upper extremities, but can affect both.

Diagnosis

The diagnosis of erythromelalgia is clinical, requiring a strong history and physical exam, as no objective laboratory criteria are available [69, 76]. During the initial evaluation, it is important to consider an evaluation for other associated conditions to differentiate between its primary and secondary forms. Several sets of criteria have been proposed to make the diagnosis of erythromelalgia, although consensus on the "standard" criteria is lacking [71, 78, 79].

The differential diagnosis of secondary erythromelalgia is broad (see below) although associated myeloproliferative disorders are the greatest concern [71, 80–84]. Abnormalities in a variety of laboratory blood tests may be seen, although none is necessary to make the diagnosis. Laboratory testing should focus on basic laboratory tests and an evaluation for secondary erythromelalgia. Such studies include comprehensive metabolic panel, complete blood count, inflammatory markers, thyroid function testing, urinalysis, serum protein electrophoresis, and workup for autoimmune disease [69, 71]. Genetic testing may be diagnostic in those suspected of having familial erythromelalgia for *SCN9A* mutations [69].

Further diagnostic testing may be pursued if the clinical and/or laboratory evaluation suggest it is warranted. Autonomic reflex screening may demonstrate abnormalities with small fiber disease [85]. Additional abnormalities may be seen in EMG studies, quantitative sudomotor axon reflex screening, and thermoregulatory sweat testing given that large and small fiber neuropathy in patients with erythromelalgia may be present. Skin biopsies may reveal decreased nerve density [86]. In the vascular lab, studies may reveal increased temperature and laser Doppler-measured perfusion in the setting of normal arterial Doppler signals.

Treatment

Management of erythromelalgia is challenging as there is no definitive treatment available. Patient education, avoiding aggravating factors, cooling techniques, and selective medications may all play a role in management [69, 87].

In the literature, treatment options for erythromelalgia are limited to case reports and small case series [87]. Such interventions include sodium nitroprusside infusions, vasoactive drugs including β-blockers, magnesium, prostaglandin E_1, iloprost (prostacyclin analog), and ergot alkaloids. In cases where the patient's symptoms are more neurologic, some reports suggest starting with neuroactive drugs rather than vasoactive drugs, such as SSRIs, tricyclic antidepressants, gabapentin, pregabalin, and benzodiazepines. Many others have also used sympathetic blocks, epidurals, sympathectomies, nitroprusside infusions, and calcium antagonists [87]. Several treatments, while potentially efficacious, may paradoxically exacerbate symptoms so this should be considered prior to recommending.

As the reports are largely anecdotal and there is no evidence-based approach to guide management, we recommend conservative intervention. Environmental factors should be modified by avoiding the heat or warm temperatures above the threshold of symptoms. Using air conditioning, cooling devices or exposure to cooler temperatures may reverse uncomfortable episodes. Alcohol and other triggers of flushing should be minimized or avoided. Stress-related flushing can be managed with appropriate psychotropic medications. Patients with secondary causes of erythromelalgia should be treated for their underlying disorder whenever possible. We suggest a trial of aspirin or NSAID's in all cases, but recognize that it is most helpful in cases secondary to a myeloproliferative disease. Overall we have been disappointed with vasoactive drugs.

Causes of Secondary Erythromelalgia

Myeloproliferative diseases (e.g., polycythemia vera).

Rheumatic diseases (e.g., cutaneous vasculitis, systemic lupus erythematosus, rheumatoid arthritis).

Cardiovascular disease (e.g., hypertension, diabetes mellitus).

Complications of drug therapies (e.g., verapamil, nifedipine, nicardipine, pergolide, bromocriptine, ticlodipine, norepinephrine, iodide contrast).

Metabolic (e.g., diabetes).

Infectious (e.g., HIV, HBV, EBV).
Neurologic disease (e.g., multiple sclerosis, neurofibromatosis).
Malignancies (e.g., colon, thymoma, astrocytoma).
Toxins (e.g., mercury poisoning).

Thoracic Outlet Syndrome

Description

Thoracic outlet syndrome (TOS) is a term that was first introduced in 1956 to describe the spectrum of upper extremity symptoms due to the compression of the neurovascular bundle passing through the confined space of the thoracic outlet [88]. Before the use of TOS, patients presenting with upper extremity symptoms were often labeled by the anatomic structure thought to be producing the symptoms, such as first rib [89] and costoclavicular syndrome [90].

The three main subtypes of thoracic outlet syndrome are defined by the neurovascular bundle primarily affected by pathologic compression as they traverse the thoracic outlet with clavicle above and first rib below (Fig. 11.8). Each subtype is described after the predominantly affected structure in the thoracic outlet. Thus, (1) neurogenic TOS results from brachial plexus compression; (2) venous TOS results from subclavian vein compression; and (3) arterial TOS results from subclavian artery compression.

Compression of the brachial plexus commonly leads to numbness, dysesthesia, and weakness of the upper extremity. Venous compression may result in deep vein thrombosis with associated swelling. Arterial compression can lead to distal thromboembolism, claudication, or even acute arterial thrombosis [91, 92].

Etiology

Neurogenic TOS

It is the most common subtype and comprises over 95 % of all TOS patients. The symptoms are caused by anatomic narrowing or entrapment of

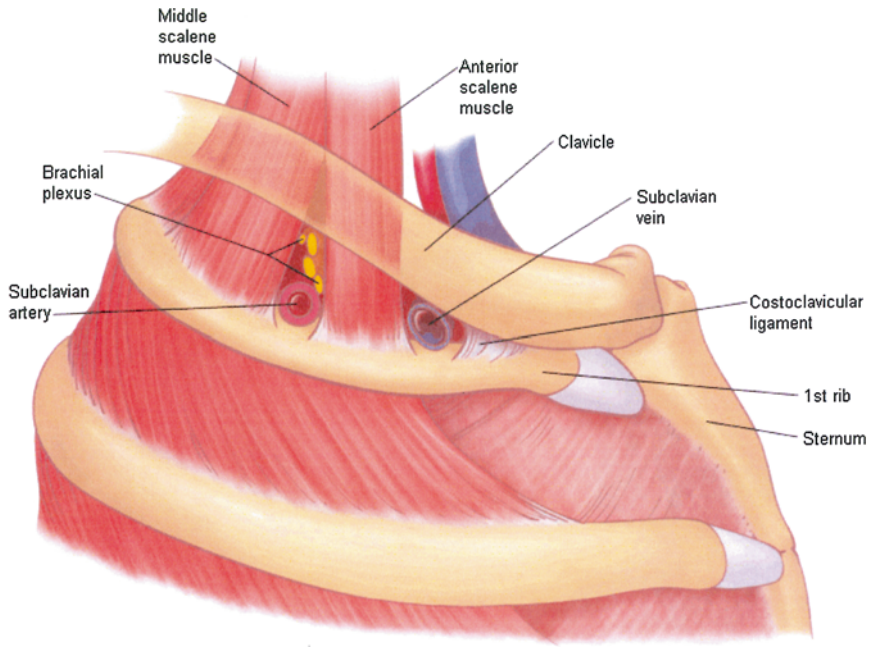

Fig. 11.8 Anatomy of thoracic outlet in cross section with the neurovascular bundle traversing the outlet with the clavicle above and 1st rib below

the nerve roots of the brachial plexus as they pass through the interscalene triangle formed by the anterior and middle scalene muscles and the first rib (Fig. 11.8).

Patients typically present with a variety of different symptoms that include pain, paresthesias, or weakness in the arm and hand. Paresthesias most commonly involve all five fingers, but are usually most noticeable in the fourth and fifth fingers and the ulnar forearm [93].

The etiology of neurogenic TOS is most often from trauma of the upper extremity or excessive repetitive activity. Examples of trauma include hyperextension neck injury, such as whiplash injury from a motor vehicle accident, or a fall on the ice or floor [94]. Repetitive injury at work, most often from sitting at a keyboard for long hours has been described in neurogenic TOS [95]. Other predisposing factors include bony abnormalities such as cervical ribs, anomalous first ribs, and congenital narrow scalene triangles which can lead to neurogenic TOS following neck trauma.

Venous TOS

Venous TOS comprises 2–3 % of all TOS patients. Symptoms are those of an obstructed vein such as arm swelling, cyanosis, pain, and paresthesia. It typically is seen in patients who perform vigorous repetitive exertion of the upper extremities, usually with the arms above shoulder level [96]. Fatigue of the forearm can occur within minutes of using the affected arm. Swelling can be accompanied by pain and cyanosis of the affected extremity; paresthesias in the fingers are common but are due to swelling in the hand rather than nerve compression. Neck pain and headaches are uncommon.

Upper extremity swelling due to different degrees of venous compression or overt deep vein thrombosis is the key finding of venous TOS. Historically, it is referred to as a spontaneous upper extremity thrombosis or Paget–Schroetter syndrome. This syndrome will classically present as blue, swollen, heavy, and painful arm with symptoms appearing within 24 h of the inciting event.

Arterial TOS

Arterial TOS is the least common type of TOS, and accounts for <1 % of all TOS. Despite being the least common, it can have the most serious consequences. Symptoms typically develop spontaneously and are unrelated to trauma or work. The etiology is almost always associated with an anomalous rib or a cervical rib. Patients present with ipsilateral hand and digit ischemia, typically from a distal thromboembolism from a lesion in the subclavian artery. Hand or digit ischemia will have symptoms of pain, pallor, paresthesia, and coldness.

Digital gangrene is not unusual. It is rare to find symptoms in the shoulder, neck, or head. In the supraclavicular area, a tender lump, bony prominence, or even pulsation of the subclavian artery can be seen.

Evidence That It Presents as Raynaud's

Thoracic outlet syndrome is in the differential for Raynaud's phenomenon primarily because of the upper extremity symptoms of paresthesias, pain, and discoloration of the fingers. Cold intolerance is also reported in TOS, primarily in neurogenic TOS. Moreover, arterial TOS can present with critical ischemia, similar to Raynaud's phenomenon, where it is a medical emergency.

The key clinical feature that distinguishes TOS from Raynaud's phenomenon is that Raynaud's can affect all extremities, including toes, which is not seen in thoracic outlet syndrome. The characteristic color pattern of white, blue, and red in Raynaud's will not be commonly seen in TOS. In addition, the pain and paresthesias seen in TOS will be commonly seen in both arm and hand, and not just the fingers as we would commonly see with Raynaud's phenomenon.

Diagnosis

The clinical evaluation of each type of TOS is typically unique depending on which part of the neurovascular bundle is being compressed.

However, there could be some overlap in symptoms if more than one structure is involved.

First, a thorough history of symptoms will guide the clinician to which subtype of TOS is the culprit. Second, complete neurologic and vascular evaluation should be performed in all patients. Third, imaging studies with additional adjunct studies such as nerve blocks can be beneficial in diagnosing TOS subtypes.

Historically, compression maneuvers on physical examination such as the Adson test was thought to accurately diagnose TOS. The reason for its popularity and use is that it has been thought to be the only objective finding detectable on physical exam. By cutting off the radial pulse and eliciting neurologic symptoms by rotating the head and deep breathing, a pulse deficit was to be pathognomonic of TOS. Unfortunately, over time this test has been proven unreliable. It is prone to false positive results and the use of duplex ultrasound with these maneuvers has done little to improve its specificity [97].

Since the key symptoms have already been described, this section focuses on the techniques of diagnosing TOS subtypes.

Neurogenic TOS

Symptoms are most often of nerve irritation such as pain, paresthesia, and weakness in the arm and hand. Physical findings include tenderness over the scalene muscles, trapezius muscles, and anterior chest wall; a positive Tinel sign over the brachial plexus in the neck, and reduced sensation to very light touch in the fingers [93]. The use of common diagnostic tests such as electromyography or nerve conduction studies may be helpful, but usually are found to be normal or nonspecific in patients with neurogenic TOS [98]. A chest X-ray or neck X-ray is used to detect cervical ribs. Cervical MRI or CT scan can also detect cervical spine disease that can be associated with neurogenic TOS. MR neurography is another recent imaging technique that injects dye around the plexus to demonstrate deviations in its normal course [99]. More recently, evidence suggests that a reliable method of diagnosing neurogenic TOS is achieved by injecting neuromuscular blocking agents into the anterior scalene muscle at its attachment to the first rib [100]. Multiple studies have shown that injections of dilute lidocaine or bupivacaine in the anterior scalene muscle under ultrasound or computed tomography guidance are effective in mitigating symptoms associated with neurogenic compression within the interscalene triangle [101, 102].

Venous TOS

Symptoms include pain, discoloration, and swelling in the arm or hand associated with activity. It may present in variety of ways because there can be either acute versus chronic occlusion of the axillosubclavian vein. Acute symptoms may result from positional venous obstruction without thrombosis. Chronic obstruction from stenosis or an occlusive thrombus can lead to collateralization visible on exam. Duplex ultrasound or venography is commonly used to diagnose venous TOS. Venography has been shown to be more reliable than ultrasound [98].

Arterial TOS

Symptoms include pain, claudication, pallor, and poikilothermia in the affected arm or hand. Duplex ultrasound is the initial imaging choice, but conventional arteriography can also help with surgical planning in patients who have acute arterial insufficiency or ischemia. Since greater than 80 % of symptomatic patients with cervical ribs or other bony anomalies at the thoracic outlet are found to have evidence of arterial pathology [103], routine arterial imaging studies such as ultrasound, CT, and MR angiography can produce high quality images of the central vasculature (Fig. 11.9).

Management

Neurogenic TOS

Physical therapy is commonly initiated for neurogenic TOS since exercises to strengthen the muscles surrounding the shoulder and postural exercises help the patient to sit and stand straighter. Thus, it can potentially decrease the pressure on the neurovascular bundle in the

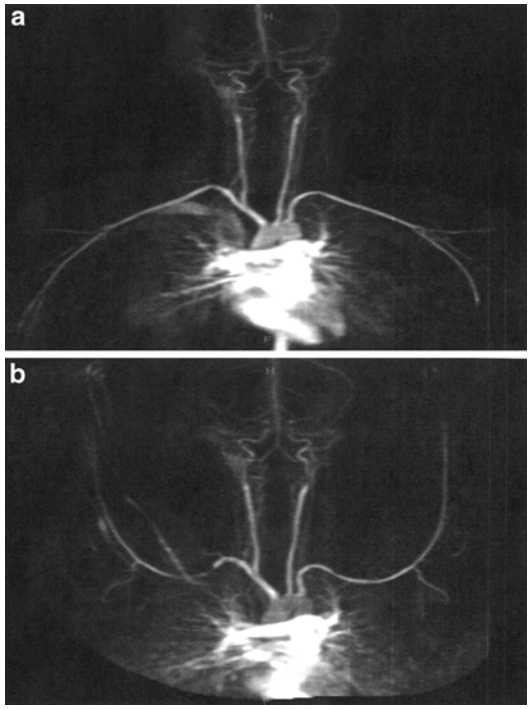

Fig. 11.9 MR Angiography: A 22-year-old with arterial TOS. There is *right* sided stenosis of the subclavian artery with arms abducted in frame b

thoracic outlet. Lidocaine or bupivacaine blocks in the anterior scalene muscle can mitigate symptoms. Botulinum toxin A (botox) using imaging guidance into the anterior scalene muscle has been suggested to provide more durable symptom relief than anesthetic blockade alone [104–106]. Patients who fail conservative treatment may be suitable candidates for surgical intervention aimed at relieving extrinsic compression of cervical nerve roots within the thoracic outlet, such as complete first rib resection and anterior scalenectomy (FRRS).

Venous TOS

Patients presenting with acute thrombosis are initially treated with catheter-directed thrombolytic therapy. Success rates for reestablishing subclavian vein patency are much higher provided thrombolysis is performed within 2 weeks of the onset of symptoms [107, 108]. Following restoration of patency, early or immediate surgical decompression of the thoracic outlet with FRRS has been shown to decrease the duration of symptoms without increasing complication rates [109–111].

Arterial TOS

For patients with mild acute arterial ischemia due to distal embolization from arterial TOS, catheter-directed thrombolysis may be appropriate. However, almost all symptomatic patients with arterial TOS require varying degrees of surgical intervention. Surgical embolectomy and thoracic outlet decompression by removal of bony abnormalities may be necessary. If arterial stenosis or dilation is severe, arterial reconstruction may be required, but is associated with significant morbidity.

For a complete summary of subtypes of thoracic outlet syndrome (TOS) and management, see Table 11.3.

Complex Regional Pain Syndrome (CRPS)

Description

Complex regional pain syndrome is a condition characterized by pain in a limb, in association with sensory, vasomotor, motor, and dystrophic changes. Pain is the leading symptom in CRPS, but is also often associated with limb dysfunction and psychological stress. It frequently arises after an injury, surgery, or vascular event such as stroke to the affected body region, commonly the extremities.

CRPS has been subdivided into Type I and Type II by the International Association for the Study of Pain (IASP) [112]. CRPS I (formerly known as reflex sympathetic dystrophy) corresponds to patients without a definable nerve injury; while CRPS II (formerly known as causalgia) occurs after damage to a peripheral nerve.

The inciting events of CRPS are most commonly fractures, sprains, and surgery. However, it has also been reported that injections, local infections, burns, frostbites, pregnancy, stroke, or

Table 11.3 Summary table of symptoms, diagnosis, and management of TOS

TOS subtype	Symptoms	Diagnostic studies	Medical management	Surgical management
Neurogenic	Pain, paresthesias of arm and hand	Chest X-ray Cervical spine X-ray Nerve conduction studies Lidocaine, botulinum toxin A blocks	Physical therapy Lidocaine or botulinum toxin blocks	FRRS
Venous	Pain, paresthesias from hand or arm swelling, vein collateralization on exam	Chest X-ray Cervical spine X-ray Duplex ultrasound CT venography Conventional venography	Anticoagulation/ thrombolysis	FRRS
Arterial	Pain, pallor in arm or hand. Claudication	Chest X-ray Cervical spine X-ray Duplex ultrasound CT angiography Conventional Arteriography	Anticoagulation/ thrombolysis	Cervical rib resection FRRS Possible arterial reconstruction Surgical embolectomy

FRSS first rib resection and scalenectomy, *TOS* thoracic outlet syndrome, *CT* computed tomography

myocardial infarction can precipitate CRPS [113–115]. No precipitating event was identified in 35 % of patients in one report [116].

The major characteristics of CRPS are sensory, autonomic, and motor disturbances. In terms of sensory disturbances, pain is classically out of proportion in both intensity and duration to the original trauma. Some distinct sensory abnormalities in CRPS are: dysynchiria (perception of pain or odd sensations when watching a mirror image of the unaffected limb being stimulated by light touch or pressure in a region that corresponds to an area of allodynia or paresthesia on the painful extremity), synchyria (perception of cold stimulus in both the affected and unaffected extremities when the stimulus is applied to the healthy limb in a region corresponding to an area of paresthesia), allochiria (a unilateral tactile stimulus is perceived only in the analogous location on the opposite extremity), and sensory extinction (simultaneous bilateral tactile stimulation is perceived in only one limb) [117, 118, 125]. Autonomic disturbances such as redness and swelling of the affected extremity are also common. Trophic changes include thin and shiny skin, brittle nails, and atrophy of muscles and bones leading to patchy osteoporosis or osteopenia which can be seen on X-rays. The vast majority of patients with CRPS I and II have some type of motor disturbance, most commonly weakness or limited active range of motion.

CRPS has been described in three clinical stages. The first stage is the acute phase where pain and sensory abnormalities such as sensitivity to touch or cold and localized edema occur. Vasomotor disturbances also occur with variable intensity, producing altered color and temperature. The second stage is marked by the dystrophic stage marked by soft tissue edema, thickening of skin and articular soft tissues, and muscle wasting. The third stage is the atrophic phase where motor and trophic changes progress while pain and sensory abnormalities decrease. There can be waxy trophic skin changes and brittle ridged nails. It is important to note however studies have not confirmed the existence of such stages, but instead suggested that there were distinct subtypes of CRPS [113].

Etiology

There are numerous etiological pathophysiological events that have been postulated in the development of CRPS including neurogenic inflammation, abnormal cytokine production, and altered blood flow. However, all such studies have not included appropriate controls and were limited in the number of patients that were studied.

Evidence That It Presents at Raynaud's

CRPS has a myriad of autonomic and motor disturbances but it can present similarly to Raynaud's when patients present with a cold, bluish, or pale extremity from the onset of symptoms. However, they will also commonly have hyperhidrosis or hypohidrosis which should not be seen in Raynaud's. The key difference from Raynaud's is that CRPS patients have persistent pain and allodynia and CRPS is commonly associated with an inciting injury.

Diagnosis

The diagnosis of CRPS is largely clinical, but it can be difficult early on because there may be a lack of objective findings. The IASP developed diagnostic criteria for CRPS but these have been found to have low specificity. Modified criteria otherwise known as the "Budapest Criteria" for CRPS have been validated to higher specificity that the initial IASP criteria [119]. The Budapest criteria state that all the following statements must be met: (1) The patient has continuing pain which is disproportionate to any inciting event; (2) The patient has at least one sign in two or more of the categories of "sensory, vasomotor, sudomotor/edema, motor/trophic disturbances"; (3) The patient reports at least one symptom in three or more of the four categories; and (4) no other diagnosis can better explain the signs and symptoms.

Patients with CRPS should first have a thorough neurological examination. Nerve conduction testing and electromyography should be done to exclude nerve entrapments or lesions. Autonomic testing can also be done by testing resting sweat output (RSO), resting skin temperature (RST), and quantitative sudomotor axon reflex test (QSART). A retrospective study of 396 patients compared the results of these types of autonomic testing, and showed that an increased RSO predicted the diagnosis of CRPS with a sensitivity and specificity of 94 and 98 % [120]. Autonomic testing with RST, RSO, and QSART can be costly and thus is commonly only used if the diagnosis is in doubt. Imaging studies such as scintigraphy may reveal increased uptake in the region of peripheral joints of the involved extremity [121]. A meta-analysis of 24 randomized trials that evaluated the effectiveness of three different imaging techniques in the diagnosis of CRPS type I supported the use of triple-phase bone scan in ruling out CRPS type I since it had a greater sensitivity and higher negative predictive value than MRI and plain films [122]. Plain radiographs of the involved extremity often demonstrate osteopenia.

Management

Since the etiology of CRPS is largely unknown, the mainstay of treatment is physical therapy and occupational therapy to improve range of motion and to avoid atrophy and contractures. Medical treatment for pain relief commonly includes analgesics and NSAIDs. A recent randomized controlled trial demonstrated that neridronate, a bisphosphonate, can significantly reduce spontaneous and stimulus-evoked pain and improve functional status in patients with early disease (<6 months duration) and abnormal uptake in 3-phase bone scintigraphy [123].

A recent Cochrane systematic review of the interventions for treating pain and disability in adults with CRPS was conducted and concluded that there was critical lack of high quality evidence for the effectiveness of most therapies for CRPS [124]. In fact, in this Cochrane review, the authors stated that there is moderate evidence that anesthetics and intravenous regional blockade with guanethidine are not effective. No randomized controlled trials have compared sympathectomy to placebo but it has been reported to be helpful in some patients [125].

Thus, if a patient is discovered to have CRPS, we would recommend initial physical and occupational therapy and common analgesics such as NSAIDs. In refractory cases, a bisphosphonate and/or regional blockade with anesthetic or sympathectomy can be considered on a case by case basis.

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Nailfold Capillaroscopy

12

Maurizio Cutolo and Vanessa Smith

Abbreviations

ACR	American College of Rheumatology
ANA	Anti-nuclear antibodies
CTD	Connective tissue disease
DM	Dermatomyositis
EULAR	European League Against Rheumatism
EUSTAR	Eular Scleroderma Trials and Research group
MCTD	Mixed connective tissue disease
NPV	Negative predictive value
NVC	Nailfold videocapillaroscopy
PPV	Positive predictive value
RP	Raynaud's phenomenon
SDS	Scleroderma spectrum
SDS	Scleroderma spectrum disease
SLE	Systemic lupus erythematodes
SS	Sjögren's syndrome
SSc	Systemic sclerosis
UCTD	Undifferentiated connective tissue disease
VEDOSS	Very early diagnosis of systemic sclerosis

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Key Points

1. Nailfold capillaroscopy evaluates capillary morphology non-invasively, and is a key investigation in separating primary from systemic sclerosis (SSc)-related Raynaud's phenomenon (RP).
2. Low-magnification techniques (stereomicroscope, dermatoscope, ophthalmoscope) allow global evaluation of the whole nailfold.
3. High-magnification videocapillaroscopy allows detailed observation of individual capillaries.
4. Qualitative assessment allows identification of the characteristic features of the "scleroderma pattern" (including giant capillaries, microhaemorrhages and capillary loss), and classification into "early", "active" and "late" scleroderma patterns.
5. (Semi)quantitative assessment allows measurement of the number of capillaries, and their dimensions.
6. Capillaroscopy is included in the 2013 ACR/EULAR classification for SSc.

Introduction

Capillaroscopy: From the Beginning up to Now

Nailfold capillaroscopy evaluates the morphology of capillaries and has been performed since the seventeenth century [1]. In the twentieth century

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optimisation of technical aspects, from the application of periungual oil to facilitate visualisation before capillaroscopic assessment, to the ability to capture images, and it is also during that era that literature describes the first morphologic distinctions between primary RP (not related to another condition) and secondary RP (mostly related to SSc) [2]. Two eminent schools emerged in the second half of the twentieth century and first quarter of the twenty-first century. First of all the school of Maricq with the wide-field technique applied capillaroscopy in a wide range of different settings, resulting in a vast publication list (see below) [3, 4]. Unforgettably she (together with LeRoy) first put forward the theory that morphologic capillaroscopic alterations in patients with the RP were harbingers of a future development of SSc [5]. Secondly, the Italian school with the most prominent name Cutolo launched the classification of capillaroscopic images in patients with RP and SSc that is widely used nowadays (see below) [6]. The last quarter of the twentieth century up until now has been booming years for further exploration of capillaroscopy [7]. In this way, half of the literature that has been published between 1927 and 2013 concerning RP and capillaroscopy (approximately 8,597 hits on Pubmed) has been published in the last 25 years. Notable hallmarks are studies focusing on the biomarker characteristics (=ability of capillaroscopy to predict future disease-related clinical complications) and practicability of the technique [8–12]. Additionally, first steps towards (semi)-automatisation of interpretation of capillaroscopic images have been taken [13]. Last but not least, corroborating the diagnostic role of capillaroscopy in patients with RP, capillaroscopy is now incorporated in the EULAR/ACR criteria for the diagnosis of SSc, as well as in the (very) early diagnosis of SSc [14–16].

Nailfold Capillaroscopy: Methods

What Is Nailfold Capillary Microscopy (Capillaroscopy)?

Capillaroscopy is a tool to examine the morphology of nailfold dermal papillary capillaries non-invasively. This is achieved by looking through the epidermis, after application of a drop of oil (Fig. 12.1a, b). The nailfold and especially its distal capillary row are suitable for capillary examination as its papillae run parallel to the surface of the nail. Subsequently the capillaries of the distal row are visible in their whole length and appear as red,

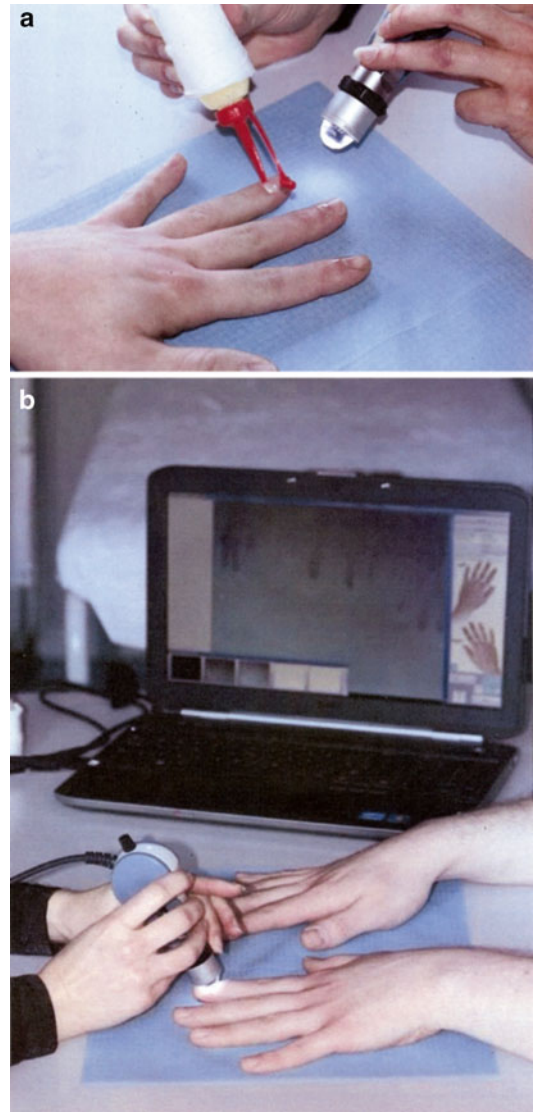

Fig. 12.1 (**a**, **b**) The nailfold videocapillaroscope. The morphology of the nailfold dermal papillary capillaries is being studied by first putting a drop of oil on the nailfold and afterwards putting the device (*lens*) on the nailfold. The capillaries can be immediately visualised on the screen of the computer

hairpin-shaped loops (consisting of an afferent limb, a transitional [or apical] limb and an efferent limb) that parallel the axis of the finger in a healthy subject. It is an indispensible tool (together with detection of anti-nuclear antibody and of antibodies specific for connective tissue diseases [CTD]) in the diagnostic work-up of patients with RP because it can distinguish primary (idiopathic) RP from secondary RP (see Chap. 6).

How to Perform Capillaroscopy

Techniques: The Wide-Field, High-Magnification and the (Semi)-automated Technique

Capillaroscopy may be performed with a lens with low and high magnification. The instruments with low magnification (e.g. stereomicroscope [magnification ×14], dermatoscope, ophthalmoscope) allow a global evaluation of the entire nailfold area (wide-field capillaroscopy) [17]. These instruments allow a panoramic vision of the whole nailfold microvascular network. In this way, prompt localisation of abnormalities and analysis of architectural characteristics are performed (pattern recognition or qualitative assessment). The videocapillaroscope not only allows low magnification but also has the advantage of sequential high magnifications (magnifications ×100, ×200, ×600) which enable detailed observations of separate capillaries. When using the videocapillaroscope with a magnification of ×200, four consecutive images of 1 mm per nailfold are often taken, in order to view representative sections of the whole nailfold. Next to the wide-field and the high-magnification technique the semi-automated nailfold videocapillaroscopy (NVC) has emerged recently. This technique combines the advantages of the two previous techniques: concomitant high magnification combined with a panoramic view of the whole nailfold, facilitated by frame registration software [13].

Number of Fingers to Be Studied

Different investigators have studied different numbers of nailfolds (e.g. 10 nailfolds, 8 nailfolds and 1 nailfold [finger 4]). For example, ten fingers have been evaluated in the seminal study describing "normal" capillaroscopic appearances in a study population of 800 healthy subjects by using stereomicroscope [18]. On the other hand, in the screening of a patient with RP with the manual capillaroscopic techniques with qualitative assessment (see below), examination of eight fingers is usually recommended [6]. This is based on the fact that there may be a high variability in morphology between fingers in patients affected by a secondary RP. Of note, the thumbs are usually spared in secondary RP [19] and not evaluated.

Interestingly, it is noteworthy that preliminary study on semiautomatic nailfold capillaroscopy has recently demonstrated the ability through quantitative assessment (see below) to separate healthy controls and patients with primary RP from secondary RP due to SSc by evaluating only one finger (ring finger of nondominant hand) [13].

Interpretation

The capillaroscopic images can be analysed qualitatively and (semi)-quantitatively.

Qualitative Assessment

In qualitative assessment (=pattern recognition) an overall interpretation is given after commenting on the visibility of the image, the morphology of the capillaries, the density and dimensions of the capillaries and the architecture [20]. Pattern recognition is the same process that allows recognition of a familiar face or voice [18]. It readily allows the clinician to distinguish normal and non-specific changes (in patients with primary RP [see below]) from an abnormal capillaroscopy due to a secondary RP due to SSc (see below). NVC, dermatoscopy as well as preliminary (semi)-automated capillaroscopy have in common that they are all able to discern a normal capillaroscopy from the specific changes found in SSc through pattern recognition [13, 21, 22].

(Semi)-quantitative Assessment

In quantitative assessment measurements can be made of certain characteristics of individual capillaries. For example, the diameter of capillaries can be quantified [23, 24]. Notably, capillary diameters in patients with secondary RP due to SSc are significantly larger than those in primary RP or healthy controls [23]. Also the number (and other characteristics [see below]) of capillaries can

be measured either manually or semi-automatically. These can be reported through scores (semi-quantitative assessment) or as numbers per unit of quantity (e.g. per mm) [10, 13, 23]. Of note, the number of capillaries per mm is the most powerful predictor between a primary and secondary RP due to a scleroderma spectrum disorder [23, 25]. A recent important preliminary development is the semi-automated quantitation of capillary characteristics, performed on images acquired using a computer-based system [13]. Next to being less time consuming than manual quantitation an additional advantage of this technique is the fact that repeat images over time from the same patient can be compared. The latter may be a quality that facilitates monitoring. Semi-automated quantitation (based on the following features: width of capillaries, tortuosity, derangement and intercapillary distance) identifies differences between patients with primary RP and those with SSc [13].

Manual quantification of capillaroscopic characteristics is used in secondary RP as biomarker and as outcome measure. In this way quantification has been used to predict development of future digital trophic lesions in patients with secondary RP due to SSc [8, 26, 27]. In addition, it has been used as outcome measure in trials with vasomodulating therapy in a patient population with RP [27–30].

Investigation of a Patient with RP: Role of Capillaroscopy

Early Distinction Between a Primary and Secondary RP Due to SSc

Medical doctors are frequently referred patients with RP, a frequent symptom in the general population. The challenge is to distinguish patients with a primary RP (not connected to any CTD) from patients with a secondary RP (due to a CTD). Literature attests through both cross-sectional and short- and long-term prospective follow-up that about 13.6 % of patients presenting with RP as the only initial symptom will develop a CTD [31, 32]. 12.6 % go on to develop SSc and only 1 % develops another CTD (such as systemic lupus erythematosus [SLE]) [31]. Consequently the key point in evaluating a patient with RP is to detect those who will further on develop SSc. In 1992 LeRoy and Medsger proposed criteria to distinguish primary from secondary RP due to SSc [5]. Key criteria for primary RP are to have a negative anti-nuclear antibody (ANA) factor and normal nailfold capillaries. Key criteria for a secondary RP due to SSc is to have specific capillaroscopic alterations (the scleroderma pattern) and the presence of SSc-specific antibodies. Retrospective validation of these criteria allows correct classification of a patient in one clinical consultation in 89 % [33]. A 20-year prospective study of 586 patients with only RP at baseline demonstrated a positive predictive value (PPV) of 79 % and a negative predictive value (NPV) of 93 % of these criteria at last follow-up [31]. Of note, capillaroscopy does not play a pivotal role in detecting CTD other than SSc in a patient population with merely the RP as presenting system (see below).

What Is Normal in Primary RP?

A normal capillaroscopic pattern, by qualitative assessment, is characterised by a homogeneous distribution of hairpin-shaped capillaries as a "comb-like structure", with a density of between 9 and 14 capillaries per mm (Fig. 12.2) [17, 18]. Yet, there exists a wide intra- and inter-individual variation in a normal population. The manuscript by Andrade et al. described the range of normal in 800 healthy subjects [18]. These authors evaluated ten nailfolds per subject with the wide-field technique. Apart from the stereotype hairpin-shaped open loop, there are common subtle morphological variations in the distal row capillaries and additionally unusual distinctive morphological alterations that are considered as anomalies (=pathological findings) (see Table 12.1). Importantly, anomalies must occur isolated or in a very low prevalence within a subject in order to be able to interpret the image as still being normal. When anomalies occur in a high prevalence within a subject or when several types of anomalies occur together the odds are high that there is an underlying microangiopathy (secondary RP). In this way Andrade et al. showed that only 8 % of healthy subjects presented two types of anomalies and even less (1 % of healthy subjects)

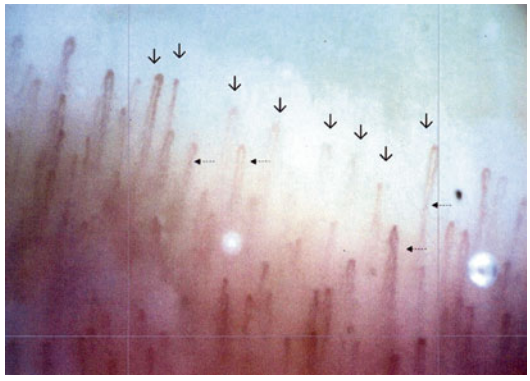

Fig. 12.2 Normal and non-specific changes in a patient with primary RP. *Image*: Finger 4 left. *Description*: qualitative assessment. *Magnification*: ×200. *Morphology*: Open, hairpin and crossing (*dashed arrow*). *Dimensions*: Within normal limits. *Architecture and distribution*: Capillaries are regularly arranged in a parallel fashion. *Number*: 8/mm (the grid width is exactly 1 mm). *Interpretation*: Capillary image with some non-specific changes (*crossing*). This patient was ANA negative suggesting (in combination with the capillaroscopic appearances) a diagnosis of primary RP

showed three types of anomalies, whilst a single anomaly occurred in 25 % of healthy subjects.

Of note with the videocapillaroscopic technique the above-described subtle alterations have been defined as being non-specific (see also below) [34]. Additionally, for simplicity the anomalies in morphology have been categorised as (neo)angiogenesis (see Table 12.2) [26].

Table 12.1 Capillaroscopic findings in healthy subjects (after Andrade et al. [18]), wide-field technique

Stereotype open loop	*Hairpin shape*
Subtle alterations	*Tortuous* (the limbs are curled but do not cross)
	Crossed (the limbs cross each other once or twice)
	Cuticulitis (the limbs are not visible; only tiny red dots in high density are apparent)
Anomalies	*Ectasia* (limbs are moderately enlarged, about four times the normal width, or with the diameter of a limb >20 μm)
	Megacapillary (aneurysmatic loop, with the width of limbs ten times the normal one)
	Meandering (the limbs are crossed upon themselves or with each other several times)
	Bushy (the limbs originate small and have multiple buds)
	Bizarre (striking atypical morphology although not conforming to the four previous defined categories)

Table 12.2 Definitions describing capillaroscopic characteristics with the wide-field and videocapillaroscopic technique [18, 26, 34]

<table>
<tr><th colspan="2">Widefield technique</th><th colspan="2">Videocapillaroscopic technique</th></tr>
<tr><td colspan="4">1.Stereotype open loop = hairpin shape</td></tr>
<tr><td rowspan="3">2.Subtle alterations</td><td>Tortuous</td><td rowspan="3">Non specific changes in morphology</td><td rowspan="3">2.Normal and non specific changes</td></tr>
<tr><td>Crossed</td></tr>
<tr><td>Cuticulitis</td></tr>
<tr><td rowspan="5">3.Anomalies</td><td>Ectasia</td><td>Non specific changes in dimension</td></tr>
<tr><td>Megacapillary</td><td>Giant</td><td rowspan="4">3.Anomalies</td></tr>
<tr><td>Meandering</td><td rowspan="3">Neoangiogenesis</td></tr>
<tr><td>Bushy</td></tr>
<tr><td>Bizarre</td></tr>
</table>

What Are Pathognomonic Abnormalities in Patients with RP Due to SSc?

Patients with RP who have an underlying clinically recognisable (=with skin involvement) SSc show a very characteristic combination of capillary abnormalities in the nailfold, which can easily be assessed through qualitative assessment (=pattern recognition). Maricq et al. described with the wide-field microscope technique (magnification ×12–14) the scleroderma pattern [4]. This pathognomonic combination contains the following: a striking widening of all three segments of the capillary loop (arterial, venous and intermediate), loss of capillaries and disorganisation of the nailfold capillary bed. Many branched "bushy" capillaries may also be observed. Through quantitative assessment, a decreased capillary density has been shown to be the best predictor of a secondary RP due to a scleroderma spectrum (SDS) disease. More specifically, the loss of capillaries to a number of lower than 30 capillaries per 5 mm (=one nailfold) has a specificity of 92 % [25].

In 2000, Cutolo et al. qualitatively assessed the nailfolds of an SSc cohort of patients fulfilling the American College of Rheumatology (ACR) criteria for SSc with the NVC technique (magnification ×200) (Figs. 12.3, 12.4 and 12.5). According to the different proportions of the hallmark parameters of the scleroderma pattern (giants, capillary loss,

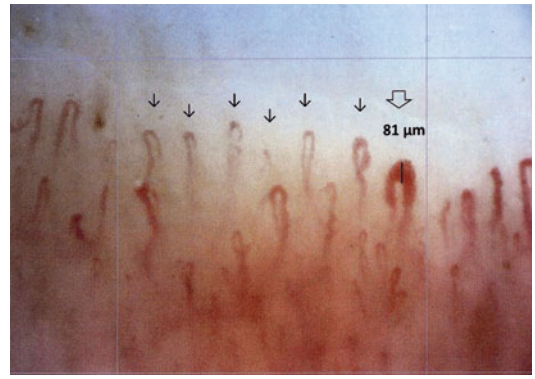

Fig. 12.3 An early scleroderma pattern belonging to a patient with puffy fingers, RP and ANA+. *Image*: Finger 3 right. *Description*: Qualitative assessment. *Magnification*: ×200. *Morphology*: Open shape of capillaries. Presence of a haemorrhage (outside the grid). *Dimensions*: Giant (*open down arrow*) (cfr. measurement of transitional segment of the one marked capillary=81 µm). *Architecture and distribution*: Slight derangement of capillary architecture. *Number*: 7/mm. *Interpretation*: The combination of minimal reduction of capillaries, haemorrhage and giant capillary is representative of the "early" scleroderma pattern. The patient meets the criteria for very early diagnosis of SSc

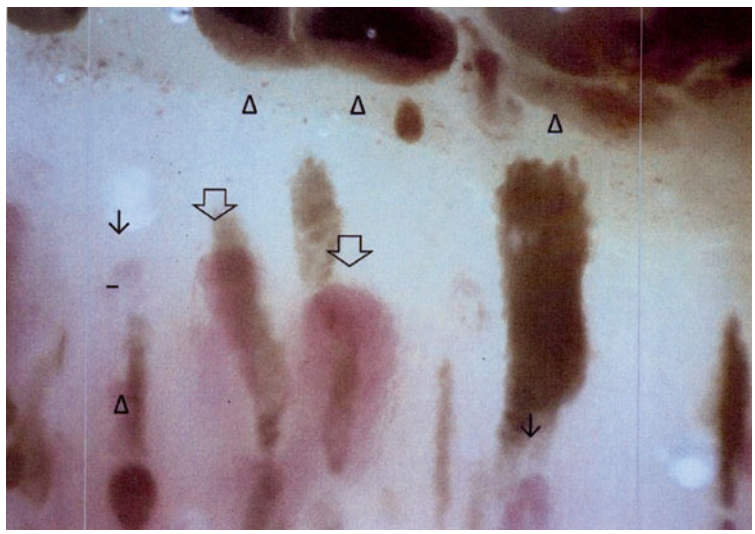

Fig. 12.4 An "active" scleroderma pattern belonging to a patient with diffuse cutaneous SSc. *Image*: Finger 2 right. *Description*: Qualitative assessment. *Magnification*: ×200. *Morphology*: Open shape of capillaries. Presence of haemorrhages (*open triangle*). *Dimensions*: Ectasia (*dash*), giant capillaries (*open left headed arrow*). *Architecture and distribution*: No derangement of capillary architecture. *Number*: 4/mm. *Interpretation*: The combination of reduction of capillaries, haemorrhage and giants is representative of the "active" scleroderma pattern

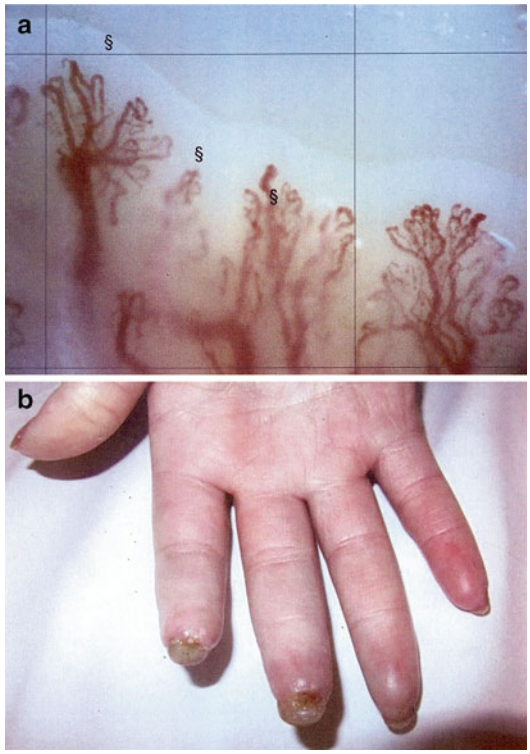

Fig. 12.5 A "late" scleroderma pattern in a patient with limited cutaneous SSc and digital ulcers. *Image*: Finger 4 left hand (**b**) *Description*: Qualitative assessment (**a**) *Magnification*: ×200. *Morphology*: Three neoangiogenetic capillaries (*section symbol*). *Dimensions*: Diameter of loops falls within the range of normal (<20 μm). *Architecture and distribution*: Derangement. *Number*: 3/mm. *Interpretation*: The combination of reduction of capillaries and ramification is characteristic of the "late" scleroderma pattern

Table 12.3 Scleroderma patterns according to Cutolo et al. [6]

Early	The combination of a few giant capillaries, few capillary microhaemorrhages, no evident loss of capillaries, and relatively well-preserved capillary distribution
Active	The combination of frequent giant capillaries, frequent capillary microhaemorrhages, moderate loss of capillaries, absent or mild ramified capillaries with mild disorganisation of the capillary architecture
Late	The combination of almost absent giant capillaries and microhaemorrhages, severe loss of capillaries with extensive avascular areas, neovascularisation with ramified/bushy capillaries, and intense disorganisation of the normal capillary array

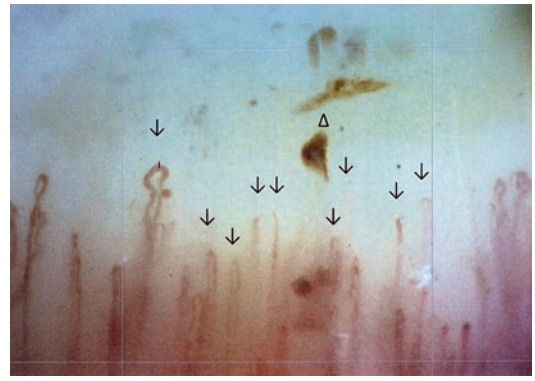

Fig. 12.6 Non-specific changes hinting at microangiopathy (secondary RP). *Image*: Finger 4 left. *Description*: Qualitative assessment. *Magnification*: ×200. *Morphology*: Open, hairpin. Presence of a non-punctate haemorrhage (*open triangle*). *Dimensions*: Some ectasia (*dash*). *Architecture and distribution*: The capillaries lie parallel to each other. *Number*: 9/mm. *Interpretation*: Presence of combination of non-specific alterations: non-punctate haemorrhage (pathological), non-specific change in dimension: ectasia. This combination may indicate microangiopathy

haemorrhages and (neo)angiogenesis [definitions, see below]) Cutolo et al. defined three patterns "early", "active" and "late" (see Table 12.3) [6].

Giant Capillaries

Homogeneously enlarged microvascular loops (giant capillaries) are the earliest and most striking feature of secondary RP. The enlargements show a characteristic symmetrical shape involving afferent, transitional and efferent branches of the capillary (diameter >50 μm), or a horseshoe shape (with the diameter of the transitional limb being wider than the other two limbs) [20].

Microhaemorrhages

Microhaemorrhages appear as easily detectable dark spots and arise from microvascular extravasation of red blood cells from the capillary loop. They are believed to bridge the appearance of giant capillaries, their impending collapse and the subsequent loss of capillaries. Of note, punctate haemorrhages may occur in healthy controls. All other types of haemorrhages (see Fig. 12.6) are likely to reflect microangiopathy.

Capillary Loss

Logically, as SSc is a microobliterative disease, there is a lowered capillary density. The number

of capillaries can be evaluated in several ways. In a recent, pan-European multicentre study (59 participating centres), capillary density was measured by counting the capillaries linearly over 1 mm [26].

(Neo)angiogenesis

Further on in the disease course neoangiogenesis and abnormal morphologies occur [6]. Highly convoluted and branched capillary loop clusters, surrounded by a dropout of normal capillary loops, are characteristic features of (neo) angiogenesis in SSc. Per consensus, (neo) angiogenesis has been defined as all morphologies that are not the stereotype hairpin morphology, or the subtle non-specific changes (tortuous or crossing) (see Table 12.1) [26].

Of note, these scleroderma-type changes may also be seen in diseases, other than clinically recognisable SSc, such as in patients with "early" SSc (see below), dermatomyositis (DM), mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD), even though in much lower prevalences than in SSc [35, 36]. Maricq et al. suggested that all these diseases may share some common pathogenetic factors and referred to these diseases as the family of SDS disorders. Contrarily to ([very] early) SSc the sensitivity of capillaroscopy in DM and MCTD is too low to be able to regard capillaroscopy as a diagnostic tool (see below) [37].

What Capillaroscopic Images Do We Find in Patients with RP and CTD Other than SSc?

RP occurs in other CTD than SSc, even though in lower prevalences [38]. This lower prevalence may be a reason why capillaroscopy does not play a major role in prediction of future development of a CTD other than SSc. In this way a recent prospective study could not show any predictive value of capillaroscopy in RP patients who eventually developed a CTD other than SSc [37]. Capillaroscopy also does not play a discriminant role in distinguishing patients with primary or secondary RP due to CTD other than SSc [17, 39]. In contrast with the SDS disorders, the other CTD, such as SLE, and Sjögren's syndrome (SS), do not have "unique" or "specific" capillary patterns [37]. A variety of capillary abnormalities have been observed, for example lowered capillary density, avascular areas, elongated capillaries, widened loops, prominence of the subpapillary plexus, haemorrhages, bushy capillaries and bizarre capillaries, which in contrast to SSc do not occur in specific combinations [34]. These abnormalities by themselves are not predictive of any defined condition and may be referred to as non-specific. Additionally, next to the variety of capillary abnormalities a significant proportion of patients with RP and CTD other than SSc show the stereotype hairpin or subtle morphological changes (tortuous and crossing) as the dominant morphological pattern [34]. As these subtle morphological changes can occur in a healthy normal population and also in certain CTD, they too are denoted to be non-specific [34].

"Early" Diagnosis of SSc

Systemic sclerosis is a rare multisystemic CTD characterised by microvascular damage, specific immunologic abnormalities (i.e. presence of ANA and SSc-specific auto-antibodies) and progressive fibrosis of skin and internal organs. Microvascular damage and SSc-specific antibodies are usually present years before the clinically overt disease. In this way, the first specific microvascular SSc-specific change predictive of future development of SSc is the presence of a giant capillary [31]. Secondly, clinically overt disease occurs with capillary loss (lowered capillary density) [31]. Further on in the disease neoangiogenesis occurs [6]. A patient with only RP at baseline, but with the combination of SSc-specific changes on capillaroscopy and the concomitant presence of an SSc-specific antibody, will in 5 years transition to SSc in 65.9 % and in 10 years follow-up in 79.5 % [31]. Moreover even merely evaluating SSc-specific capillaroscopic changes in a patient with RP at baseline may be informative of future development of SSc [40]. Of note, highlighting the role of ANA and SSc-specific microvascular changes recently the VEDOSS (very early diagnosis of systemic sclerosis) criteria (in which RP, puffy fingers, ANA and capillaroscopic changes ply a central role) have been published to very "early" detect SSc. These criteria are based on expert opinion, obtained through three Delphi rounds within an international forum of experts in SSc,

and are currently being validated [15]. These criteria run in line with the LeRoy's criteria but differ as to the extent of cutaneous signs of the disease [16]. In this way next to SSc pattern on capillaroscopy and SSc-specific antibodies, like the LeRoy's criteria, also puffy fingers are a hallmark criterion in the VEDOSS criteria.

How Often Should Capillaroscopy Be Performed in a Patient with RP?

The frequency of performing capillaroscopy in a patient with RP varies between and within countries and also may depend on the availability of antibody detection. If the capillaroscopy does not show a scleroderma pattern and if all SSc-specific antibodies are negative then the chance to transition to a secondary RP due to SSc is only 1.8 % after long-term follow-up. In such cases patients can be reassured [31]. If not all SSc-specific antibodies are at hand, then every 6-month follow-up is required, as 16 % of patients may transition to a scleroderma pattern within 5 years of follow-up [41].

Relationship Between Altered Peripheral Blood Flow and Altered Capillaroscopy in Secondary RP

Capillaroscopy generally provides static information on microvascular involvement (morphologic alterations). Laser blood flow analysis provides dynamic information on microvascular involvement as it measures reactivity (flow) (see Chap. 13). Both tools have been used in the evaluation of RP and treatment trials in patients with RP and SSc-related digital vasculopathy. In addition severity of microangiopathy in SSc has been correlated with peripheral blood flow [42, 43].

Expert Opinion

Nailfold capillaroscopy is a readily available non-invasive bedside examination tool that provides a view of the microcirculation in patients with RP. The morphology of the nailfold capillaries can distinguish primary RP from secondary RP due to SSc. The current "gold standard" method to use is NVC, but for the practicing physician without access to this, then a dermatoscope, ophthalmoscope or (when available) a stereomicroscope will allow detection of the more obvious abnormalities. All are safe, non-invasive tools. We recommend NVC if available and if not, then dermatoscopy (but with limitations). High-magnification NVC images can be assessed qualitatively and scored (semi)-quantitatively in order to assess the status of the microcirculation, defining severity and providing insights into associated clinical consequences.

Although non-specific findings can occur in healthy controls, primary RP and various causes of secondary RP, specific patterns of microangiopathy (scleroderma patterns) can be observed by nailfold examination in patients with SSc or another SSc-spectrum disorder, e.g. dermatomyositis. In addition, unique nailfold capillary changes seen in patients presenting with RP can provide predictive value to determine who will go on to develop SSc, or who have early SSc, namely the "early", "active" and "late" patterns. Nailfold capillary morphology can provide a view of the status of the underlying peripheral microvasculature in patients with SSc. In addition, the microvascular alterations that characterise the scleroderma patterns are thought to reflect the dynamic and progressive vascular damage which occurs in SSc. The three different NVC patterns are associated with progressive peripheral blood flow impairment as can be assessed by laser Doppler. It is likely that in the near future, nailfold videocapillaroscopy may be used increasingly in longitudinal studies of patients with SSc, examining sequential changes to define vascular disease activity and to guide therapeutic decisions. Last but not least, corroborating the diagnostic role of capillaroscopy in patients with RP, nailfold capillaroscopy is now incorporated in the new EULAR/ACR criteria (2013) for the diagnosis of SSc, as well as in the (very) early diagnosis of SSc, improving both specificity and sensitivity of criteria.

Conclusion

Capillaroscopy (together with SSc-specific antibodies) plays a pivotal role in detection of patients with RP prone to develop SSc. Within

patients with secondary RP it also has a role in prediction of clinical complications and monitoring of therapeutic trials. Development of (semi)-automatic techniques is central on the research agenda.

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Non-invasive Methods of Assessing Raynaud's Phenomenon

13

Andrea Murray and John D. Pauling

Abbreviations

ABPI	Ankle brachial pressure index
CST	Cold stress test
DDD	Distal-Dorsal difference
EDV	End diastolic velocity
FSP	Finger systolic pressure
IRT	Infrared thermography
LD	Laser Doppler
LDF	Laser Doppler flowmetry
LDI	Laser Doppler imaging
LSCI	Laser speckle contrast imaging
NCM	Nailfold capillary microscopy
PORH	Post-occlusive reactive hyperaemia
PRP	Primary Raynaud's phenomenon
PSV	Peak systolic velocity
RP	Raynaud's phenomenon
SRP	Secondary Raynaud's phenomenon
SSc	Systemic sclerosis

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Key Points

1. Several non-invasive methods can be used to assess digital vascular structure and function objectively: these include infrared thermography laser Doppler techniques, Doppler ultrasound, finger systolic pressure measurement and plethysmography.
2. Non-invasive methods can differentiate between primary and secondary RP provide insights into pathophysiology, and monitor treatment response (although further work is required to validate them as outcome measures).
3. Recent developments in infrared thermography and laser Doppler systems are increasing their accessibility to clinical researchers: as a result they are being more widely applied in research studies of RP.
4. Lack of consensus on a standardised approach to imaging protocols often prevents useful comparison between studies: larger multi-centre studies are required using agreed protocols and including assessment of reproducibility.
5. A number of exciting new technologies are emerging which hold further promise for the objective assessment of digital vascular structure and function.

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Introduction

Attacks of Raynaud's phenomenon (RP) are typically associated with digital cutaneous colour changes, reflecting the perfusion and oxygenation of digital blood during attacks. In light of the episodic nature of RP, it is unusual for clinicians to have the opportunity to witness evidence in the clinical setting (Fig. 13.1). A characteristic history of RP is sought from patients to determine its likelihood. A history of increased insensitivity to cold and the presence of two digital colour changes is used to diagnose RP (see Chap. 2) [1]. Vasoconstriction in response to cold exposure is, however, an important component of thermoregulation leading an early twentieth century physician to dryly observe "we are all subjects of RP to a greater or lesser degree" [2]. Most of the healthy population will have experienced symptoms of RP in response to sufficient cold exposure and establishing a diagnosis based on patient self-report carries a risk of misdiagnosis. Similarly, underreporting of RP symptoms may falsely reassure clinicians managing patients early in the course of conditions such as systemic sclerosis (SSc). A great deal of work has therefore been undertaken to attempt to develop objective methods for assessing and diagnosing RP.

A similar reliance on patient self-report has emerged in the assessment of Raynaud's severity. Self-report measures of RP are subjective and heavily influenced by factors such as seasonal variation, health beliefs, coping skills, habituation and psychological factors. They require prolonged periods of assessment with the subsequent potential for "diary fatigue". To date, no objective methods of assessing digital microvascular perfusion have been recommended for use in therapeutic trials of RP despite the obvious merits of such an approach [3].

In this chapter, we review objective methods for assessing both microvascular and macrovascular structure and function in RP. While some have both clinical and research applications, most are currently used in research. An emphasis is placed on those that facilitate functional assessment of the vasculature in RP. We review the contribution of these methods in disease classification, in developing our understanding of the pathogenesis of RP and the potential value of such methods as objective tools in therapeutic trials of RP. Before describing the various imaging tools, we first discuss some of the considerations, common to all techniques, which are required when undertaking vascular imaging studies in RP.

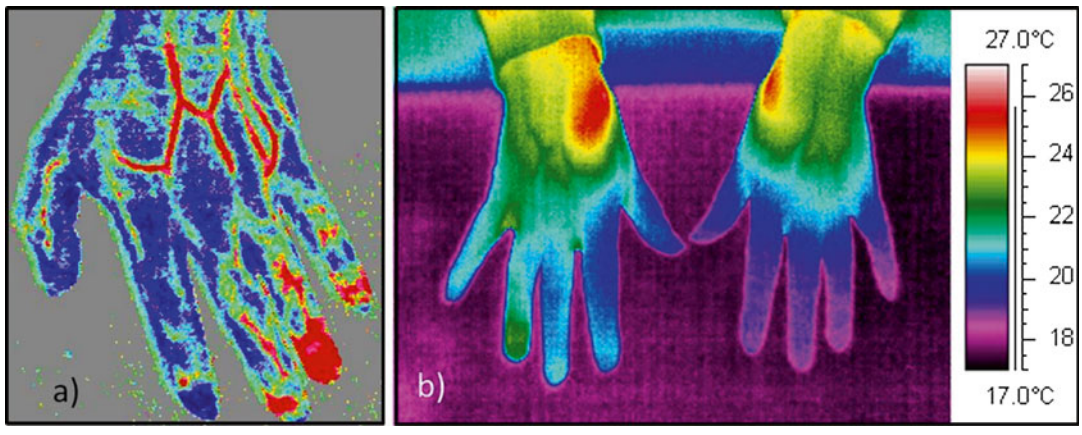

Fig. 13.1 Captured images of a Raynaud's attack. Taken with (**a**) LDI (*blue* representing relatively low blood flow and red relatively high flow; (**b**) IRT (temperature scale on the *right* hand side). Both LDI and IRT images show *Right* hand showing partially re-perfused/rewarmed fingers with index finger being vasoconstricted

Considerations When Undertaking Vascular Imaging Studies

Considerations for Baseline Assessment

Given the requirement for measurements to be independent of external environmental conditions, it is important to follow a standardised approach to vascular imaging, whatever the method, to reduce variation and the contribution of confounders [4–6]. Subjects should be asked to avoid vasoactive mediators such as alcohol, vigorous exercise, caffeine and nicotine for a minimum of 4 h prior to assessment [7, 8]. Imaging should be undertaken in a temperature-controlled laboratory. The room air temperature should be monitored throughout and ideally maintained at an ambient 23 °C (±0.5 °C). Higher room temperatures may lead to sweating (and evaporative cooling), whereas lower temperatures are likely to enhance normal sympathetic control of vascular smooth muscle tone. There should be an equilibration period, at rest, of at least 20 min to allow subjects to acclimatise under a steady state temperature before undertaking baseline vascular imaging assessment. Cross-sectional studies should allow for the effects of age and gender on blood flow [9–12]. Longitudinal studies should also, where possible, take account of circadian, seasonal and female hormonal changes, the last two of which may be of particular importance in RP [10, 13, 14].

Provocation Testing to Assess Functional Vascular Responses

Since the abnormalities in blood vessels of patients with RP are primarily functional (although patients with secondary RP [SRP] can also have structural change), dynamic provocation tests are often incorporated to provoke a change in the blood flow that can be quantified. The most widely evaluated provocation test is the cold challenge (or cold stress test, CST), which was developed to assess sympathetic vasoconstriction to cold exposure [15]. The CST seldom precipitates an attack of RP in vivo (in order to avoid discomfort for the patient) but provides useful insight into local microvascular reactivity to cold exposure that baseline assessment alone cannot provide and the CST has been used to aid disease classification [16–20]. The test typically involves placing gloved hands (to avoid evaporative cooling) into a water bath and monitoring the recovery patterns of rewarming. Total body cooling has been less extensively evaluated [21]. The temperature chosen for CST is not critical providing the test is standardised across all subjects studied. Temperatures of 20 °C have been used successfully and have the advantage of allowing rapid recovery of temperature in all but the more severely affected subjects [22, 23]. Lower temperatures of 15 °C have also been successfully used [24]. It is generally agreed that temperatures above 20 °C (approaching room temperature) would provide too mild a stimulus to promote vasoconstriction. Temperatures below 15 °C should be avoided as the level of stimulus may be unnecessarily uncomfortable for patients with RP. Furthermore, temperatures of <13 °C can result in cold induced vasodilatation secondary to loss of vascular smooth muscle contractility and reduced release of neurotransmitters from sympathetic nerves leading to paradoxical vasodilation [25]. Local heating has also been used to assess maximal vasodilation [26, 27] and local heating has been used alongside a CST [24, 28]. Local heating has been shown to induce vasodilation by two different mechanisms. Initial peak vasodilation is due to axon reflex-dependent hyperaemia and is followed by a more prolonged nitric oxide-induced increase in perfusion [15]. Other methods for inducing hyperaemia include examining functional changes following vascular occlusion (post-occlusive reactive hyperaemia [PORH]) [29, 30], which identifies structural changes and/or damage to macrovascular smooth muscle function. Local percutaneous administration of ionised chemicals via application of low electric current (μA), known as iontophoresis, can be used to induce local endothelial-dependent or non-endothelial-dependent vasodilation [31–35].

Vasodilators have also been applied topically [36] to skin or injected [37]. Other physiological tests have been proposed such as arm movement tests which allow assessment of the venoarteriolar reflex [38]. Each of these dynamic studies greatly expand the number of potential endpoints which include absolute perfusion differences from baseline, relative changes and assessment of curve characteristics such as area under the curve, maximum/minimum perfusion and gradients of slopes.

Methods for Assessing the Vasculature in RP

Table 13.1 summarises the major non-invasive methods for assessing vascular structure and function (i.e. perfusion) in RP. Nailfold capillaroscopy is considered separately in Chap. XX. The basic principles and their application in the assessment of RP are described in further detail here.

Infrared Thermography

Infrared thermography (IRT) cameras quantify IR emissivity to estimate the surface temperature of an object [6]; they are used clinically for the assessment of RP. IRT cameras operate in a similar manner to those in the visible wavelength range that are used to take video and photographs; however, they have sensors sensitive to the infrared portion of the electromagnetic spectrum (in the region of 9–12 μm) rather than those wavelengths observed by eye (approximately 400–1,000 nm). Changes in skin temperature due to cutaneous perfusion and hence blood convection are detected by IRT, providing a safe, non-invasive, indirect measure of cutaneous microvascular function [39]. The emergence of affordable uncooled focal plane arrays and the subsequent digitalisation of image processing has facilitated near real-time thermographic assessment, greatly expanding the application of thermal imaging in both industry and medicine.

IRT in the Assessment of RP: Physiological Studies

The majority of thermographic studies of RP have incorporated a CST. The major limitations of using IRT to assess microcirculatory responses to CST include the direct effects of conductive and convective heat exchange on surface skin temperature, and limited temporal resolution with delays translating alterations in microvascular tone into changes in surface skin temperature. The majority of IRT studies of RP have examined the hands, although studies of the feet have been reported [40]. The dorsum of the hands is typically assessed (for ease) although IRT assessment of the dorsal and palmer aspects of the hands do not generally differ significantly [41].

A major challenge when comparing the results of individual IRT studies of RP lies in the diversity of the IRT protocol and the conditions of provocation tests such as the CST [42]. Winsor and Bendezu made the first attempts to use IRT to assess peripheral circulatory diseases in the early 1960s [43]. The principle aim of early work was to differentiate between healthy controls and patients with RP. It was noted that subjects with RP often exhibit cooler fingers (dorsal aspect of the index to little fingers) in relation to the more proximal dorsum of the hands (radiocarpal to metacarpal joints of dorsum) at baseline (Figs. 13.2 and 13.3) [44]. This negative "thermal gradient" (when the mean temperature of the dorsum of the hands was subtracted from the temperature of the fingers) could be amplified by undertaking a local CST and taking a second thermal image following a 10 min recovery period. In contrast, the opposite was found in healthy controls, in whom the temperature of the digits at baseline was typically higher than the dorsum of the hand and amplified 10 min following CST due to a healthy hyperaemic response [4] (Fig. 13.2). This positive "thermal gradient" is caused by greater perfusion within glabrous (from Latin for hairless) regions of skin, such as the fingertips, which are densely populated by thermoregulatory arteriovenous anastamoses [45]. Non-glabrous skin, such as that of the dorsum of the hands, has few, if any, arteriovenous anastamoses.

Table 13.1 Non-invasive clinical and research techniques for assessing Raynaud's phenomenon

Technique	Method	On-going developments	Microvascular or macrovascular	Clinical uses	Research uses
Nailfold capillaroscopy (NCM)	Direct visualisation and measurement of nailfold capillary structure (including size) and morphology	Automated measurement of capillary structure, blood flow and oxygenation	Microvascular	Visualising capillaries for differentiation of PRP and SRP (qualitative/semi quantitative analysis)	Measurement of capillary size and assessment of shape/pattern to monitor progression of disease
IRT	Measuring skin temperature as an indirect measure of blood flow		Microvascular	Differentiation of PRP and SRP (in combination with temperature challenge)	Progression of disease and response to treatment
Laser Doppler flowmetry and imaging (LDF and LDI) and laser speckle contrast imaging	Measuring relative skin perfusion	Dual wavelength, line scanning and whole field techniques	Microvascular		Differentiation of PRP and SRP, progression of disease and response to treatment
Arterial Doppler ultrasound (US)	Measuring flow in upper and lower limb arteries including fingers (waveform and pressures), measuring vessel flow and size	Colour Doppler imaging of vessels	Macrovascular (arterial)	Assessing macrovascular dysfunction due to, e.g. arterial blockage (ABPI)	Differentiation of PRP, SRP and HC in response to challenges, assessing response to treatment, imaging of vessels
Finger systolic pressure (FSP)	Measuring digital systolic pressure in response to dynamic temperature challenge, usually cooling		Macrovascular		Combined with dynamic challenges to compare between PRP and SRP and in response to treatment
Plethysmography	Measures changes in venous blood volume/flow and allows determination of circulatory capacity		Macrovascular (venous)		Assessing differences in PRP and SRP and pathophysiology. Response to therapeutic intervention

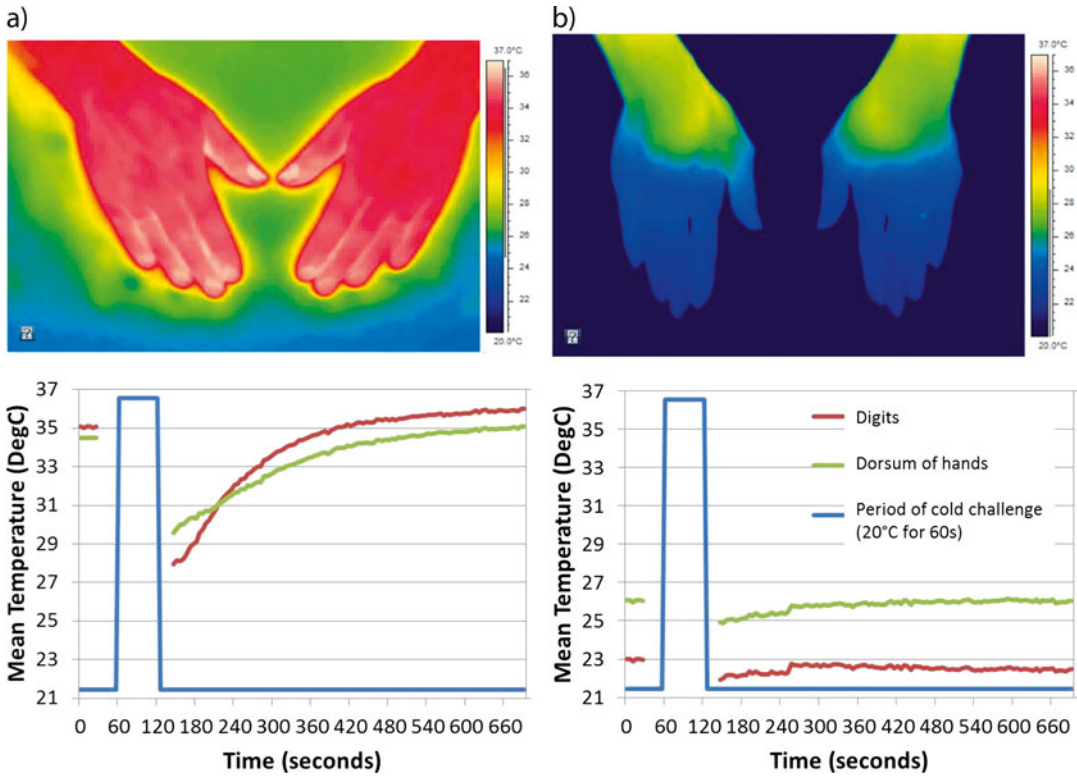

Fig. 13.2 IRT images of the dorsum of the hands at 23 °C with accompanying rewarming curves generated over 10 min following cold challenge in (**a**) a healthy control and (**b**) Raynaud's phenomenon. In the healthy control there is a positive distal-dorsal difference (DDD) at baseline which returns during rewarming after cold challenge. In Raynaud's phenomenon, the digits and dorsum are colder at 23 °C (more *blue* on false colour mapping) than in healthy controls and a negative DDD exists which persists following cold challenge

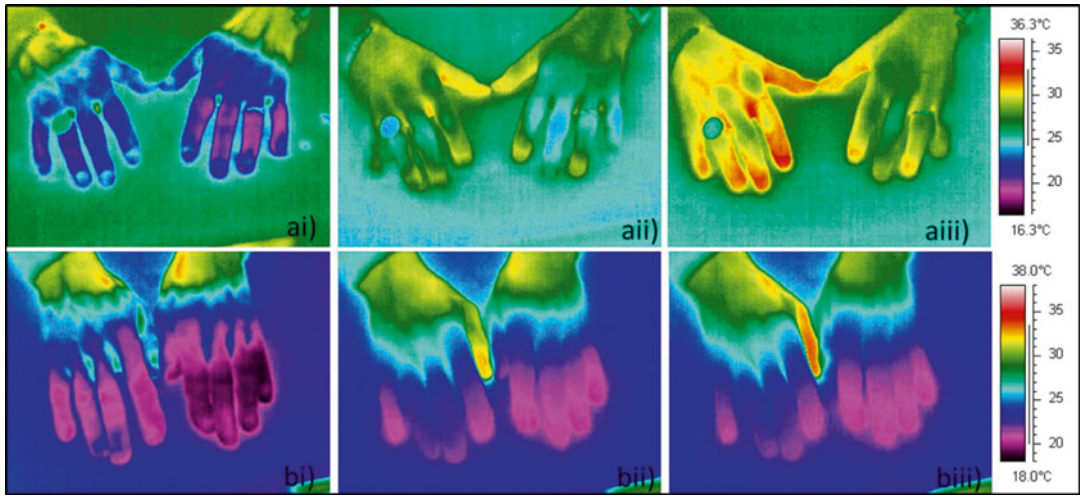

Fig. 13.3 IRT images following cold challenge. IRT images of patients with (**a**) PRP and (**b**) SSc (**i**) immediately after and at (**ii**) 7 and (**iii**) 15 min following cold challenge

Ring et al. proposed a method that combined the thermal gradient at baseline with that 10 min following local CST (20 °C for 60s) for both hands to identify patients with healthy perfusion at baseline in whom an exaggerated and prolonged vasoconstrictive response to cold exposure occurs (consistent with RP) [6]. Using a cut off of −4 °C, the combined thermal gradient effectively differentiated between groups of RP compared with healthy controls [4]. Other methods evaluating changes in the longitudinal thermal gradient following CST were proposed around the same time [46]. Early studies incorporating a cold challenge were limited to a single post-CST image (typically 10 min post cold challenge) due to early difficulties in obtaining thermographic images. Advances in thermographic imaging have enabled continuous recording of digital temperature recovery following cold exposure, allowing detailed analysis of rewarming curve characteristics. These advances in IRT imaging have expanded the number of thermographic parameters available, with particular interest emerging for those capable of differentiating between primary RP (PRP) and SRP. Interrogating the rewarming curve has facilitated capture of absolute temperature recordings at multiple time-points, the lag phase before recovery starts, the maximum gradient of the temperature recovery curves and the maximum percent recovery during 15 min post-cold challenge [47]. Early studies of these novel thermographic parameters differentiated between healthy controls and patients with RP, with strong trends for differentiating between PRP and SRP [47]. The Distal-Dorsal Difference (DDD; a refined thermal gradient calculated by subtracting the temperature of the fingertip from the temperature of the corresponding dorsum for each of the digits) also allows differentiation between PRP and SSc (warming the hands to 30 °C after the cold challenge enhances the discriminatory capacity of the DDD, Fig. 13.4) [24, 28].

Combining the thermal gradient at baseline with that following CST (as proposed by Ring et al. to aid differentiation between healthy controls from patients with RP), does not aid differentiation between PRP and SSc, due to a disproportionate effect of the cold challenge on patients with PRP (narrowing differences in digital perfusion present at baseline) [48]. IRT has recently been used to confirm long-held clinical suspicions of relative sparing of the thumbs in both PRP and SSc [49, 50]. Other thermographic parameters have been developed but less extensively evaluated. For example, Foerster et al. proposed a Tau cold response index that evaluated the time to achieve 63 % rewarming [51, 52].

Reproducibility of IRT in the Assessment of RP

There have been differing views regarding the reproducibility of thermographic responses to cold challenge although recent studies adhering to standardised protocols have identified good to excellent reproducibility [28, 41, 53, 54].

IRT as an Endpoint in Therapeutic Trials of RP

Therapeutic trials have attempted to use IRT as an endpoint in the evaluation of treatments for RP and a systematic review of the design and outcome of these studies has been reported [55]. To date, no thermographic parameter has emerged as the preferred parameter for use in clinical trials of RP. The majority of trials incorporating IRT were small, open-label trials evaluating peripheral microvascular responses to a number of established treatments for RP including prostaglandins [22, 46, 56–62], calcium channel antagonists [63], angiotensin II antagonists [64], nitrates [65] and selective serotonin reuptake inhibition [66]. A number of non-pharmacological treatments have also been assessed using IRT including low level laser therapy [67–70], autologous transplant of bone-marrow derived cells [71], auricular electroacupuncture [72] and surgery [73, 74]. Thermographic protocols and endpoints used in clinical trials vary significantly between studies. Without a gold standard against which to compare, it is difficult to critique the effectiveness of the individual thermographic endpoints used in previous studies.

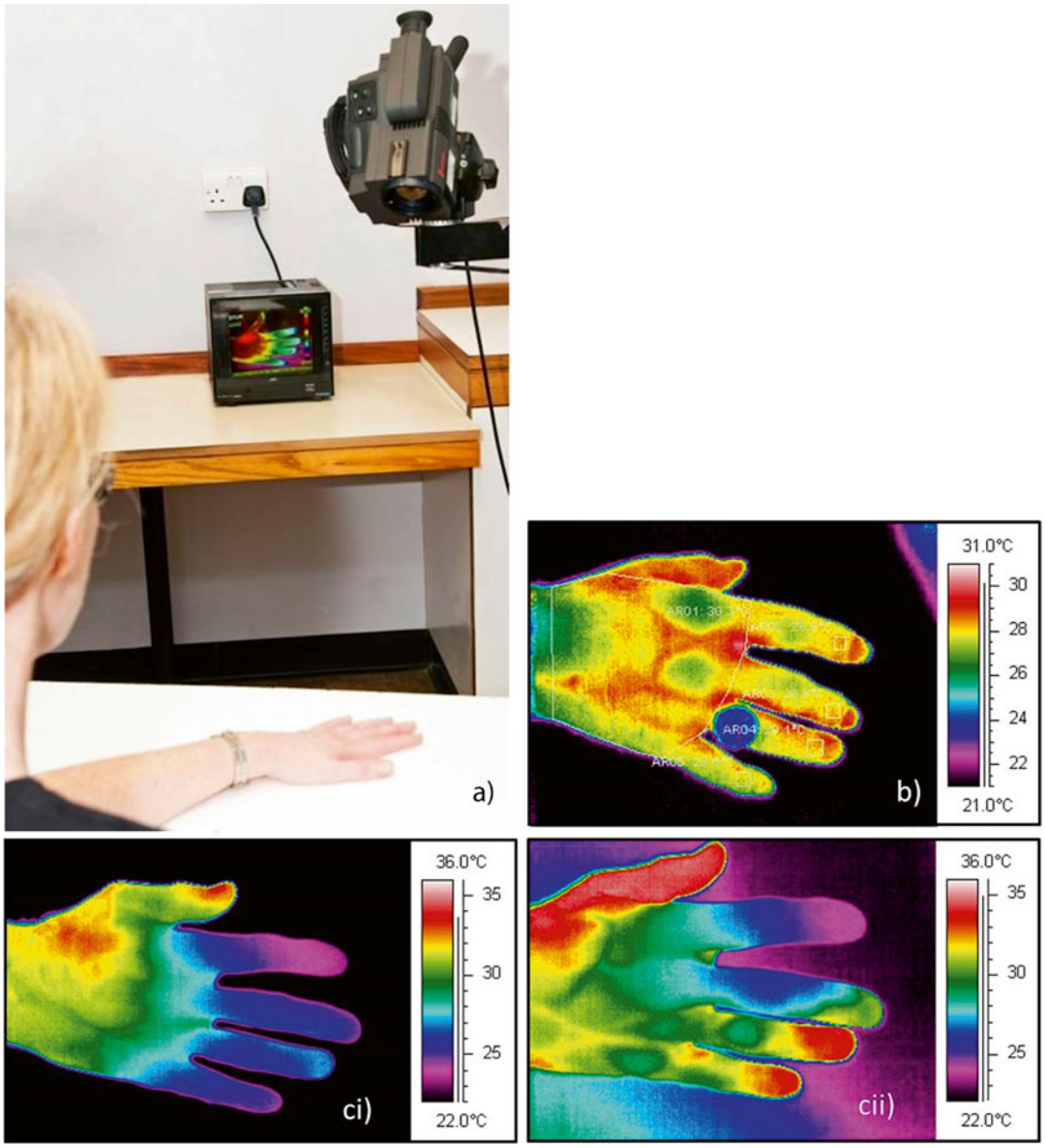

Fig. 13.4 IRT images. (**a**) Being acquired following a cold challenge (Copyright of Salford Royal NHS Foundation Trust); (**b**) of a patient with PRP at 23 °C; (**c**) of a patient with SSc at (**i**) 23 °C and (**ii**) 30 °C

Several studies identified improvements in both self-report assessment of RP and thermographic parameters. In these studies, improvement in the absolute basal digital temperatures [61, 62], changes in the thermal gradient following CST [22, 23, 68], absolute digital temperatures following cold challenge [69] and the percent rewarming 10 min following cold challenge [66] mirrored improvements in clinical self-report parameters following intervention. IRT responses to intervention should be further refined in clinical practice and future therapeutic trials of RP.

Expert Opinion on Infrared IRT

IRT provides a safe, non-invasive method for the dynamic assessment of digital microvascular perfusion abnormalities in RP. Objective assessment of digital vascular function using IRT overcomes limitations of subjective self-report assessment and IRT has the potential to become a more important tool in the diagnosis, classification and assessment of therapeutic response in RP. A consensus approach to thermographic protocol, along with sharing of data from individual centres would facilitate easier comparison and refinement of thermographic parameters used in the assessment and diagnosis of RP.

Laser Doppler Techniques

Different Laser Doppler Methods

Laser Doppler (LD) techniques, in the context of assessing RP, remain research tools. LD measurements of blood flow take several forms however the techniques are based upon the same theory; the Doppler effect [75, 76]. The Doppler effect occurs when there is relative movement between the source of a wave (such as a laser) and an observer. The frequency of the backscattered wave reaching the observer changes by a small amount (kHz), proportional to the relative speed of the observer and wave's source. In LD measurement techniques, low power (milliwatt) laser light incident on the skin is either immediately reflected back from the surface or enters the skin. The light that enters is absorbed by or scattered from structures within the skin including both stationary structures such as collagen and moving erythrocytes in blood vessels. In contrast to the light that undergoes scattering from stationary cells and structures, light from moving cells undergoes a small frequency change. This small change is detected once light has been backscattered out of the skin and is incident on the detector. The change in frequency is directly proportional to the speed and concentration of the erythrocytes, thus allowing a measure of blood flow in the small volume interrogated [77]. Tissue perfusion should be defined as volume per unit area per unit time, however, measurements derived from laser imaging tools are relative rather than absolute; therefore, they are typically described in arbitrary flux units [75]. Various LD methods have emerged and have been used to demonstrate abnormalities in cutaneous perfusion of the digits in RP [77].

Laser Doppler Flowmetry

The most basic application of LD is single point laser Doppler flowmetry (LDF, also known as laser Doppler velocimetry and anemometry). The technique relies on placing a small probe on the skin (Fig. 13.5). Within the probe are two or more optical fibres. One fibre delivers laser light to the skin; the other(s) collect the back scattered light exiting the skin delivering it to a photodetector. In addition to the wavelength of the light used, the distance between the fibres also determines the depth of tissue penetration. The further apart the fibres, the deeper the light can be scattered and backscattered before being detected. The major limitations of LDF are that it is a contact technique, is prone to movement artefact and only detects signal from a small volume of the skin; the latter leads to poor repeatability (due to the challenge of attaching the LDF probe in the same place at each assessment and the heterogeneity of the cutaneous microcirculation) [78, 79].

Laser Doppler Imaging

Laser Doppler imaging (LDI) has several forms. The main advantages over LDF are that movement artefacts can be more easily avoided by taking measurements over an area and that the systems are non-contact. In a single laser beam scanning system the low powered laser beam scans over the skin in a raster scan motion (Fig. 13.6) measuring blood cell velocity at multiple single points to build up a near real time, two-dimensional map of tissue perfusion over several minutes (Fig. 13.6) [75]. Sensitivity to blood cell speed is governed by bandwidth and

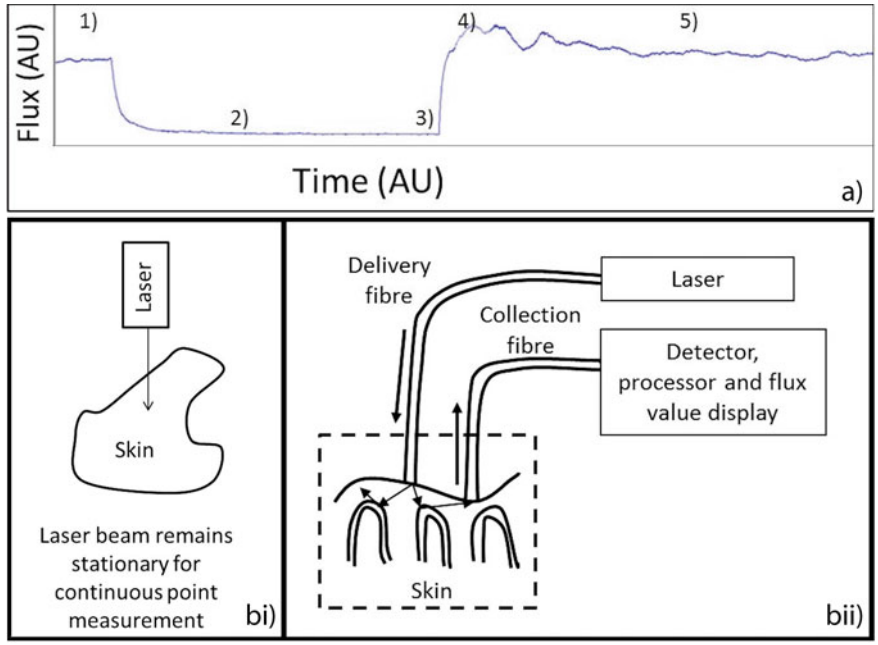

Fig. 13.5 Laser Doppler flowmetry. (**a**) LDF signal following digital occlusion and release. Flux versus time (Arbitrary units [AU]). (1) Steady-state flow, (2) occlusion, (3) point of release, (4) peak hyperaemic response, (5) return to steady state flow. (**bi**, **ii**) Schematic demonstrating LDF technique which can be performed by an LDI system in free space with no movement of the beam, or more usually, with fibres

integration time (i.e. speed of scan; slower scan speeds [longer exposure time at each point] allowing higher sensitivity to slower blood flows) [80]. LDF can also be carried out by LD imagers (without fibres). The laser is shone onto the skin in free space keeping the beam stationary and taking continuous measurement. Single point scanning LDI has overcome some of the limitations of LDF, although the temporal resolution of large scan areas can be limited by prolonged scanning times (lasting up to several minutes) precluding useful assessment of cutaneous microvascular responses to fast physiological stimuli [75, 80–82]. In order to obtain faster scans, more recent developments include full line perfusion imagers, where the single laser beam is replaced with a divergent laser line that requires scanning across the skin in one direction only. The backscattered beam is collected onto a line array of detectors rather than a single detector. This array of detectors leads to images having lower resolution (dependent on the number of detectors) but has the significant advantage of much faster scans (Fig. 13.7) [54].

Laser Speckle Contrast Imaging (LSCI)

Laser speckle contrast imaging (LSCI), another variation of the LD technique, allows full field, near real-time dynamic vascular assessment (Fig. 13.8) [75, 83–88]. In laser speckle techniques a single beam is expanded in two dimensions with optics in order to image a whole area of perfusion simultaneously. Directing a laser source at the optically rough surface generates a speckle pattern in the focal plane of the imaging lens (a series of small light and dark patches due to the interference of scattered reflections from the uneven surface, this is known as an interference pattern, [75]). If the surface remains static (e.g. onto skin with no underlying perfusion) then this speckled interference pattern will not change. If a laser is shone onto the skin in areas where there is underlying movement due to perfusion then the speckle pattern will change. If blood flow in the skin is fast then the pattern changes quickly, leading to a decrease in the speckle contrast over time. The difference between

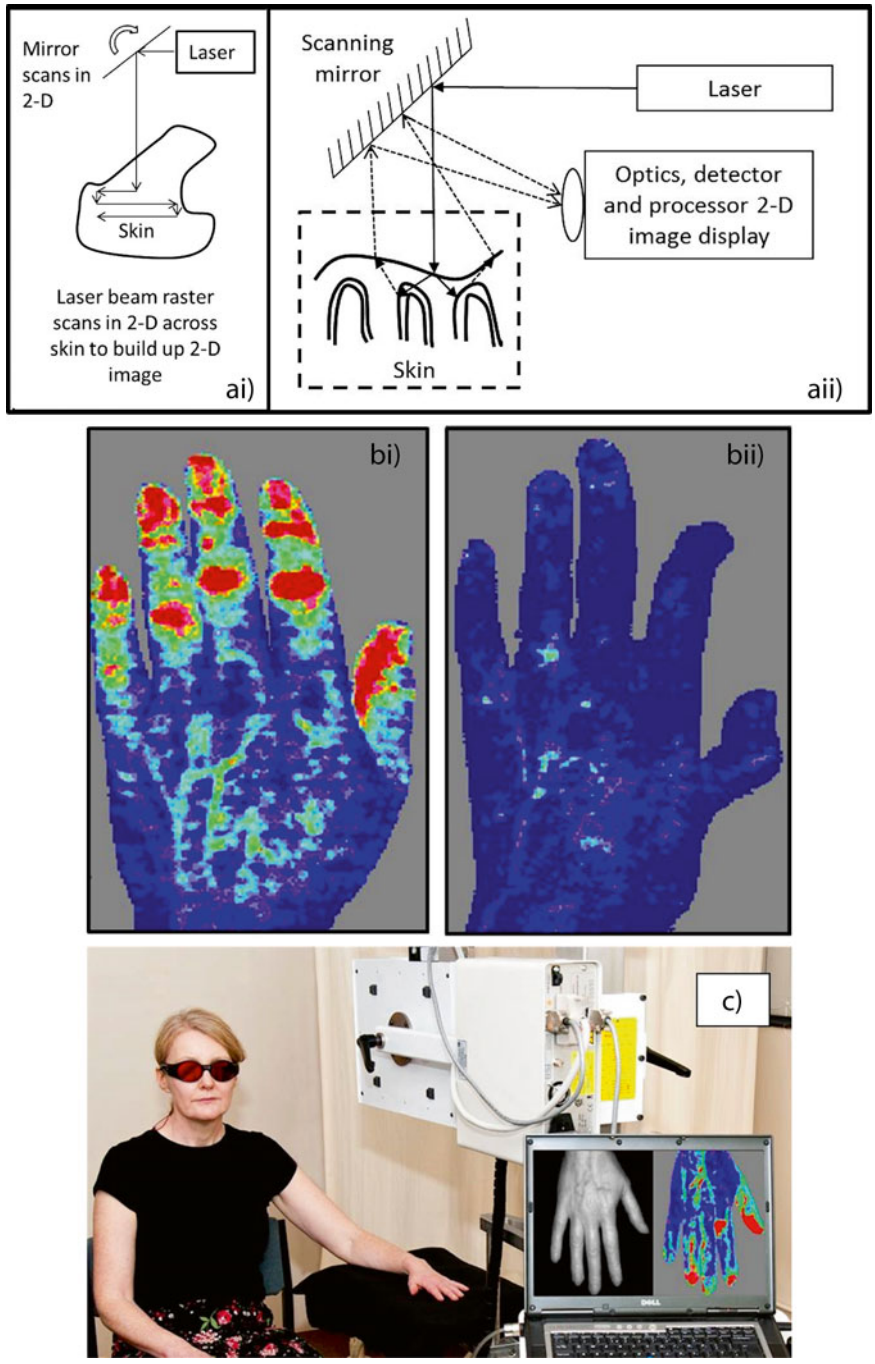

Fig. 13.6 Laser Doppler imaging. Schematics of LDI (raster scan mode), (**ai**) at surface of the skin and (**aii**) into the skin. LDI examples of (**bi**) healthy control and (**bii**) patient with SSc at baseline. *Blue* representing relatively low perfusion and *red* higher cutaneous perfusion. The images clearly show decreased perfusion in the patient with SSc at room temperature (23 °C). (**c**) LDI in use (Copyright of Salford Royal NHS Foundation Trust, with thanks to Tonia Moore and Joanne Manning)

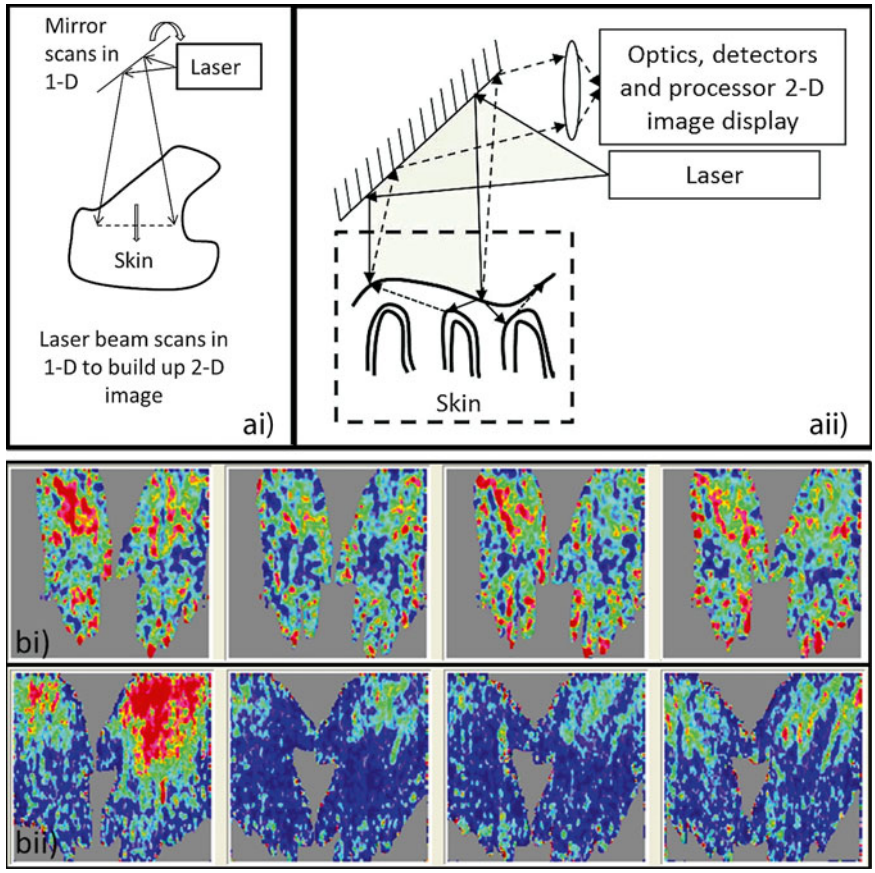

Fig. 13.7 Full line perfusion imaging. Schematics of full line perfusion imaging, (**ai**) at surface of the skin and (**aii**) into the skin. Set of full line perfusion laser Doppler imaging at baseline (first frame on *left*) and at 0 s, 15 s and 15 min following cold challenge for (**bi**) a healthy control and (**bii**) a patient with SSc. All images use the same arbitrary perfusion scale

patterns over a small time frame can be calculated providing a measure of magnitude of change and therefore blood flow. On face value, the physics of LSCI appear distinct from LD however the dynamics of the speckle pattern produced is primarily the result of Doppler shifts and the mathematical formulae used to interpret images do not differ greatly from those used in LDI [75]. LSCI offers the advantage of high resolution compared to scanning LDI but at the cost of area imaged (mm^2 vs. cm^2, larger areas can be imaged at the cost of spatial resolution). Another advantage is speed; as the full field is measured several frames can be taken per second reducing movement artefacts and allowing visualisation of pulsatility [84]. Additionally, whereas with LDI raw flux requires distance calibration, with LSCI it does not, allowing images to be initially acquired at distance and then smaller areas of interest to be studied in detail by zooming in. While LD techniques have traditionally required rigorous training and safety precautions, the low power divergent laser beams used in LSCI do not carry concerns regarding eye safety. For full field imaging the imaging depth of the laser is less than single point scanning at the equivalent wavelength. This is partly due to the detection/analysis method (frequency-weighted mean is used for LDI flux but this is not available for speckle) and partly due to the expanded beam that has less power per unit area and therefore fewer photons entering the skin (i.e. fewer penetrating more

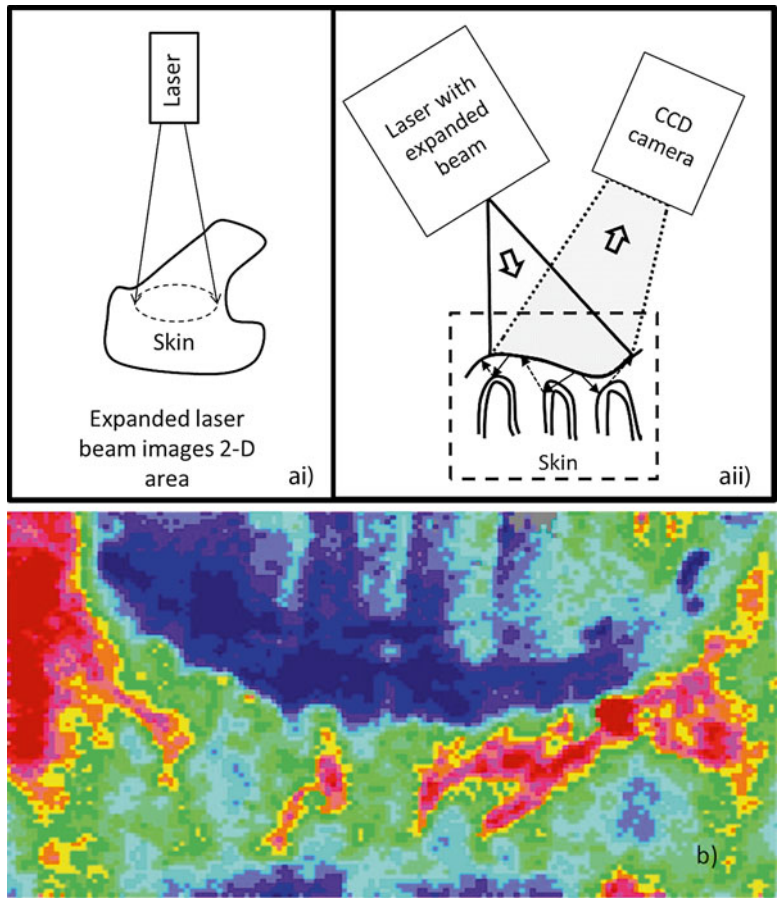

Fig. 13.8 Laser speckle contrast imaging. (**a**) Schematics of Laser Speckle Contrast Imaging (**ai**) at surface of the skin and (**aii**) into the skin. (**b**) Example of speckle contrast image of the nailfold. *Blue* is low and red relatively high perfusion. Red lines represent the location of enlarged capillaries in a patient with SSc.

deeply into the skin and being backscattered). Sensitivity to slower perfusion is achieved by longer exposure times at the compromise of frame rate.

Depth of Blood Flow Measurement

The penetration depth of the laser light and, therefore, the depth of blood flow measurement is dependent upon the interaction of the laser light with the skin (which scatters and absorbs photons). This is determined by both the underlying skin structures and the wavelength of the laser light used, since melanin and haemoglobin, the two main chromophores in the skin, have wavelength dependent absorption. Green and blue wavelengths are preferentially absorbed, limiting penetration depths to the upper layers of skin where capillaries are located; red wavelengths penetrate more deeply to thermoregulatory blood vessel layers and infrared wavelengths penetrate further and also show less dependence on skin pigmentation [89]. This provides an opportunity to study microvascular function at varying levels within the skin such as superficial nutritive capillary flow compared with deeper dermal vascular perfusion and thermoregulatory arteriovenous anastamosis function (for example with dual wavelength systems [77, 90]). Increasing the laser power of a system also increases imaging depth since increased numbers

of photons enter the skin and more of these are able to travel deeper into skin before being scattered or absorbed. LD systems tend to have red and/or infrared wavelengths achieving a depth of imaging in human skin up to approximately 1 mm.

LD Techniques in the Assessment of RP; Physiological Studies

A large number of single site, cross-sectional physiological studies have been carried out using LD techniques, several are summarised in Table 13.2. LD methods, often used in conjunction with dynamic challenges such as post-occlusive or thermal hyperaemia and cold challenge, have been found to be capable of differentiating between healthy controls and RP groups [19, 91, 92]. A large study incorporating multiple techniques revealed good specificity and sensitivity for line scanning LDI, IRT and nailfold capillary microscopy (NCM) in differentiating between control, PRP and SSc groups [54].

Recent studies have begun to evaluate the application of LSCI in SSc [93–95]. Ruaro et al. have identified lower digital perfusion in patients with SSc (after cessation of vasodilator therapy) compared with healthy controls and lower digital perfusion in patients with SSc with either active or a history of digital ulceration [94]. Della Rossa et al. have demonstrated more pronounced microvascular responses and delayed recovery following cold challenge in patients with SSc compared with PRP and healthy controls [93]. Studies of LD techniques in combination with other techniques are presented in Table 13.3.

The key points that these studies highlight are that: (a) At baseline, in comparison to a healthy control group those with PRP or SRP are not always differentiated; (b) the change in PRP group measurements after dynamic challenge often show a trend towards difference from SRP groups but do not always reach significance. It is difficult to know whether these baseline and post challenge inconsistencies are due to the study population or the laboratory conditions/protocols, observers and/or equipment. It is possible that more translational, robust and reproducible protocols regarding acclimatisation may help elucidate these issues; (c) in those with SRP, dysfunction tends to be distal, i.e. in the fingers as opposed to in the dorsa of the hands or forearms [29, 96]; (d) however, the more severe the SRP disease the more likely dysfunction will occur more proximally as well as distally and this dysfunction appears to be more reversible in early patients, suggesting that they may be more responsive to treatment [97].

Reproducibility of LD Techniques

Good reproducibility of LDF has been found with local heating, post occlusive hyperaemia and local cooling [18, 91, 98, 99]. Bartelink et al. found that finger skin temperature measured using a thermocouple was more reproducible under local cooling than LDF [19]. This may be due to movement artefact issues. Early studies have also identified good reproducibility with LSCI assessments of digital vascular function in healthy controls [41, 82, 100] and patients with SSc [94]. One study identified poor reproducibility of LSCI assessment at the nailfold in SSc (ICC 0.15) although repeatability was only assessed in a small number of subjects in this study [54].

LD Methods as an Endpoint in Therapeutic Trials of RP

Therapeutic trials of RP incorporating LD techniques have been undertaken but, as with IRT, the majority of studies are small, single site, explorative open-label studies (Table 13.4). Moreover, as with IRT, comparison between therapeutic trials of RP incorporating LD is difficult owing to variation in study design, intervention, LD technique and lack of standardisation of the microvascular imaging protocol or LD endpoints. Pharmacological interventions which have been evaluated using LD include prostaglandins [57, 101, 102], glyceryltrinitrate [36, 103, 104], calcium channel antagonists [57, 63], statins [105, 106], phosphodiesterase inhibitors [107, 108],

Table 13.2 Summary of cross-sectional studies utilising dynamic challenges to assess RP in combination with LD techniques

Dynamic challenge	Authors, year	LD technique[a]	Site of interest	Groups[b]	Details of dynamic challenge(s)	Outcome
Heating	Walmsley and Goodfield (1990) [26]	LDF	Foot	15 HC, 9 PRP, 7 SSc	Local heating (probe, up to 44 °C)	Data for those with PRP and SSc overlapped with that of the control group. The authors found that healthy women's vasodilation lay between that of healthy men and those with PRP and concluded an abnormal vascular response in PRP
	Clark et al. (1999) [201]	LDI	Hand and finger	17 HC, 7 PRP, 9 dcSSc, 24 lcSSc	Ambient room warming 23 and 30 °C (20 min)	Significant differences found between the lcSSc and control groups for maximum flux difference between fingertips of the same hand at 23 °C and maximum DDD at 30 °C
	Roustit et al. (2008) [27]	LDF	Finger	10 HC, 10 PRP, 16 SSc	Local heating (probe 42 °C for 30 min, and 44 °C for 5 min) ± topical lidocaine/prilocaine	Patients with SSc showed an abnormal response to heating following local anaesthesia as compared to controls and patients with PRP
	Figueiras et al. (2011) [18]	LDF	Forearm and finger	27 HC, 28 RP, 53 SSc	Local heating (probe 42 °C, 30 min)	Differences found at finger but not forearm in patients with SSc as compared to those with PRP and controls
Heating and occlusion	Boignard et al. (2005) [91]	LDF	Finger	(1) 20 SSc, 20 PRP, 20 HC (2) 10 rheumatoid arthritis (and RP); 10 PRP	(1) Finger occlusion local heating (42 °C for 30 min and then to 44 °C for 5 min) (2) Local heating	Patients with SSc showed different heating characteristics in the perfusion curve, including lower vasodilation as compared to patients with PRP and controls. Occlusive hyperaemia was significantly reduced in patients with SSc. Thermal hyperaemia was more sensitive and specific than post-occlusive hyperaemia for differentiating SSc from primary RP. Patients with rheumatoid arthritis also showed lower vasodilation than PRP
Heating and occlusion	Murray et al. (2006) [29]	Dual wavelength LDI	Hand and finger	29 HC, 29 SSc	Local heating (probe 34–40 °C, 6 min, dorsum) Digital occlusion (200 mmHg, 2 min)	No differences between groups at dorsum due to heating, only differences at finger in response to occlusion. Data suggests abnormal microvascular response is localised to the digits, affecting both smaller and larger vessels
Heating and cooling	Lau et al. (1995) [21]	LDF	Finger	21 HC, 7 PRP, 22 Undifferentiated connective tissue disease, 27 SSc	Ambient chamber warming and cooling 40 and 12 °C	Patients with PRP had normal perfusion at both 40 and 12 °C but showed faster vasoconstriction and slower vasodilation in response to cooling and warming, indicative of altered sympathetic activity. Those with SSc showed decreased finger blood flow at 40 °C
Heating, cooling and iontophoresis	Gardner-Medwin et al. (2001) [14]	LDF, finger skin temperature (thermocouple)	Finger	10 PRP (women) 20 HC (10 female, 10 male)	Whole hand warming (35 °C) or cooling (15 °C) Iontophoresis of ACh and NaNP (0.1 %, 150 μm, 1 min)	Four visits (2 summer, 2 winter; one heating, one cooling per season). All participants had colder skin in winter than summer but this was exaggerated in patients with PRP. Vasodilation in response to iontophoresis with ACh (endothelium dependent) but not NaNP (independent) was reduced in the PRP group as compared to HC women but more so in winter

(continued)

Table 13.2 (continued)

Dynamic challenge	Authors, year	LD technique[a]	Site of interest	Groups[b]	Details of dynamic challenge(s)	Outcome
	Gunawardena et al. (2007) [202]	LDI/LDF	Hand and finger	17 HC, 10 PRP, 20 SSc	Local heating (probe 44 °C, 6 min, finger) Contralateral whole hand cooling (18 °C, 30 s) ACh and NaNP iontophoresis (2 % 5 %, 250 μA, 5 min)	Vasodilation was lower in SSc than controls. Response to cooling and ACh iontophoresis were lower in SSc compared to PRP. No difference was observed between PRP and controls or with NaNP iontophoresis in any group
Cooling	Brain et al. (1990) [37]	LDF	Forearm	8 HC, 8 PRP	Local cooling test (probe, 5–6 °C, 2 min) Injection of CGRP, PGE2 and histamine	Blunted hyperaemic response after cooling for PRP. In response to local injection of CGRP, PGE2 and histamine no differences were found between the two groups
	Gasser et al. (1992) [17]	LDF, finger skin temperature (thermocouple)		39 HC, (with history of cold hands), 39 HC (no history)	Contralateral whole hand cooling (4 °C, 30 s)	Significant differences were found between the groups at both baseline and after cooling
	Bartelink et al. (1993) [19]	LDF	Hand	99 PRP, 97 SRP, 101 HC	Whole hand cooling (water, 16 °C, 5 min)	Significant differences between females and males were found in all groups and between HC and RP groups but not between PRP and SRP groups. Study also assessed sensitivity and specificity (see relevant section above)
	Mirbod et al. (1998) [203]	LDF, finger skin temperature (thermocouple)	Finger	5 Hand-arm vibration syndrome, 4 numbness (no RP), 5 HC	Whole hand cold challenge (10 °C, 10 min)	The control group had significantly higher finger skin temperature and finger blood flow after cold challenge
	Cracowski et al. (2002) [20]	LDF	Finger	11 SSc, 11 PRP, 11 HC, all female	Ambient room temperature cooling (25–15 °C, 40 min)	Urine samples were obtained before and after cooling to assess levels of oxidative stress. Significant differences in oxidative stress were found between patients with SSc and both those with PRP and controls. Although blood flow decreased more in patents with SSc and PRP than in controls no correlation was found between FBF and oxidative stress levels
	Correa et al. (2010) [178]	LDI	Finger	14 SSc, 12 HC	Whole hand cold challenge (10 °C or 15 °C for 1 min)	Baseline and perfusion following cold challenge were found to be significantly lower in the SSc group
	Roustit et al. (2011) [205]	LDF	Hand and finger	21 PRP, 20 HC	15 °C or 24 °C ± administration of local anaesthesia	Significant differences found between groups at the dorsum but not finger or forearm and also found that the exaggerated vascular response to cooling seen in RP could be reduced by topical local anaesthesia

Occlusion and cooling	Grattagliano et al. (2010) [206]	LDF	Finger	49 LcSSc, 10 dcSSc, 25 PRP, 31 HC	Occlusion (brachial artery) Cooling (16 °C, 90 s) bilateral hand	The SSc groups had significantly different responses to both cooling and occlusion The authors suggest these challenges as possible methods of differentiating lcSSc and dcSSc
Occlusion	Cracowski et al. (2006) [30]	LDF	Finger	43 SSc, 33 PRP, 25 HC	Brachial artery occlusion	Oxidative stress status was assessed by urinary levels of the F2-isoprostane. An inverse correlation between occlusive hyperaemia and urinary F2-isoprostane levels was found in the SSc group
Iontophoresis and occlusion	Anderson et al. (1996) [96]	LDF	Forearm	10 HC, 8 PRP, 10 SSc	ACh and NaNP iontophoresis (1 %, 100 μA, 30 s) Adrenaline iontophoresis (1 %, 200 μA for 120 s, monitored by brachial occlusion)	There were no differences between groups
	La Civita et al. (1998) [207]	LDF	Finger	11 SSc, 16 HC	Iontophoresis of ACh and NaNP (1 %, 30 mA, short bursts) Digital occlusion (250 mmHg, 3 min)	Response to iontophoresis of both ACh and NaNP and to occlusion were lower in the SSc group HC
Iontophoresis	Anderson (2004) [31]	LDI	Finger	10 LcSSc, 10 PRP, 11 HC	ACh and NaNP iontophoresis (120 s, 30 mA)	No differences were found in the baseline perfusion values between groups, vasodilation was decreased in the SSc group compared to PRP and controls groups for both ACh and NaNP
	Murray et al. (2005) [35]	LDI	Finger	10 HC	Iontophoresis of ACh (1 %, 100 μA, 2 min)	Pilot study of whole finger iontophoresis, investigated as a possible treatment for severe ischaemia. A significant local perfusion increase was found at the treated site
	Easter et al. (2005) [33]	LDF	Finger	15 HC, 15 PRP, all women sub-divided into pre- and post-menopausal groups	Pulsed ACh iontophoresis (0.1 mA-0.2 mA). Aspirin (a cyclo-oxygenase inhibitor) was then given and iontophoresis repeated	Differences between groups implicated the role of oestrogen in PRP to regulate endothelium-dependent vasodilator and/or vasoconstrictor cyclo-oxygenase inhibitor products
	Murray et al. (2008) [32]	LDI	Finger	8 HC, 8 SSc	Iontophoresis of ACh and NaNP (1 %, 0.5 % 200 μA, 2 and 5 min)	Whole finger iontophoresis, investigated as a possible treatment for severe ischaemia. Perfusion increased in both patients and controls, but significantly more so in controls. Perfusion was significantly higher for 5 min vs. 2 min. No significant differences were found between NaNP and Ach in either group
	Rossi et al. (2008) [34]	LDF	Finger	26 SSc, 20 HC	Iontophoresis of ACh and NaNP (pulsed 1 %, 0.1 mA and 1 %, 0.2 mA)	Authors performed analysis of the component frequencies. No difference was found at baseline; however, lower vasodilation was observed in the SSc group for both NaNP and ACh (no difference between the two). Sub-analysis of the Doppler frequencies indicated dysfunction of the endothelial, sympathetic and myogenic microvasculature

(continued)

Table 13.2 (continued)

Dynamic challenge	Authors, year	LD technique[a]	Site of interest	Groups[b]	Details of dynamic challenge(s)	Outcome
	De Leeuw et al. (2008) [208]	LDF	Finger	42 Systemic lupus erythematosus, 12 RP, 19 HC	Iontophoresis of ACh And NaNP (pulsed 1 %, 0.1 mA and 0.1 %, 0.2 mA)	Patients with systemic lupus erythematosus and RP exhibited decreased vasodilatation compared with controls, those without RP did not
	Roustit et al. (2009) [209]	LDF	Finger and forearm	6 HC, 6 SSc	NaNP and NaCl (pulsed, 200 μA) ± lidocaine/prilocaine	Significant increase following iontophoresis was seen in both controls and patients at the forearm irrespective of anaesthetic administration. However it was not seen at the finger pad with or without lidocaine/prilocaine. The authors attribute this finding to increased clearance at the finger pad due to increased vascularity
	Anania et al. (2012) [210]	LDF	Hand	84 Systemic lupus erythematosus (39 with RP), 81 HC	iontophoresis ACh (2 %, pulsed 0.1 mA)	No difference even with sub-analysis of those with and without RP
Heating and iontophoresis	Bengtsson et al. (2010) [242]	LDF	Forearm	30 SLE, 20 HC	Local heating (probe, 44 °C) Iontophoresis ACh NaNP (2 %, 1 %)	No significant difference in microvascular function was found between groups
Other physiological challenges	Stoyneva (2004) [38]	LDF	Finger	15 HC, 15 PRP, 15 SSc, 15 Hand-arm vibration syndrome	Arm raising and lowering	The difference in perfusion between hands at sternum level and 40 cm below was significant between both healthy controls and PRP compared with SRP. An increased loss of venoarteriolar reflex was observed for SRP as compared to PRP. The author concludes that the loss of reflex is due to local vasomotor dysfunction, indicative of postganglionar sympathetic insufficiency with vascular tone failure or altered smooth muscle cells' responses
	Kido et al. (2007) [211]	LDF	Finger	8 SSc, 6 HC	Arm raising and lowering Cooling (whole hand, (4 °C, 10 s)	Patients with SSc showed significantly lower steady-state perfusion, the trend was also lower after cooling but not statistically significant. Raising hands showed significant differences between groups

DDD, distal-dorsal difference. This is the temperature/blood flow difference between the distal phalanx and dorsum of the hand

[a]*LDF* laser Doppler flowmetry, *LDI* laser Doppler imaging, *ACh* acetylcholine chloride, *NaNp* sodium nitroprusside

[b]*HC* healthy controls, *PRP* primary Raynaud's phenomenon, *SRP* secondary Raynaud's phenomenon, *SSc* systemic sclerosis, *lcSSc* limited cutaneous SSc, *dcSSc* diffuse cutaneous SSc

Table 13.3 Studies utilising multiple measurement techniques

Imaging techniques used	Authors, year	Details of imaging techniquesa	Site of interest	Groupsb	Dynamic challenge	Outcome
LD and FSP	Maricq et al. (1996) [146]	LDF and FSP	Finger	96 PRP, 108 SSc, 88 subjects complaining of cold sensitivity of the fingers,120 HC	Room temperature of 18 or 23 °C. Local finger cooling (30, 20, 15 and 10 °C)	Significant differences between groups with FSP. Finger blood flow and finger skin temperature had larger variance and did not reach significant differences between groups
	Bornmyr et al. (2001) [177]	LDI and FSP	Finger	15 HC, 6 traumatic vasospastic disease	(1) Local heating (probe, 30 °C, 6 min) and cooling (15 °C, 3 min, 10 °C, 3 min) (2) FSP/strain gauge before and after cooling to 10 °C (separate visit)	Finger blood flow (LDI) and FSP did not correlate. Authors concluded that and that although FSP gave better discrimination between controls and vasospastic groups better methods of demonstrating cold-induced vasospasm were required
	Salvat-Melis et al. (2006) [176]	(1) LDF (2) FSP	Forearm and finger	(1) 21 HC, 21 PRP, 21 SSc (2) 39 SSc	(1) Local heating (probe up to 44 °C, 35 min) Brachial occlusion (2) FSP at 44 °C	(1) Abnormal vasodilation at the finger but not the forearm was found. Occlusion showed a trend for, but non-significant, decrease at the finger but not at the forearm in patients with SSc (2) Thermal hyperaemia data were not found to be associated with skin thickness (modified Rodnan skin score) or macroangiopathy (FSP)
LD and IRT	Seifalian et al. (1994) [98]	LDI and IRT	Fingers and hands	10 SSC, 8HC	No dynamic challenge for this part of the study (cold and hot challenge in HC only in first part of the study)	Perfusion and temperature were significantly lower in patients with SSc compared to healthy controls
	Schlager et al. (2010) [173]	LDI and IRT	Hands	25 PRP, 22 HC	Whole hand cooling (water, 20 °C, 1 min)	Significant differences in response to cold challenge between groups
	Clark et al. (2003) [179]	LDI and IRT	Hands	17H, 40 RP (7 PRP, 33 SRP)	Room warming from 23 to 30 °C	Poor correlation between IRT and LDI at finger, dorsum and gradient between (distal dorsal difference)
LD, IRT and NCM	Murray et al. (2009) [54]	Full line perfusion imaging vs IRT LSCI (of the nailfold) vs NCM	Hands and fingers	16 SSc, 14 PRP, 16 HC	Whole hand cooling (15 °C, 1 min)	Significant differences were found between groups for reperfusion/warming curve characteristics. The study concluded that LDI and IRT each independently provide good discrimination between patients with SSc and those with primary RP and healthy controls. Poor correlation was found between LSCI and NCM capillary density and width

(continued)

Table 13.3 (continued)

Imaging techniques used	Authors, year	Details of imaging techniquesa	Site of interest	Groupsb	Dynamic challenge	Outcome
LD and NCM	Ziegler et al. (2004) [212]	LDF anemometry (LDF of the nailfold capillaries)	Finger	78 PRP 16 Hand-arm vibration syndrome	Occlusion (brachial artery) to stop/release for max perfusion at NCM Whole hand cooling (12 °C for 3 min)	No difference was found in LDF after cooling but hyperaemic response time was longer in patients with hand-arm vibration syndrome indicating macrovascular involvement in contrast to PRP
	Szabo et al. (2008) [213]	LDI and NCM	Hands	30 HC, 30 PRP, 30 Sjogren's syndrome with RP, 30 poly/dermatomyositis	No dynamic challenge.	Decreased capillary density was observed in Sjogren's syndrome and Poly/dermatomyositis groups. Changes in morphology were observed in the Poly/dermatomyositis group. Significant differences were observed between hand perfusion in the control group and those of the patient groups
	Rosato et al. (2009) [175]	LDI and NCM	Hands	142 SSc, 88 PRP, 147 HC	No dynamic challenge	Significant differences in perfusion between all three groups were identified. No direct relationship between NCM categories and perfusion was found
	Cutolo et al. (2010) [174]	LDF and NCM	Finger	34 SSc 16 HC	(1) Administration of iloprost for 7 days (24 h, 4 μg/h). (2) local heating (probe, 36 °C)	Perfusion significantly lower in the SSc group. Those categorised as late from NCM visualisation had significantly lower blood flow than early or active. Iloprost significantly improved perfusion
LD and NCM	Rosato et al. (2011) [97]	LDI and NCM	Hands and fingers	40 SSc, 38 PRP, 32 HC	Whole hand cooling, (4 °C, 5 min)	Baseline perfusion was significantly less in patients with SSc as compared to controls. NCM was also carried out and the authors observed that in early and active disease only the fingers appear to be affected by the cold challenge (undergoing incomplete reperfusion over a 15 min follow-up); however, with late disease the dorsa of hands are also affected
	Piotto et al. (2013) [214]	LDI and NCM	Finger	5 HC, 5 PRP, 5 SSc, All juveniles	Whole hand cooling (15 °C, 1 min)	Baseline perfusion could differentiate between SSc and control groups but not SSc and PRP; however, all groups could be differentiated following cold challenge. In addition a positive correlation was found capillary density and perfusion
	Ruaro et al. (2013) [94]	LDF, LSCI, and NCM	Hand	61 SSc, 61 HC	No dynamic challenge	Positive correlation between LDF and LSCI and capillary pattern (late having lowest perfusion)

LD, US and NCM	Sulli et al. (2014) [215]	LDF, US imaging, and NCM	Finger	57 SSc, 37 HC	No dynamic challenge	Dermal thickness (US) increased with NCM early, active, late categorisation. Perfusion had an inverse relationship to NCM category. Patients had thicker dermal levels and lower perfusion than controls
LD and Doppler US	Rajagopalan et al. (2003) [216]	LDF, Doppler US imaging	Finger and forearm	40 PRP or SRP (10 systemic lupus erythematosus, 14 SSc, 6 Sjogren's syndrome, 4 Undifferentiated connective tissue disease, 2 Polymyositis, 2 Rheumatoid arthritis, 2 mixed connective tissue disease)	Flow mediated dilation of brachial artery and nitroglycerin mediated dilation Brachial artery diameter, in response to whole hand cold challenge. LDF finger, brachial artery occlusion	No differences were found between PRP or SRP groups in flow mediated dilation or nitroglycerin dilation PRP and SRP groups had similar abnormal responses to cold challenge Only area under the hyperaemia curve was significantly different SRP and PRP with LDF measures
LD, Doppler US, NCM, PPG	Rosato et al. (2011) [131]	LDI, Doppler US, NCM, PPG	Finger and Hand	36 SSc (21 dcSSc, 15 lcSSc), 20 HC	Doppler US radial and ulnar palmar artery patency, RI and PI NCM early, active, late LDI fingers and hand PPG finger	69 % of SSc had peripheral arterial disease RI and PI were significantly higher in SSc Increasing degradation in artery patency showed a positive relationship with the early, active, late categorisation of NCM. RI and PI increased with increasing microvascular abnormality Perfusion (LDI) was higher in the HC group, negative correlation as found between LDI perfusion and RI and PI
LD, laciticemy and NCM	Correa et al. (2010) [178]	LDI and NCM and fingertip lacticemy (an invasive test to determine biochemical microcirculation components)	Finger	44 SSc, 40 HC	Whole hand cooling (15 °C, 1 min)	Baseline and reperfusion significantly lower in the SSc group compared to controls. No correlation was found between NCM and finger perfusion

[a]*LDF* laser Doppler flowmetry, *LDI* laser Doppler imaging, *LSCI* laser speckle contrast imaging, *NCM* nailfold capillaroscopy, *US* ultrasound, *PPG* photoplethysmography, *RI* resistive index, *PI* pulsatility index, *IRT* infrared thermography

[b]*HC* healthy controls, *PRP* primary Raynaud's phenomenon, *SRP* secondary Raynaud's phenomenon, *SSc* systemic sclerosis

Table 13.4 Treatment and clinical trial studies of RP utilising non-invasive imaging techniques

Intervention	Authors, year	Study design	Intervention	Groups[a]	Outcome measures[b]/ imaging protocol	Response
Prostanoids	Yardumian et al. (1988) [217]	Randomised crossover	IV iloprost and placebo Variable dosage from 1.0 to 3.0 ng/kg/min; 5 h on 3 consecutive days	10 SSc 1 Mixed connective tissue disease 1 Undifferentiated connective tissue disease	Finger skin temperature and finger blood flow with LDF. Finger measurements immediately before, and at 1 and 6 weeks after	A significant increase in finger blood flow was observed after iloprost as compared to placebo which lasted up to 6 weeks
	Wigley et al. (1992) [102]	Multi-centre, double blind placebo controlled parallel	IV iloprost (0.5–2.0 ng/kg/min) or saline, 6 h, 5 days	35 SSc (subset with ulcers)	FSP, finger skin temperature with cold challenge, measurements at baseline, day 5 of therapy and biweekly for a 10 week follow-up	FSP and skin temperature improved in iloprost group only and ulcer healing occurred with iloprost group only
	Zardi et al. (2006) [218]	Not stated	Iloprost infusion (2 ng/kg/min, 6 h/day), 5 days	15 SSc	Doppler US, portal vein flow volume ultrasonography equipment	Significantly increased velocity and flow volume after treatment
	Shah et al. (2013) [101]	Two centre, open label, escalating doses	Oral treprostinil diethanolamine 2 mg and 4 mg (or maximally tolerated)	19 SSc with digital ulcers	Finger skin temperature and LDI hands and fingers before and after dosing	Significant increases in perfusion were found after treatments
	Blaise et al. (2013) [243]	Proof-of-concept	Iontophoresis of treprostinil and iloprost	20 HC only	LDI of forearm	Authors suggest that the sustained vasodilatation observed could be investigated as a new local therapy for digital ulcers in scleroderma
Prostaglandinss (PGE)	Mohrland et al. (1985) [244]	Multi-centre, placebo-controlled, double-blind study	PGE, IV 10 ng/kg/min, 72 h follow-up	55 PRP or SRP	Finger skin temperature (thermocouple), FSP finger, local warming/cooling 30, 15, and 10 °C	Improvement immediately after treatment for both PGE and placebo but not sustained at 4 weeks. No significant differences between treatment groups
	Wise and Wigley (1994) [219]	Double blind, placebo controlled, crossover study	Single 400 μg oral dose of misoprostol	8 RP, 6 HC	Finger skin temperature, FSP, LDF, finger, cold challenge (−5 °C)	No differences found between groups

Glyceryltrinitrate (GTN) and NO generating gel	Tucker et al. (1999) [103]	Single-blind, randomised, placebo controlled crossover	Nitric-oxide-generating gel [0×5 mL of each KY jelly and sodium nitrite (5 % weight/volume) and KY jelly and ascorbic acid (5 % weight/volume)]. Applied to the skin of the forearm (3 cm^2)	20 RP, 10 HC	Forearm and finger, PPG and LDF	Baseline lower in SSc group. Significant increases found at both forearm and finger after treatment compared to placebo for both volume (PPG) and blood flow (LDF) in RP
	Anderson et al. (2002) [36]	Open	Topical GTN, 2 % ointment, placebo gel and no treatment administered to adjacent digits for 1 min	10 HC, 10 PRP and 13 LcSSc	LDI fingers, baseline, immediately 10 and 20 min after treatment	GTN caused significantly increased perfusion as compared to placebo and no treatment at all time points; however, there was no difference at baseline or after treatment between groups
	Hummers et al. (2013) [104]	Multi-centre, double-blind, randomised, placebo-controlled, crossover	GTN gel formulation (MQX-503) 0.5 % or 1.25 % GTN or placebo	37 PRP/SRP	Finger skin temperature and FBF with LDI. Baseline and following 5 min of cold chamber exposure (−20 °C)	Time to reach baseline after cold challenge was shorter in the treatment groups compared to placebo
Calcium channel blockers (CCB)	Corbin et al. (1985) [147]	Randomised double-blind crossover	Nifedipine, increased from 5 mg to 15 mg over 4 weeks. Given three times daily.	23 RP	FSP	No difference in FSP before and after nifedipine treatment
	Gush et al. (1987) [63]	Placebo-controlled single-dose	20 mg sublingual nifedipine and matching placebo	9 RP	IRT, Doppler US, LDF	Data suggested protective response against reduction of blood flow, possibly useful if self-administered prior to cold exposure
	Leppert et al. (1989) [148]	Single-blind study	Isradipine 1.25 mg and 2.5 mg for 3 weeks each	10 RP	FSP, local cooling (10 °C)	FSP improved in both treatment groups, more in the higher dose treatment group
	Weber and Bounameaux (1990) [220]	Double-blind, crossover	5 mg nifedipine sublingually	10 RP	FSP, cold challenge (10 and 15 °C)	FSP improved significantly after nifedipine as compared to placebo. Authors suggest low-dose nifedipine 15–30 min before predictable cold exposure as prophylaxis

(continued)

Table 13.4 (continued)

Intervention	Authors, year	Study design	Intervention	Groups[a]	Outcome measures[b]/ imaging protocol	Response
	Kallenberg et al. (1991) [169]	Single blind study	6 Weeks felodipine, dose being titrated every 2 weeks, from 5 to 20 mg once daily if symptoms persisted	10 PRP	Finger plethysmography, cold exposure	Recovery from cold exposure for the 20 mg was significantly larger than placebo. 10 mg was noted to be the optimal dose
	Wollershiem et al. (1987) [221]	Placebo-controlled single-dose	10 mg sublingual nifedipine	16 with PRP/SSc	Finger and whole hand cooling (16 °C, 5 min). LDF 0, 4, 8 weeks	Improvement in blood flow observed following administration but no long term effects found leading the authors to suggest a nifedipine as a prophylactic treatment or one that could be delivered during an RP attack
	Wu et al. (2008) [222]	Open-label non-randomised	Nifedipine or a combination of two Chinese herbal medications, 4 weeks of treatment	47 Connective tissue disease patients with RP	Baseline and post treatment, whole hand cold challenge (15 °C, 1 min), LDI	Improvement only in the nifedipine group
	Csiki et al. (2011) [223]	Pilot	Beta-blocker metoprolol/ combined beta-blocker and CCB therapy (felodipin)/no treatment	46 PRP and hyper-tension	Baseline measurements of hand and suprasystolic brachial artery occlusion, LDI	Co-administration of beta-blockers and CCB was more beneficial to patients
Angiotensin converting enzyme (ACE) inhibitor	Janini et al. (1988) [224]	Double-blind crossover	20 mg enalapril daily, 3 weeks	9 PRP, 8 SSC	FSP (cold challenge)	No difference in FSP in response to cold challenge between active and placebo treatments
Statins	Sadik et al. (2010) [225]	Double blind, randomised, parallel group, placebo control	Atorvastatin 20 mg/day or placebo for 8 weeks	36 SSc	Baseline, 4 and 8 weeks assessed by response to iontophoresis with acetylcholine chloride (ACh, measured by LDI) and NCM	No changes in response to iontophoresis or in capillary architecture were found at 8 weeks as compared to baseline
	Rossi et al. (2012) [105]	Open label	Simvastin (20 mg/day for 10 weeks)	15 SSc with hyperchol-esterolemia	LDF, response to finger occlusion	Statin increased vasoreactivity in patients after 10 week period

	Timár et al. (2013) [106]	Prospective case series	20 mg rosuvastatin daily, 6 months	21 lcSSc 7 dcSSc	Doppler US flow mediated dilation of brachial artery, ABPI LDF finger, brachial artery occlusion	Brachial artery flow mediated dilation significantly improved upon rosuvastatin therapy (significant in lcSSc and trend in dcSSc). No change in ABPI No changes in LDF at forearm
Phosphodiesterase type 3 inhibitor (PDE-3)	Rajagopalan et al. (2003) [226]	Double blind, randomised, placebo control	Cilostazol, 100 mg twice daily, 6 weeks	19 PRP, and 21 SRP (5; systemic lupus erythematosus, 7 SSc, 3 Sjogren's syndrome, 2 undifferentiated connective tissue disease, 1 polymyositis, 1 Rheumatoid arthritis, 1 mixed connective tissue disease)	Doppler US flow mediated dilation of the brachial artery and nitroglycerin-flow mediated dilation. Brachial artery diameter at baseline and after whole hand cold challenge LDI digital occlusion	Brachial artery diameter had increased in treatment groups at 6 weeks (both PRP and SRP) At baseline there was a (non-significant) trend for increased flow mediated dilation in PRP versus SRP. No change in FMD was found after cilosazol At baseline and following treatment no differences were found for nitroglycerin flow mediated dilation between groups LDI occlusion response was unchanged in both groups
Phosphodiesterase type 5 inhibitors (PDE-5)	Fries et al. (2005) [108]	Double-blinded, placebo-controlled, fixed-dose, crossover study	Sildenafil (50 mg twice daily), 4 weeks	20 Patients with symptomatic SRP	Outcome measures included NCM with LD anemometery (LDF) in 3 capillaries	After the 4 week sildenafil treatment blood flow within the vessels had significantly increased
	Caglayan et al. (2006) [227]	Open label study	Vardenafil10 mg twice daily, 2 weeks	40 Patients with PRP and SRP	During cold exposure (4 °C) finger blood flow was measured by LDF baseline, 1 h and 2 weeks	Improvement in response to cold challenge was found in 70 % of patients
	Friedman et al. (2007) [107]	Double blind placebo controlled crossover	Tadalafil (10 mg) single dose	18 PRP, 2 SRP	Finger blood flow measured by LDF during whole hand warming and cooling	Single dose had no effect as compared to placebo
	Caglayan et al. (2012) [228]	Randomised, double-blind, placebo-controlled crossover study	Vardenafil (10 mg twice daily), 6 weeks	53 Patients with PRP and SRP	Finger blood flow as measured by LDI	Non-significant improvement in blood flow with vardenafil

(continued)

Table 13.4 (continued)

Intervention	Authors, year	Study design	Intervention	Groups[a]	Outcome measures[b]/ imaging protocol	Response
Angiotensin II receptor antagonists	Pancera et al. (1997) [171]	Single-blind, crossover	Two-week course of picotamide (300 mg two times daily) or losartan (12.5 mg once daily) with an interval of a week of placebo between the active treatments	15 PRP	Finger plethysmography	Statistically significant improvement only observed following losartan
	Dziadzio et al. (1999) [64]	Randomised, parallel-group trial	12 Weeks of either losartan (50 mg/day) or nifedipine (40 mg/day)	52 patients with PRP or SSc	Whole hand cooling (15 °C for 1 min) as measured by IRT and LDF	Baseline LDF and IRT were lower in the SSc group but only LDF was significant. Although there was a reduction in the severity of RP episodes following treatment with both treatments (more so with losartan) there was no change in response to LDI or IRT
Endothelin-l (ET-1) receptor antagonists	Hettema et al. (2009) [229]	Mechanistic pilot	Bosentan (62.5 mg b.i.d. for 4 weeks, followed by the target dose of 125 mg b.i.d. for 12 weeks) and a 4 week follow-up period	15 Patients with SSc	NCM and LDF iontophoresis of ACh and NaNP, finger	No changes in NCM or LDF were found
	Rosato et al. (2010) [112]	Open-label, single-centre study	Bosentan (62.5 mg, b.i.d. for 4 weeks, followed by the target dose of 125 mg b.i.d.)	30 SSc and pulmonary arterial hypertension	Baseline 4, 8, and 16 weeks with LDI. NCM to categorise patients (early, active, late) Three sites on the dorsum hand and fingers	Finger blood flow was improved after 8 and 16 weeks. The study suggested that bosentan was most effective in patients with the early and active capillaroscopic pattern
Adrenoreceptor agonists	Lindblad and Ekenval (1990) [230]	Not stated	α2-Adrenoreceptor agonist, rauwolscine delivered iontophoretically 10 mmol/L	6 Hand arm vibration syndrome	LDF local cooling finger, (probe, 20 °C, 30 s)	There was no vasoconstriction in response to the cold challenge following iontophoresis
Alpha-adrenergic blocker	Aylward et al. (1982) [231]	Not stated	Thymoxamine hydrochloride, 40 mg, 4-times/day, 11–19 months	17 RP	Digital artery patency, Doppler US, cooling (10 and 21 °C)	Vessel patency rates improved significantly during treatment

	Wise et al. (2004) [172]	Single-centre, double-blind, placebo-controlled, randomised crossover	OPC-28326 (oral doses of 10 mg or 40 mg) or placebo	12 SSc	Finger strain-gauge occlusion plethysmography, finger skin temperature (thermocouple), time to recovery after whole hand cooling (−20 °C)	Recovery time (finger skin temperature) tended to be lower with 40 mg dose than placebo. It was also shorter with the 10 mg than placebo but this difference was not significant
Vasopressin V1a receptor antagonist	Hayoz et al. (2000) [232]	Single centre, double blind, placebo controlled, randomised crossover	Oral SR49509, 300 mg once a day for 7 days	20 RP	FSP, finger skin temperature with whole hand cold challenge, (3 min 15 °C) at baseline, 2 and 4 h after treatment (only on first and last days of treatment).	Significant reduction in FSP response to cold in active treatment arm and significantly reduced rewarming time
Serotonin antagonist	Roald and Seem (1984) [154]	Double blind crossover study	Oral ketanserin, 20 mg three times day; after 10 days 40 mg ketanserin three times day for total 3 weeks	10 Connective tissue disease and RP	Finger, LDF, PPG, finger skin temperature, whole hand cooling (15 °C, 2 min)	Reduction in recovery time after cold challenge seen with LDF
	Lukác et al. (1985) [233]	Randomised double-blind trial	Oral ketanserin, 60 mg daily (month 1), 120 mg (months 2 and 3)	15 SSc	IRT, Doppler US, NCM	Improvement in the treatment group as compared to the placebo group
	Larsen et al. (1986) [234]	Double blind crossover study	20 mg ketanserin three times daily for the first week followed by four weeks at 40 mg three times daily	12 Traumatic vasospastic disease	FSP and rewarming time after cold provocation	Improvement in FSP and faster rewarming time after treatment with ketanserin than after placebo
	Klimiuk et al. (1989) [235]	Not stated	Ketanserin IV 10 mg bolus, followed by an infusion over 72 h and then oral therapy	11 SSc	IRT, Doppler US and LDF	Significant improvement found after treatment
Rho kinase inhibitors	Fava et al. (2012) [236]	Double-blind, placebo-controlled, randomised 3-period crossover study	Rho kinase inhibitor (single oral fasudil [40 mg or 80 mg]	17 SSc and RP	Finger skin temperature (thermistor) and LDI cold challenge (whole hand cooling to −20 °C)	No significant improvement in skin temperature or blood flow was found

(continued)

Table 13.4 (continued)

Intervention	Authors, year	Study design	Intervention	Groups[a]	Outcome measures[b]/ imaging protocol	Response
Antioxidant	Sambo et al. (2001) [155]	Multi-centre, open clinical	IV N-acetylcysteine (NAC), 5 day starting with a 2 h loading dose of 150 mg/kg, then 15 mg/kg/h 20 day follow-up	22 SSc	Whole hand cooling (10 °C) for 3 min cold PPG	Recovery time following cold challenge significantly reduced after treatment
Anticoagulant	O'Reilly et al. (1979) [237]	Randomised placebo controlled	Intermittent heparinisation, 3,000 IU IV each week for weeks; plasma exchange, 2.0-2.5 L/week, 4 weeks, 70–75 % of total plasma exchanged on each occasion	27 RP	Digital Doppler US, digital cooling (15 °C) and warming (45 °C) baseline, 6 weeks and6 months post treatment.	No difference in vessel patency in the 9 patients on heparin but improvement in those undergoing plasma exchange
Calcitonin-gene-related peptide (CGRP)	Shawket et al. (1989) [109]	Double-blind comparing 3 vasodilators	IV CGRP; 2, 4, 8, 16 ng/kg; Adenosine triphosphate (ATP); 5,50,75, and 125 μg/kg; Prostacyclin epoprostenol (PGI2); 2,4,6, and 8 ng/kg; 20 min (5 min at each dose)	8 RP 8 HC	Hand and cheek LDF measurements made continuously during infusion	CGRP induced increased blood flow in RP group in face and hands, in HC group in face only. PGI2 induced increased blood flow in hands and face of RP and HC. ATP caused no significant changes in blood flow in RP group but increased skin blood flow in face or HCs
	Bunker et al. (1993) [110]	Randomised, double blinded, placebo	IV CGRP 0.6 mg/min, 3 h/day for 5 days or saline	10 SRP with digital ulcers	Finger skin temperature (thermocouple), hand and finger blood flow with LDF baseline and following infusion	Significant increases in finger blood flow were found but not finger skin temperature. Changes in blood flow were reflected by ulcer healing in four of the five CGRP-treated patients but none in the saline-treated patients
Botox	Neumeister (1) 2009 [238] (2) 2010 [239]	Two retrospective studies	Injected with 50–100 units of onabotulinumtoxin A	(1) 19 RP and chronic ischemic hand pain, several with and ulcers (2) 33 RP	LDI was carried out in a subset of patients	Following treatment with botox 84 % of patients reported pain reduction and 10 of the 14 patients undergoing LDI showed increased perfusion. All ulcers went on to heal. In the later study similar results were found 33 patients with RP

Sympathectomy	Ruch et al. (2002) [113]	Follow-up	Periarterial sympathectomy	22 SSc (29 hands)	Pre and post finger blood flow, LDF, whole hand cooling (4–8 °C for 20 min)	Finger blood flow increased in 22 hands at a mean of 31 months after sympathectomy
	Maga et al. (2007) [240]	Not stated	Thoracic sympathectomy	25 RP	Occlusion finger blood flow as measured by LDF	Found improvement in 25 patients with RP up to 5 years after sympathectomy
Stem cells	Nevskaya et al. (2009) [241]	Case studies	Local injection of cells from peripheral blood and bone marrow in combination with mononuclear cells	2 SSc	A number of outcome measures including flow-mediated brachial artery reactivity measured by ultrasonography, LDF and IRT	Several LDF parameters imply improved vessel reactivity and perfusion
	Ishigatsubo et al. (2010) [71]	Efficacy and safety	Injection of autologous transplantation of bone-marrow-derived cells	8SSc ulcers resistant to treatment	LDF, IRT and NCM	Increased skin temperature and blood flow and new capillaries as visualised by NCM following treatment
Alternative therapies	Schlager et al. (2011) [72]	Not stated	Acupuncture	26 RP	LDI and thermography whole hand cold challenge (20 °C, 1 min)	No significant difference was seen with either imaging technique after treatment

[a]*HC* healthy controls, *RP* Raynaud's phenomenon, *PRP* primary Raynaud's phenomenon, *SRP* secondary Raynaud's phenomenon, *SSc* systemic sclerosis, *lcSSc*, limited cutaneous SSc
[b]*LDF* laser Doppler flowmetry, *LDI* laser Doppler imaging, *NCM* nailfold capillaroscopy, *ACh* acetyl choline chloride, *NaNp* sodium nitroprusside, *US* ultrasound, *ABPI* Ankle brachial pressure index, *IV* intravenous, *FSP* finger systolic pressure, *PPG* photoplethysmography, *IRT* infrared thermography

angiotensin II receptor antagonists [64], calcitonin gene-related peptide (CGRP) [109, 110] and endothelin receptor antagonists [111, 112]. The effects of non-pharmacological treatments such as digital sympathectomy [113] and acupuncture [72] have also been assessed using LD. No preferred LD approach or endpoint has emerged for use in clinical trials and consensus for a standardised approach would be of great benefit. The improved temporal resolution of LD over IRT makes LD techniques attractive for use in studies measuring the immediate effects of therapy for RP (LDF may be particularly useful here as the probe can remain in position throughout the study). LSCI has been used in a single therapeutic trial of RP and has potential for development in this field [114].

Expert Opinion on LD Techniques

The different LD systems available provide flexibility for objective and near real-time assessment of cutaneous perfusion in RP. Although traditionally requiring more rigorous training and safety precautions than IRT due to laser safety, LSCI systems now remove some of this concern. As with IRT, standardisation of multi-centre approaches to protocols, dynamic challenges and endpoints should aid validation of LD techniques and hence progress its role from research to clinical tool. LD systems have the potential to transform our approach to drug development by facilitating early phase proof-of-concept work or dose-ranging phase 2b studies, potentially reducing the number of negative larger late-phase clinical trials in RP.

Doppler Ultrasound

Single point Doppler ultrasound (US) uses the change in the frequency (analogous to LDF) of high frequency sound waves (MHz) scattered from blood cells in vessels to determine blood flow values observed as waveforms (Fig. 13.9). An index matching gel is used to allow good conductance of the waves in to the skin from the small handheld transducer which also collects back reflected waves. Single point Doppler US has been used primarily as a clinical tool to assess the macrovasculature of the upper and lower limbs in RP, performing ankle brachial pressure indices, discussed below. US imaging (which often incorporates Doppler imaging) provides two-dimensional maps of skin and tissue layers. It uses the amount of time taken for sound waves entering the skin to return to the transducer (i.e. the echo time, sound waves travel at different speeds through different tissues) and the wave's amplitude to build up images of the tissue underlying the skin. The Doppler signal is then superimposed onto this structural image allowing visualisation of blood flow through vessels.

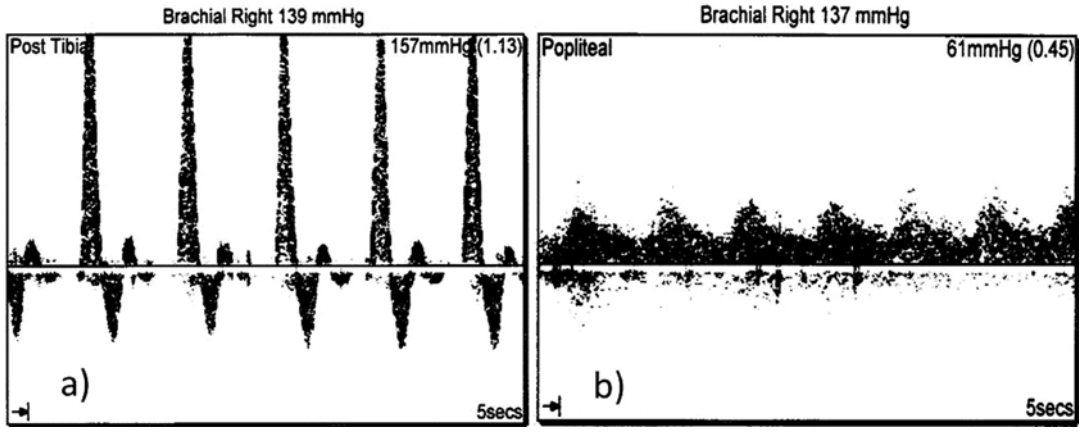

Fig. 13.9 Doppler ultrasound measurements. Examples of (**a**) normal waveforms and (**b**) decreased amplitude waveforms (with reduced ABPI) suggestive of large vessel disease (with thanks to Tonia Moore and Joanne Manning)

Ankle Brachial Pressure Index

The ankle brachial pressure index (ABPI) is the ratio of the systolic blood pressure in the lower compared to the upper limbs. ABPI is used in clinical practice to exclude concomitant macrovascular disease which can contribute to lower limb digital ischaemia in patients with SSc [115, 116]. The test utilises Doppler US to provide pulse waveforms of the brachial, dorsalis pedis and posterior tibial arteries (or brachial, radial and ulnar arteries if only upper limb tests are required). If systolic pressure and waveform amplitude are reduced distally this is indicative of arterial disease. Studies indicate that ABPI is generally normal in both PRP and SRP indicating normal macrovascular function although the presence of anti-centromere antibodies may be weakly associated with a reduced ABPI in SSc [117, 118].

Doppler Ultrasound Measurement in the Assessment of RP

Doppler US imaging has been used as a research tool in several studies to measure structural and functional parameters in RP. Structurally, decreased brachial artery diameters have been found in patients with SRP as compared to controls [119] and decreased brachial, radial and digital artery diameters identified in SRP compared to PRP [120]. In terms of vascular function, digital vasospasm and vessel closure, in response to cold challenge has been assessed using US [121, 122] and Doppler US can be used to differentiate between healthy controls and RP [121, 123–125], between groups of patients with PRP and SRP, and between patients with PRP and undifferentiated connective tissue disease [126, 127, 129]. The cold challenge has also been used to demonstrate reductions in the flow volume and delayed recovery in patients with SRP compared with PRP [120]. There have been contrasting findings as to whether endothelium-dependent and endothelial-independent digital and brachial artery vasodilation differ between SRP and healthy controls [119, 128]. Endothelium-dependent increases in digital arterial diameter have been found to be higher in healthy controls compared with RP but the reverse is true of endothelial-independent vasodilation [130]. Rosato et al. have presented data on resistive indices (RI) of the digital artery, a ratio of the difference between the peak systolic velocity (PSV) and end diastolic velocity (EDV) over the PSV, i.e. RI = (PSV − EDV)/PSV. Resistive indices were found to be higher in SSc compared to controls [131]. In separate work, the RI was found to be significantly higher for patients with dcSSc than controls [132]. Increased resistance was also found in patients with hand-arm vibration syndrome [133]. Other endpoints measured in the digital artery include: Pulsatility index, PI = (PSV − EDV)/(time averaged maximum velocity), which was found to be increased in patients with SSc as compared to controls [131]; flow volume, which after cold challenge was found to be significantly less in SRP than PRP and time for flow to start/recovery was found to be longer for SRP than PRP [120]. Studies have found good reproducibility of US [122]. Studies of Doppler US used in combination with other imaging techniques are presented in Table 13.3 and those involving treatments or clinical trials are summarised in Table 13.4.

Expert Opinion on Doppler US

Doppler US is a useful clinical tool at identifying those with concomitant macrovascular disease. It is a contact technique which requires specialist training both to obtain and interpret measurements. Developments in Doppler US imaging have allowed many new endpoints and parameters to be measured offering the possibility of more sensitive identification of macrovascular structural or functional changes, but these methods require further validation.

Finger Systolic Pressure

The techniques discussed thus far have been stand-alone imaging techniques. Finger systolic pressure (FSP) is a macrovascular research tool,

a dynamic challenge, which is used in combination with measurement/imaging techniques to measure digital blood pressure. To measure FSP a digital blood pressure cuff is placed around the proximal phalanx and the cuff inflated to suprasystolic pressure until pulsation ceases (closing pressure). The pressure is then gently lowered and the pressure at which the pulse reappears during deflation (opening pressure) is recorded. The opening pressure is known as the FSP. The reoccurrence of the pulse is measured by one of several techniques including: plethysmography (strain gauge or electronic (digital) [134–136], LDF [135, 137, 139] or NCM [138]. FSP is frequently used in combination with temperature challenge. Either the ambient temperature is raised or lowered or, to provide changes in skin temperature directly, water is circulating in a second cuff placed around the middle phalanx of the same finger.

Several studies have used FSP to differentiate between control and RP groups, although patient numbers tend to be small [140, 142, 143]. FSP has also been used to differentiate between PRP and SRP and controls [141] and to discriminate between those with and without traumatic vasospastic disease [134, 144, 145]. Maricq et al. reported good specificity and sensitivity between groups of PRP, SSc and healthy controls using FSP following local finger cooling [146]. However several studies [135, 147, 148] describe low sensitivity and/or large overlap between RP patient and control group values. In a study assessing reproducibility of FSP it was proposed that there is an adaptation in the response of patients to the CST when repeated longitudinally which has implications for all of the imaging techniques discussed in this chapter when monitoring CST response [149].

Expert Opinion on FSP

FSP and its associated endpoints are less well established than some of the other techniques discussed previously. However, in combination with the imaging techniques discussed above it shows promise in terms of differentiating between patient groups. The technique requires further validation and at present remains a primarily a research tool.

Plethysmography

Plethysmography is another research tool, or method of dynamic challenge, which can be combined with other techniques to determine circulatory capacity and function [150]. Venous occlusion is carried out with a pressure cuff around the body part of interest. In studies of RP this is typically the digit. Cuff pressure is increased allowing arterial inflow to continue while venous outflow remains obstructed; thus the limb volume increases. Plethysmographic studies in RP have evaluated change in flow using various methods including strain gauge [13, 151] or light (usually infrared light emitting diode and detector), known as photoplethysmograph [152, 153]. Plethysmography is usually carried out alongside temperature change, e.g. local cooling of the hand [154, 155] or in physiological studies of endothelial and non-endothelial vasodilation [156–158].

Plethysmography studies comparing groups of patients with PRP and SRP to healthy controls have had conflicting results; likely due to the differing parameters that have been measured and which dynamic challenges have been used. In several studies plethysmography has been used to effectively differentiate between RP and control groups [159–160]. Rosato et al. investigating the pulsatility of the digital arteries in patients with PRP, SSc and controls with photoplethysmography found that the different waveforms were able to differentiate between the three groups and subsets of the SSc group categorised for early, active and late NCM patterns [153]. In other studies PRP and SRP could not be differentiated [161, 163]. The differing outcomes of these studies indicate that care must be taken in terms of which outcome measures and parameters are used when looking for differentiation.

Plethysmography has been used to study the relationship between arterial flow and microvascular

perfusion and identified decreased nutritive flow in patients with SSc as compared to other patients with RP [162, 164]. Plethysmography studies have demonstrated the effects of both emotional stress and menstrual cycle in patients with RP and controls [13, 165]. They have also assessed both the severity of hand-arm vibration syndrome and differentiation of patients with hand-arm vibration syndrome from controls [166, 167]. Plethysmography has been found to provide data which corresponds to that from LD techniques [164, 168, 170]. Plethysmography has been used in therapeutic studies of RP [154, 169, 171, 172], several are summarised in Table 13.4.

Expert Opinion on Plethysmography

As with FSP, plethysmography remains very much a research tool and is less well utilised than the other techniques discussed in this chapter. It also requires combination with a measurement technique. Reproducibility or sensitivity measurements have not been well described.

Agreement Between Existing Microvascular Imaging Techniques

Many research studies use more than one technique to assess microvascular structure/function in RP. These studies are summarised in Table 13.3. The studies include comparisons of LDI and IRT [98, 173], LDF or LDI and NCM [174, 175], LDI and FSP [146, 176, 177]. Studies of LDI and IRT tend to be aiming to compare direct and indirect measures of perfusion and look for correlations [41, 54]. Seifalian et al. found a lack of correlation between LDI and IRT with hot/cold challenges [98, 179]. Schlager et al. [173] found good correlation at baseline between IRT and LDI but weaker correlation following cold challenge. Other studies have found good correlation between IRT and both LDI (line scanning) and LSCI, respectively [41, 54]. This is due to the different endpoints used again highlighting the problem in comparing studies that do not follow the same protocol. Seifalian et al. comparing LDF and LDI found good correlation [98]. Many studies utilising NCM in addition to LDF or LDI, use NCM as a confirmation of disease. However those that do compare blood flow response to NCM have had contrasting results, some finding correlation, others none, to quantitative measurements of capillary density and width [54, 178]. Other studies find correlation to the early, active, late categorization [97, 174, 175]. These study differences are, again, most likely due to the heterogeneity of study protocols used or the heterogeneity of the study populations which tend to be small.

Emerging Technologies

There are additional less extensively evaluated non-invasive imaging techniques that may emerge as useful methods for assessing microvascular dysfunction in RP. These new techniques offer alternative methods and endpoints for use in research studies and may therefore increase our ability to differentiate between PRP and SRP or be more sensitive to change.

Polarised Light Imaging

When light is scattered off predominantly inhomogeneous media there is a depolarizing effect; the incident light loses some of its polarisation. Therefore when polarised light is backscattered from skin, the light that has undergone significant scattering (usually by penetrating more deeply into skin) undergoes a greater loss of its polarisation whereas the light that has undergone little or no scattering retains its polarisation. The polarised and non-polarised components of the light, representing superficial and deeper skin layers respectively can be separated out by use of a polarizer. Polarisation imaging offers a novel method for visualising the cutaneous microvasculature (e.g. for measuring the size of capillaries). Since it monitors changes in red blood cell concentration rather than perfusion it provides different but correlating information as compared to LD techniques [180–183].

Optical Coherence Tomography

Optical coherence tomography uses broadband light to image into the skin in a similar manner to US, with a resolution of approximately 10 μm (Fig. 13.10). Studies have begun to evaluate its application in connective tissue disorders associated with RP but thus far only to assess skin properties rather than the vasculature [184–186]. It offers the option of three-dimensional imaging (although at the cost of imaging speed). Future technological improvements may allow this technique to provide measurement of blood flow in individual vessels (utilising Doppler analysis [189, 190]), and oxygenation (utilising spectroscopic analysis [188]).

Spectroscopy

Cutaneous blood oxygenation and oxidative stress, both of which are implicated in the pathogenesis of SSc and other underlying undifferentiated connective tissue disease can be assessed by single point spectroscopy [189, 190]. This is carried out utilising a bifurcated fibre to both deliver white or ultra-violet illumination to the skin and collect the emitted spectrum (analysed on a spectrometer) [191]. White light allows the absorption spectrum and hence oxygenation levels to be assessed. Ultraviolet light induces autofluorescence, shown to be associated with the concentration of end glycation products in the skin and therefore an indicator of oxidative stress [192, 193, 195]. As with LDF the main limitation of this technique is the use of a fibre and thus the small volume of skin assessed.

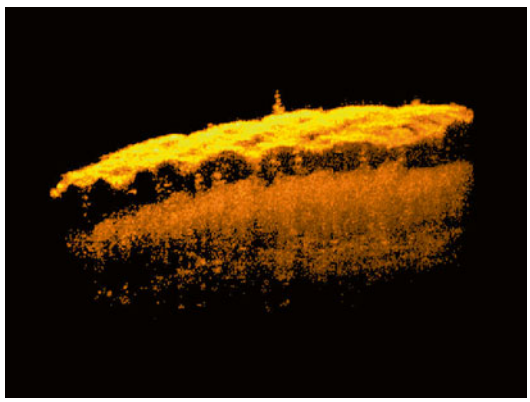

Fig. 13.10 Optical coherence tomography. Image of skin in three dimensions showing the surface (*top*) of the skin on a finger pad (peaks and troughs due to fingerprint) and showing sweat glands (*vertical* spirals) beneath the epidermis (with thanks to Graham Dinsdale)

Multispectral Imaging

Multispectral imaging overcomes the issues of sampling a small volume of skin by taking a series of larger two-dimensional images of the skin's surface whilst the skin is illuminated with white light [191, 194, 196, 197, 198] (Fig. 13.11). Images are taken over a range of narrow wavelength bands (e.g. 10 nm) allowing image "cubes" representing the skin absorption spectrum to be collected. Cubes can be interrogated at different wavelengths to assess skin oxygenation at specific sites during dynamic challenges. A version of spectroscopic imaging has also been used to allow measurement of oxygenation in individual vessels within NCM images [199]. Single point spectroscopy and multispectral imaging offer alternatives to invasive oxygenation techniques and digital pulse oximetry which may be associated with technical difficulties due to fibrosis [200].

Expert Opinion

Non-invasive imaging techniques have huge potential in the differentiation of patients with PRP and SRP (key to facilitating early diagnosis and appropriate management), in the elucidation of underlying pathophysiology and as outcome measures for treatment studies/clinical trials. Nonetheless, there are limitations with much of the work that has been undertaken so far which has restricted the use of these methods in clinical practice. Many of the studies discussed in this chapter are small single-centre studies (limiting the statistical power of the study) and lack age and gender matching (which precludes easy between-group comparison). There has been a lack of

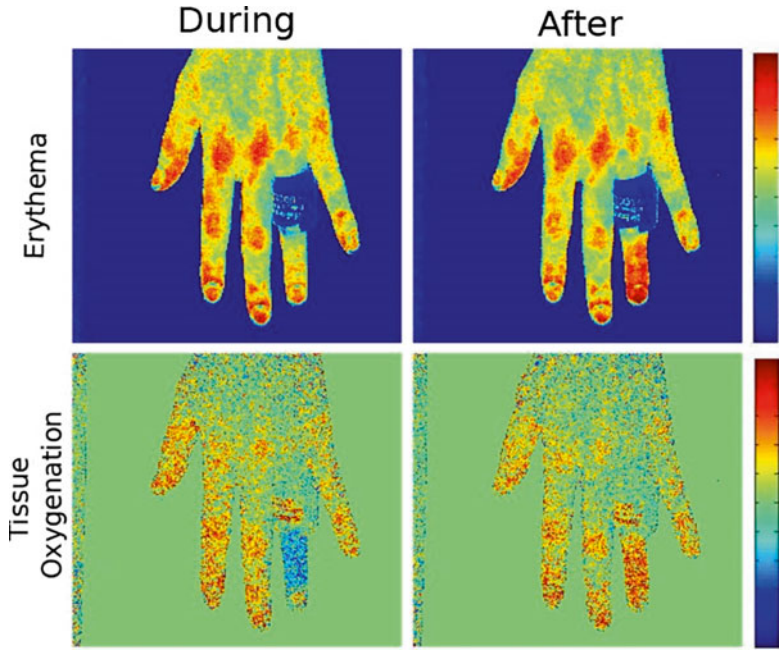

Fig. 13.11 Multispectral imaging. Images of multispectral images of skin erythema (redness representative of blood flow) and blood oxygenation during and after digital occlusion in a healthy control (finger cuff on ring finger). Scale colours to the *right* hand side of the images (*red* high erythema or oxygenation levels and *blue* low), all in relative arbitrary units. Images show decreased erythema and oxygenation during occlusion and increased levels upon release (with thanks to Ian Poxon)

consensus on a standardised approach to imaging protocols preventing useful comparison between studies. Additional reassurance is also needed regarding the reproducibility of these techniques (both in obtaining and analysing data) and of their sensitivity and specificity in combination with dynamic challenges. In order to strengthen and further validate these techniques, moving them into more mainstream clinical use, larger, multi-centre studies with agreed protocols are required. These studies should include assessment of repeatability and responses to established vasoactive therapy such as parenteral prostacyclin therapy. Objective non-invasive assessment of digital vascular function overcomes many of the limitations of subjective self-report assessment and is likely to become a more important tool in the diagnosis, classification and assessment of therapeutic response in RP in the future. A consensus approach to standardising imaging protocols and endpoints for analysis for each of the techniques is an important first step in developing and refining these techniques for more widespread use. The fall in the real cost of techniques such as IRT and laser-derived methods will allow more widespread use outside of specialist centres. The next decade promises to deliver exciting new developments within this field with growing enthusiasm for large multicentre cross-sectional studies of microvascular imaging and a determination to incorporate microvascular imaging endpoints at the core of interventional studies evaluating novel treatments for RP.

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Angiography

14

Yannick Allanore, Jean-Luc Drappé, and Thomas Reifsnyder

Abbreviations

CTA	Computed tomography angiogram
CTDs	Connective tissue diseases
DU	Digital ulcers
MRA	Magnetic resonance angiogram
RP	Raynaud's phenomenon
SSc	Scleroderma

Key Points

1. Every patient with a diagnosis of Raynaud's phenomenon (RP) should be carefully evaluated, beginning with an attempt to identify a treatable secondary cause and to define any comorbid complicating factor(s).
2. When physical findings suggest large vessel disease, then noninvasive testing in the vascular laboratory is recommended.
3. If large vessel pathology is confirmed by the vascular laboratory, then angiography [digital subtraction arteriography (DSA), magnetic resonance angiogram (MRA), computed tomography angiogram (CTA)] should be done to define the causative lesion.
4. MR angiography and CT angiography have the advantage of not requiring intra-arterial puncture visualize distal limb vessels poorly compared to conventional DSA. In addition, at the time of DSA, endovascular interventions such as angioplasty and stenting can be performed.
5. Computerized tomography has the advantage of defining vessel wall changes while MR and conventional arteriography focus on luminal changes of the vessels studied.

While uncomplicated primary Raynaud's phenomenon is undoubtedly the most common form of this vascular manifestation, one must be aware of the many causes of secondary Raynaud's phenomenon and associated comorbid conditions that can influence management. The multiple causes of RP ranging from external causes (vessel compression or trauma) to endovascular causes [vasculitis and connective tissue diseases (CTDs)] are reviewed in Chaps. 8 and 10. This chapter is focused on guidelines to the indications and use of large vessel imaging when confronted with a patient with RP. While only a small proportion of patients with RP require angiography, this is an important minority because large vessel disease amenable to specific treatment may be identified. Failure to diagnose large vessel disease may result in severe digital ischemia or the need for amputation.

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Workup of Raynaud Phenomenon

The diagnosis of Raynaud's phenomenon is purely clinical and does not require specific tests for its identification. The diagnosis of RP in the clinical setting is based upon a history of uniphasic color changes (blue or white events) or direct witnessing of an event during physical examination. Every patient with a diagnosis of RP should be carefully evaluated, beginning with an attempt to identify a treatable secondary cause and to define any comorbid complicating factor(s) by history and physical examination. Clinical clues to a secondary cause of RP include:

1. Late age of onset (over the age of 30).
2. Male gender.
3. Signs of severe tissue ischemia including skin or digital ulcers.
4. Asymmetrical attacks (especially unilateral events or isolated lower extremity involvement.)
5. Presence of painful attacks (uncomplicated attacks are uncomfortable with "pins and needles" and numbness, but generally they are not painful).
6. Absence pulses or asymmetrical blood pressure.
7. Signs or symptoms of an underlying disease such as an autoimmune disease.
8. Laboratory features that point to a secondary cause or comorbid condition.

Large vessel assessment is mainly required when digital ulcers (DUs) are severe, recurrent and/or when larger vessel obstruction is suspected; recognizing that macrovascular disease may occur concomitantly with an underlying microangiopathy. For example, patients with systemic sclerosis may in addition have proximal large vessel disease either due to the disease process or coexisting arteriosclerosis.

Evaluating Patients with RP Secondary to a CTD

Raynaud's phenomenon is a common complication in patients with connective tissue disease (see Chap. 8). In systemic sclerosis (SSc), RP is uniformly a major problem and peripheral vascular complications are common. Digital ulcers are primarily due to a vasculopathy of the peripheral arteries in the fingers and toes, in which the intima of vessels becomes thickened and the lumen occluded. The EUSTAR cohort study identified that 36 % of the patients with SSc had DU at some point and 17 % had active ongoing ulceration at inclusion [1]. There are less data about critical ischemia and progression to gangrene. Of the 2,080 Pittsburgh SSc patients, 32 % ($n=666$) of all patients with SSc had persistent DUs and overall 11 % of the SSc patients had undergone amputation or experienced gangrene [2]. Comparison of SSc cases with and without digital amputation showed that this complication was associated with older age, long history of RP, long disease duration, presence of anti-centromere antibody, and coexistence of peripheral artery disease and hypercholesterolemia [3]. Other risk factors for vascular damage are a history of smoking or the presence of an overlap between SSc microangiopathy and vasculitis; such as cryoglobulinemic vasculitis [4]. Indeed, among patients with SSc, current smokers are 3–4 times more likely than never-smokers to incur digital vascular complications. After adjusting for age, sex, and disease duration, current smokers were significantly more likely than never-smokers to have had debridement (OR 4.5, 95 % CI 1.1–18.3) or admission for intravenous vasodilators (OR 3.8, 95 % CI 1.1–12.9). Patients smoking at higher intensity were more likely to require admission for intravenous vasodilators [5]. These findings are supported by another report showing that smoking had a strong negative effect on vascular outcomes in SSc; although severe vascular damage such as gangrene was not evaluated [6]. These data support that large vessel vasculopathy and/or the presence of cardiovascular risk factors (smoking, diabetes, hyperlipidemia) increase the risk of critical ischemia and gangrene in SSc-Raynaud. In the context of SSc or another CTD, vascular imaging is not recommended unless there is a suspicion of correctable large vessel disease. The presence of recurrent DU or gangrene of a digit should lead

to noninvasive evaluation of the involved extremity's circulation. Doppler derived pressure measurements will detect hemodynamically significant large vessel disease. Color duplex ultrasound can then be used to image the affected vessels. This modality has good sensitivity and specificity for detecting significant stenoses. If a potentially significant lesion is found, then referral to a vascular specialist for angiography would be indicated.

Unilateral Raynaud's Phenomenon

One of the main clinical findings suggesting large vessel obstruction or compression is unilateral symptoms. Indeed, unilateral Raynaud's phenomenon or an asymmetric expression of vascular compromise should always lead to vascular evaluation. Most commonly, atherosclerosis is the cause of large vessel obstruction. Atherosclerotic risk factors and typical symptoms such as claudication or rest pain will lead to the diagnosis. Less commonly arterial damage and obstruction are caused by either extrinsic or intrinsic repetitive injury. The classic for external repetitive trauma is hypothenar hammer syndrome. This problem which is generally seen among workers using jackhammers, chisels, and other high impact tools is caused by repetitive trauma to the ulnar artery proximal to the superficial palmar arch eventually leading to obstruction and ischemia [see Chap. 9]. Thoracic outlet syndrome is caused by repetitive intrinsic trauma and is associated with Raynaud's phenomenon in about half the cases. Although the symptoms of pain and paresthesias are usually due to neurogenic causes, infrequently the subclavian artery is involved. Arterial involvement is nearly always associated with a cervical rib, and therefore, appropriate imaging is mandatory [see Chap. 11]. Therefore, a patient presenting with unilateral Raynaud's phenomenon or isolated digital ischemia warrants special testing to establish the cause. The exact workup is guided by the overall clinical situation. In addition to a comprehensive physical examination that focuses on the circulation, noninvasive testing should be used to detect and quantify the degree of ischemia. Utilizing Doppler ultrasound and photo plethysmography, wrist/brachial indices, ankle/brachial indices, and digital pressures can all be easily obtained. In patients with suspected thoracic outlet syndrome, these tests can also be done with the extremity in various positions to determine if the neurovascular bundle is indeed being compressed. Once the circulation has been shown to be abnormal, detecting and defining the causative lesion can be done with color duplex ultrasound. The limitations of this technique include the difficulty in defining sequential stenoses and poor visualization of the origins of the brachiocephalic trunk vessels. Therefore, once an abnormality is confirmed by pressure testing, the cost-effective next step in the workup is to proceed directly to angiography.

Causes of unilateral vasospasm mimicking Raynaud's phenomenon

- Traumatic occlusion.
- Thoracic outlet syndrome.
- Emboli.
- Atherosclerosis.
- Vasculitis.
- Systemic vascular disease with associated microvascular complication.

Angiography

Digital Subtraction Angiography

Digital subtraction angiography, although a minimally invasive diagnostic test (Figs. 14.1 and 14.2), remains the gold standard for arterial evaluation. Due to its invasive nature, there is a low, but real rate of complications such as puncture site hematoma or pseudoaneurysm, arterial dissection, and vessel occlusion. In addition there is a low risk of contrast induced nephrotoxicity (see Table 14.1). The risk of angiography is not warranted in cases of RP alone. Studies have used magnification hand angiography coupled with

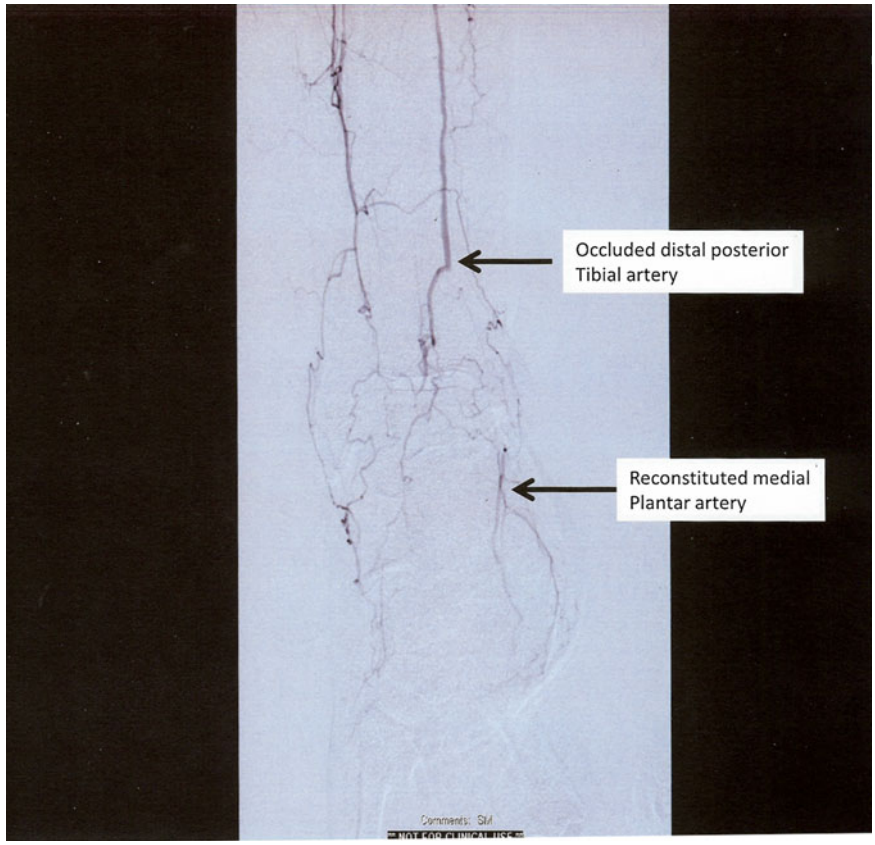

Fig. 14.1 Patient with longstanding RP and SSc and no atherosclerotic risk factors. She presented with dry gangrene of multiple toes and no palpable pedal pulses. Angiography showed severe tibial occlusive disease more typical of atherosclerotic disease

cold exposure to perform pharmacodynamic tests; the diagnostic and predictive value of such examination has never been fully demonstrated [7]. Indeed, in series of 103 patients suffering from bilateral Raynaud's phenomenon without any obvious underlying disease and who were unresponsive to nifedipine and aspirin, standardized angiograms showed findings compatible with primary vasospasm in 42 patients and atherosclerotic vascular disease in 44 patients [8]. These data were not correlated with important clinical outcomes but do demonstrate that arteriography can be helpful in select group of patients with Raynaud's phenomenon.

Assessment by angiography should be used selectively for severe cases. Generally it should be used as a preoperative planning tool as the presence of a lesion should already be known from noninvasive testing. For example, patients with SSc and severe RP characterized by refractory digital ulcerations despite medical therapy have been investigated for large artery involvement to help define therapy. In a retrospective series of 15 patients, ulnar artery occlusive disease was documented by a positive Allen test and ulnar artery angiography. Ulnar artery revascularization combined with digital sympathectomy was done in 8/15; all 8 experienced dramatic improvement in RP and healing of digital ulcers [9]. Although uncontrolled, this study in a selected subgroup of SSc who were failing conventional therapy, suggests that if ulnar artery disease is suspected by noninvasive testing then confirmed by angiography, patients can be helped by revascularization. A proposed classification of the various arterial lesions observed by angiography in patients with

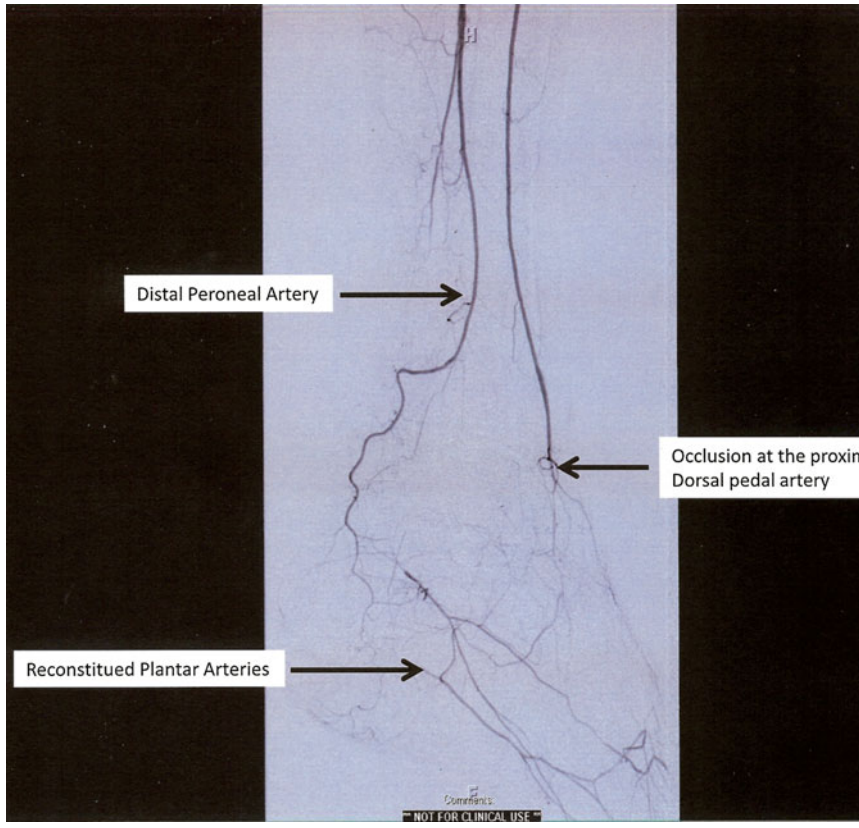

Fig. 14.2 Patient with longstanding RP and SSc. She presented with dry gangrene of multiple toes and no palpable pedal pulses. Shown are classic angiographic appearance of non-atherosclerotic vasculopathy with normal medium sized vessels that abruptly occlude near the ankle. The small vessels that remain patent appear normal

Table 14.1 Comparison of various methods of angiography

	Advantages	Disadvantages
Conventional X-ray	Standard method for viewing lumen of vessels: stenosis, occlusions, aneurysms, and other irregularities	• Requires intra-arterial puncture: bleeding, aneurysm, occlusion • Risk of ionizing radiation exposure • Contrast exposure: potential nephrotoxicity
MR angiography	• No intra-arterial puncture • Images lumen and vessel wall: detection of wall inflammation • No ionizing radiation exposure	• Long-time to perform • Exposure to gadolinium • Cannot use with devices: pacemaker, metal implants
CT angiogram	• No intra-arterial puncture • Rapid performance • Allows three-dimensional imaging of vessels and surrounding structures • Images lumen and vessel wall: thickening, calcifications, aneurysms	• Risk of ionizing radiation • Intravenous contrast: nephrotoxicity

SSc and severe RP has been published. Although unvalidated by a prospective study, this survey suggests that patients can be stratified as follows: type I and II involve the radial or ulnar arteries. (Type I with complete occlusion, while type II involved partial occlusion); Type IIIa showed tortuous, narrowed, or stenosed common digital and digital vessels and Type IIIb is a subset which involved the digital vessel of the index finger related to exposure to prolonged vibration; Type IV and V showed global involvement from the main to digital vessels (Type IV showed diffused tortuosity, narrowing and stenosis and Type V is the most severe type with paucity of vessels and very scant flow) [10]. This classification may be helpful when making surgical decisions (see Chap. 22). In fact, the main advantage of standard digital subtraction angiography is the ability to endovascularly treat many stenoses or occlusions at the time of the diagnostic test.

Magnetic Resonance Angiography

Recently, MRA has been used with and without contrast material as a safe, reliable, and accurate technique for evaluation of vascular pathologies of the hand. MRA has a major advantage over arteriography in that it is a noninvasive examination and image quality is comparable to that of conventional angiography without risk of induced vasospasm. MRA also does not require the use of ionizing radiation, and the contrast agent used, if any, is not nephrotoxic. However, contrast-enhanced MRI techniques should be avoided in patients with renal insufficiency or patients who require hemodialysis due to the risk of nephrogenic systemic fibrosis, a debilitating and potentially fatal condition. This technique can also be used for repeated examinations allowing sequential comparisons. However, MRA studies have been done in a limited number of unselected cases and not consistently in the context of critical digital ischemia; thus digital subtraction angiography is still recommended as the goal standard when evaluation is needed for diagnosis or before corrective vascular surgery.

Non-contrast MRA of the hand has also been performed; however, current experience is limited to a few specialized centers and these techniques are not widely available [11–13]. Non-contrast techniques also have the disadvantage of longer imaging time than standard contrast-enhanced techniques, which can lead to motion degradation of images in subjects that have difficulty lying still. Contrast-enhanced MR angiography offers the ability to acquire time-resolved images that also can show blood flow dynamics [14]. High-resolution is needed to visualize the small arteries of the fingers which are often less than 1 mm in diameter. The limitations of MRA are its cost, its availability, the limited depiction of small vessels beyond major digital arteries, and venous contamination; MRA may also overestimate the degree of vessel stenosis particularly at the origin of small vessels. Hand vessel visualization can be limited in the cold environment of the MRI suite and previous studies have shown that hand warming may improve vessel visualization, even among normal volunteers [13]. Lastly, the quality of the information gained from an MRA is dependent on the quality of the magnet generating the images and the experience of the radiologist reading the images.

Magnetic Resonance Angiography (MRA) Studies in Scleroderma

There have been several studies in patients with SSc that illustrate the potential usefulness of MRA studies in patients with RP and its complications. However, these studies were not referenced to digital subtraction angiography limiting firm conclusions. MRA was used to study the digital vasculature in patients with SSc by using the hand with a phased array wrist coil [15]. The MRA protocol consisted of four successive acquisitions, each lasting 52 s, of three-dimensional coronal cross-sectional images after gadolinium injection. The primary evaluation used a predefined criteria for the second to fifth fingers. The primary criteria were distality and quality of arterial opacification, avascular areas, and venous return. The time sequences are shown in Fig. 14.3. In a series of 38 consecutive and unselected SSc patients, 35 (92 %) patients had at least one true

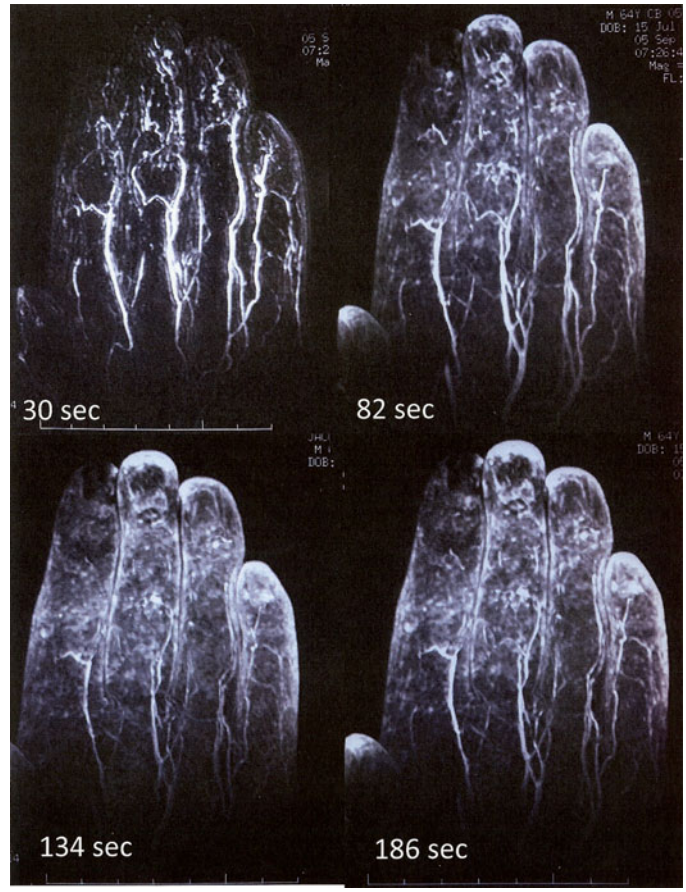

Fig. 14.3 Successive magnetic resonance arteriography images of the hand, acquired at 52-s intervals. Shown are representative images of successive arterial filling of the arteries, tissular contrast enhancement, and venous return in a patient with SSc

digital artery which did not reach the first phalanx, as assessed at the initial arterial analysis and 23 (61 %) had four or more damaged arteries. Twenty-eight (74 %) patients had thin arteries and 23 (61 %) had more than one avascular area. Current digital ulcers were substantially more frequent among SSc patients with more than four proper digital arteries which did not reach the first phalanx than other patients (10/23 vs. 0/15; $p=0.003$). All the patients had abnormal venous flux and general venous blockage was found in 12 patients (32 %) [15]. The main findings of this study are the substantial arterial and venous damage detected by MRA in patients with SSc (see Figs. 14.4, 14.5, 14.6, and 14.7). This study emphasizes that both the microcirculation and also small caliber vessels are involved in SSc as also shown by previous studies using conventional x-ray angiography.

Non-enhanced magnetic resonance imaging has also been investigated in a pilot study of six SSc patients and six controls and showed similar qualitative and semiquantitative findings as compared to the contrast enhanced MR [12]. High-resolution three-dimensional time of flight (3D-TOF) MRA at 3 T was also used for the visualization of digital arteries in SSc. In a series of 33 patients with SSc compared to normal controls, this three-dimensional method demonstrated that vessel lumen obstruction could be identified, and it is a promising method to identify and quantify the vascular involvement in SSc patients [11]. This investigation also found the severity of vascular involvement correlated with the duration of disease and that the vessels appeared different than seen in vasculitis. These methods show the heavy vascular burden seen in SSc and provide the potential

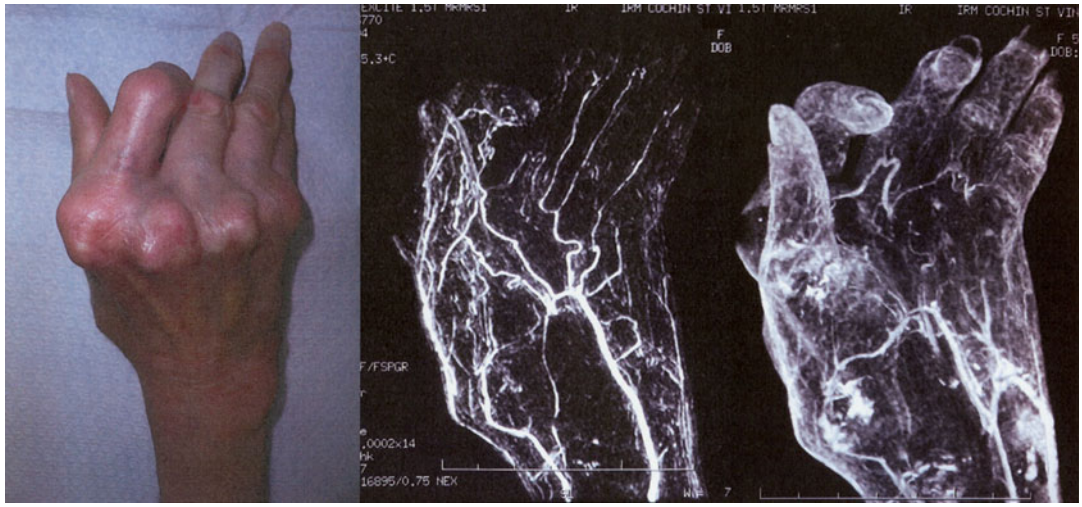

Fig. 14.4 Example of a patient with SSc with severe hand involvement. MRA demonstrates altered arterial filling with abnormal contrast intake and venous return

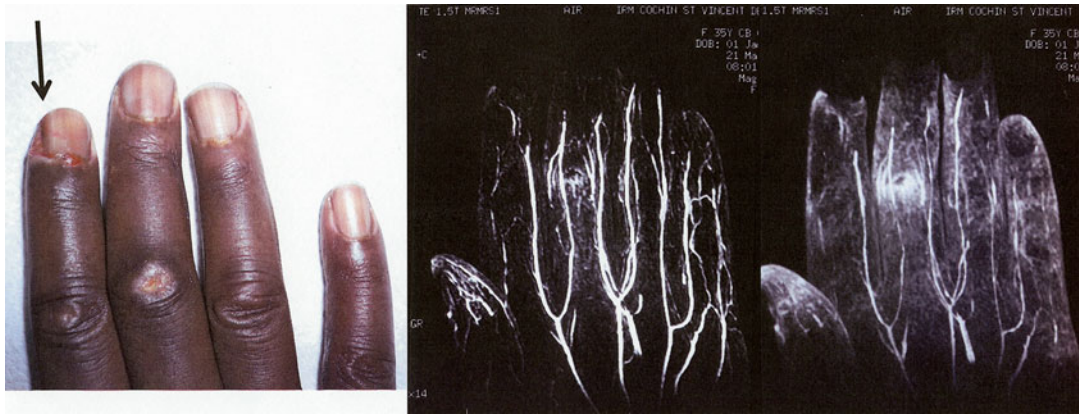

Fig. 14.5 SSc patient with altered proper digital artery filling favoring recurrent distal ulceration on the index finger

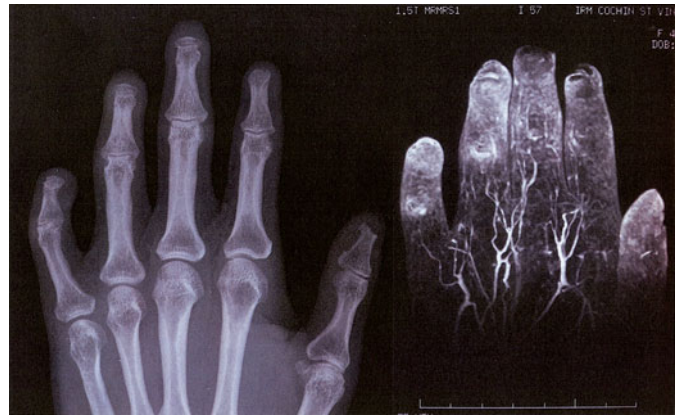

Fig. 14.6 A patient with acro-osteolysis seen on X-ray (*left*) and MRA (*right*) with very abnormal distal avascular areas

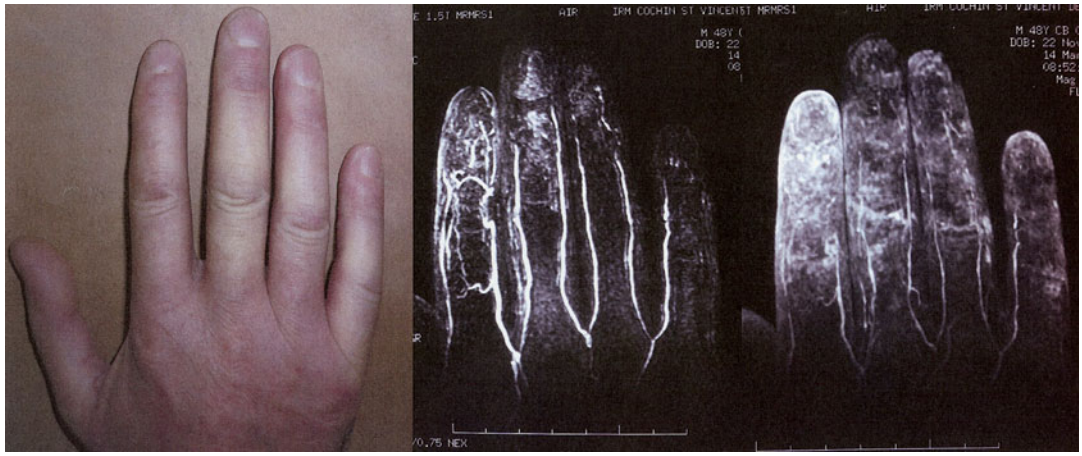

Fig. 14.7 Prototypic example of early diffuse case observed in our series of consecutive patients. Lack of filling of medial proper digital artery of the fifth and distal stop for third, fourth, and fifth proper digital arteries. Several distal avascular areas with reduced perfusion and disturbed venous return

opportunity to objectively score digital artery disease for both clinical assessment and prospective clinical trials.

Computerized Tomography Angiography

Three-dimensional (3D) images of vessels and surrounding structures can be constructed using computerized tomography (CT) technology. CT angiography (CTA) can demonstrate luminal lesions like a thrombus and vessel wall changes such as thickening seen in inflammatory vascular disease or secondary calcifications. It has the risk of radiation exposure and the need for intravenous contrast but unlike MRA, the imaging time is much shorter. Studies using a single-detector CTA in the evaluation of suspected upper extremity arterial injury showed a high sensitivity (95 %) and specificity (99 %) [16]. A systematic review and meta-analysis compared the diagnostic performance of CTA and MRA to conventional digital subtraction angiography in patients with peripheral arterial disease [17]. Out of 5,693 articles reviewed, 12 CTA and 30 MRA studies were included, respectively, evaluating 673 and 1,404 participants. Summary estimates of sensitivity and specificity were respectively 96 % (95 % CI, 93–98 %) and 95 % (95 % CI, 92–97 %) for CTA, and 93 % (95 % CI, 91–95 %) and 94 % (95 % CI, 93–96 %) for MRA. These data support the use of CTA or MRA as options to evaluate larger vessel peripheral vascular disease, thus avoiding the potential complications of digital subtraction arteriography. With comparable diagnostic accuracy, CTA has the advantage of fasting imaging times and can be used in the presence of pacemakers, defibrillators, or other metal implants. Although duplex ultrasonography has a lower sensitivity than MRA and CTA, it is cheaper, there is no radiation exposure, and no contrast agents are used. Lastly, the resolution seen with CTA limits its usefulness when imaging small vessels such as digital arteries and it has not been studied specifically in patients with RP.

Expert Opinion

In most patients, RP relates to microcirculation or digital artery impairment. In the very large majority of cases, vascular imaging is unnecessary and no special imaging test is required. When Raynaud's is unilateral or when it leads to severe tissue injury (for example digital ulceration or critical ischemia in the patient with SSc), then further imaging is indicated. Apart from a

detailed clinical examination, the diagnostic role of conventional angiography has largely been replaced by noninvasive imaging modalities, including duplex ultrasonography, CTA, and MRA. Doppler ultrasound is the first line tool to confirm the presence of large vessel involvement. If present, the location and extent of the offending lesion(s) are then defined by digital subtraction angiography, MRA or CTA. These various imaging tests will be helpful in planning any surgical interventions. These situations are complex and it is recommended that a well-trained multidisciplinary team work together, including a specialized radiologist and vascular specialist.

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Autoantibodies in Raynaud's Phenomenon

15

Victoria Flower, John D. Pauling, and Neil McHugh

Abbreviations

ACA	Anti-centromere antibodies
aCL	Anticardiolipin antibodies
ANA	Antinuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-RNA Pol	Anti-RNA polymerase
Anti-Scl 70	Anti-scleroderma 70 antibody
APLA	Antiphospholipid antibodies
APLS	Antiphospholipid syndrome
ARD	Autoimmune rheumatic disease
CENP-B	Centromere protein B
CTD	Connective tissue disease
DM	Dermatomyositis
dsDNA	Anti-double-stranded DNA antibody
DU	Digital ulceration
ELISA	Enzyme-linked immunosorbant assay
ENA	Extractable nuclear antigens
FITC	Fluorescein isothiocyanate
HEp2	Human epithelial 2 cell
IIF	Indirect immunofluorescence
IP	Immunoprecipitation
Jo-1	Histadyl tRNA synthetase autoantibodies
LA	Lupus anticoagulant
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
MCTD	Mixed connective tissue disease
Mi-2	Mi-2 antibody
PAH	Pulmonary arterial hypertension
PM	Polymyositis
PSS	Primary Sjogren's syndrome
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RP	Raynaud's phenomenon
SLE	Systemic lupus erythematosus
Sm	Smith

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SRP	Signal recognition particle
SSc	Systemic sclerosis
Th	Ribonuclease mitochondrial RNA processing
To	Ribonuclease P complexes
U1RNP	U1 ribonucleoprotein
U3RNP	U3 ribonucleoprotein
β2-GP-I	Anti-β2 glycoprotein-I

Key Points

1. Autoantibodies help to identify which patients presenting with RP are at risk of developing autoimmune rheumatic disease.
2. Autoantibodies should therefore be part of the initial assessment of the patient with RP in whom there is any concern of an underlying autoimmune disease.
3. Patients with high-titer ANA, or with disease-specific autoantibodies at any titer, but without a definite diagnosis of autoimmune disease, should be kept under review to identify systemic autoimmune disease as early as possible.
4. In the patient with RP, the specific autoantibody profile allows tailoring of screening for subclinical systemic involvement of autoimmune disease.
5. Recent work has identified autoantibodies that may contribute to the pathogenesis of vascular dysfunction in diseases associated with RP.

Introduction

Antibodies are small glycoproteins produced by plasma cells (B cells), which help the immune system to identify and remove foreign objects such as pathogens. *Auto*antibodies are those directed against host antigens. The generation of autoantibodies is a normal physiological response and may help the immune system clear cellular debris following cell death and assist with removal of abnormal cells that may otherwise progress to cancers. Under normal circumstances, clonal deletion prevents excessive proliferation of autoantibody-producing B cells which might otherwise become pathogenic. The discovery of the lupus erythematosis (LE) cell in the bone marrow of patients with systemic lupus erythematosus (SLE) in 1948 led to the identification and characterization of high levels of autoantibodies in autoimmune disease [1]. Many of the early-identified autoantibodies were directed against nuclear material (e.g., DNA), and referred to as antinuclear antibodies (ANAs). Autoantibodies may also target the extracellular matrix, cell membrane components, or cytoplasmic material. Over the last 50 years, a large number of specific autoantibodies have been identified and their clinical associations described. Autoantibodies have become vital diagnostic and prognostic tools for clinicians and shed light on possible pathogenic mechanisms of autoimmune disease.

Previous chapters have highlighted the association of Raynaud's phenomenon (RP) with autoimmune rheumatic disease (ARD). Serological testing for specific autoantibodies can aid in both diagnosis and prediction of organ-specific manifestations in systemic ARD. In this chapter, we shall report the clinical and potential pathogenic significance of autoantibodies in RP. It is vital that clinicians understand the basic principles of autoantibody tests used in order to correctly interpret the results and, as such, we will first review the various methods of autoantibody identification.

Methods of Autoantibody Detection

Indirect Immunofluorescence

Indirect immunofluorescence (IIF) has been the standard method of ANA detection for over 40 years [2] and is typically used as the initial screening tool to detect the presence of autoantibodies and prompt further investigation to further characterize the antigenic target. Its low cost, high sensitivity, and the ability to standardize the routine cell substrate make it attractive as an initial screening tool for identifying autoantibodies

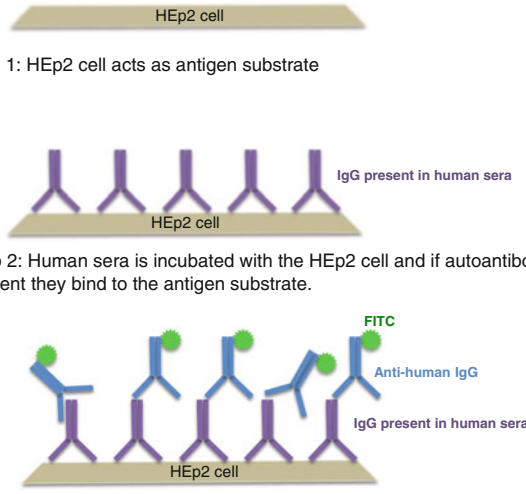

Fig. 15.1 Illustration demonstrating principle of autoantibody identification by indirect immunofluorescence

[3]. In brief, the process of detecting autoantibodies using IIF requires a relevant antigen to capture and bind autoantibodies present in the serum. The antigen is provided by either a human whole cell or tissue substrate depending on the autoantibody to be identified. In the 1970s laboratory methods evolved from the use of rodent tissue sections as antigen substrates for the screening and detection of ANA to more sensitive substrates such as human epithelial-2 (HEp2) cell lines that are routinely used today.

The antigen substrate is fixed to a microscope slide before adding the human serum to be investigated. Serum is typically diluted at least 40-fold (1/40) before undertaking tests to identify the presence of autoantibodies including by IIF. If a human IgG autoantibody is present in the sera, it will bind to the antigen on the slide. A further antibody (*anti*-IgG) with a fluorescein component (e.g., isothiocyanate: FITC) is added to bind to and saturate the human autoantibody (Fig. 15.1). Any excess FITC is washed away and the remaining fixed FITC marker produces a pattern of incandescent autoantibodies, which allows direct visualization to identify their location within the cell. Familiar patterns of immunofluorescence (Fig. 15.2) can be used to narrow the list of potential autoantibodies and direct the investigator to subsequent specific tests. The reported autoantibody titer reflects the weakest dilution at which the fluorescence can be detected; for example a positive ANA at 1:160 reflects an identified autoantibody at a dilution of 1 part serum to 160 parts saline [4, 5].

A positive ANA can be found in as many as 25–30 % of the healthy population, but often at a low titer of 1:40 [6, 7] and as a nonspecific ANA. The prevalence increases with age and in the presence of intercurrent infection or malignancy. The cutoff titer for reporting positive ANA should therefore ideally be chosen on a local level according to the population and it is the responsibility of the requesting clinician to interpret low-titer, nonspecific results within the correct clinical context.

Many autoantibodies associated with RP typically exist at high titer; for example the median titer of anticentromere antibody (ACA) in systemic sclerosis (SSc) in one study was 1:5,120 [8]. However, ACA can exist at lower titers, and therefore IIF staining patterns at lower dilutions need adequate reporting. It should be noted that other specific autoantibodies may

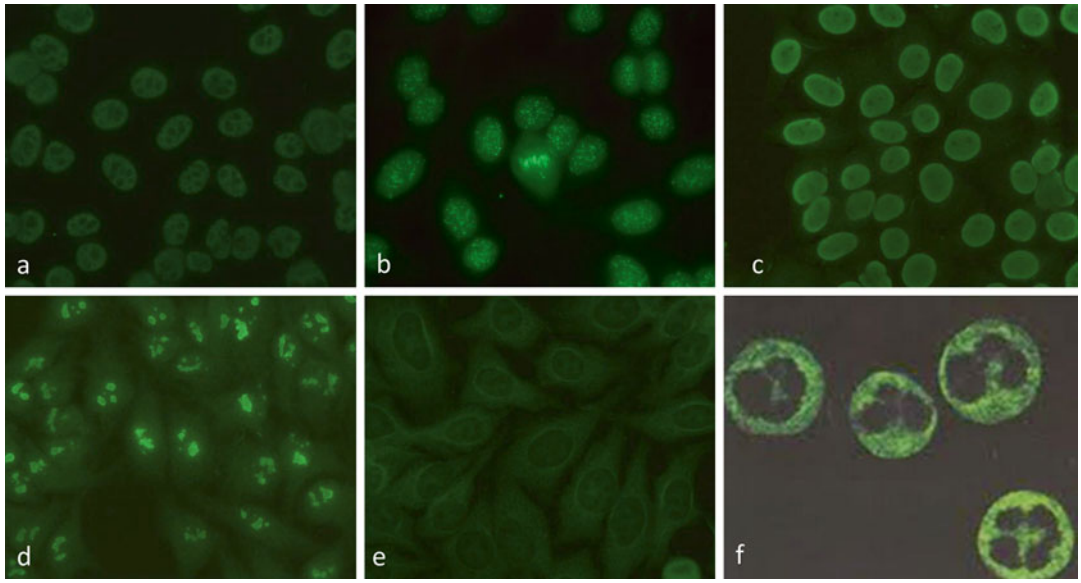

Fig. 15.2 Examples of IIF staining patterns that can be found in patients with RP secondary to autoimmune rheumatic diseases.(**a**) *Speckled-nucleolar sparing* is the most common and least specific pattern for rheumatic disease, associated with SS-A/Ro, SS-B/La, Sm, and U1RNP and thus occurs in MCTD, PSS, and SLE. (**b**) *Centromere* (ACA) pattern is identified by a characteristic speckled pattern with each speckle representing an antibody targeting centromere proteins. The pattern reflects the phase of cell division; for example central to the photo is a linear pattern in the center of the cell as chromosomes align during metaphase. (**c**) *Homogeneous* describes an even distribution of fluorescence throughout the cell nucleus. It is associated with SLE and drug-induced lupus-specific autoantibodies including dsDNA, anti-nucleosome, and anti-histone antibodies. (**d**) *Nucleolar* is most often seen in association with systemic sclerosis reflecting the presence of PM-Scl, U3RNP, Th/To, RNA polymerase I, Ku, Nor 90, or anti-Scl 70. (**e**) *Fine cytoplasmic speckle* may be missed on conventional ANA testing and occurs in the presence of Jo-1, ribosomal RNP, and anti-mitochondrial antibodies. (**f**) *Anti-neutrophil cytoplasmic antibodies* (*ANCA*) are autoantibodies that target antigens within neutrophils and as such human neutrophils are the substrate used for autoantibody detection rather than HEp2 cells. ANCA staining can be reported as cytoplasmic (demonstrated above) or perinuclear associated with PR3 or MPO, respectively. A perinuclear pattern may be hidden by strongly positive ANA staining. In the presence of the latter, ELISA may be required to further characterize potential pANCA

occur in lower titer; for example anti-scleroderma 70 (anti-Scl 70) autoantibodies in SSc and a low-titer ANA should not therefore be automatically dismissed. It is the presence of specific autoantibodies rather than the absolute titer that is important in disease classification although we shall later discuss possible associations between autoantibody titer and disease activity in RP-associated diseases.

IIF cannot confirm the antigenic target of autoantibodies to extractable nuclear antigens (ENA, e.g., Ku, Jo-1, SS-A/Ro60, Ro52, SS-B/La, RNA polymerases, and PM/Scl,) although certain IIF patterns such as anticentromere antibody (ACA) can be regarded as diagnostic.

Enzyme-Linked Immunosorbent Assay

ELISA is used to confirm the antigen target and allows quantification of autoantibody levels (e.g.,

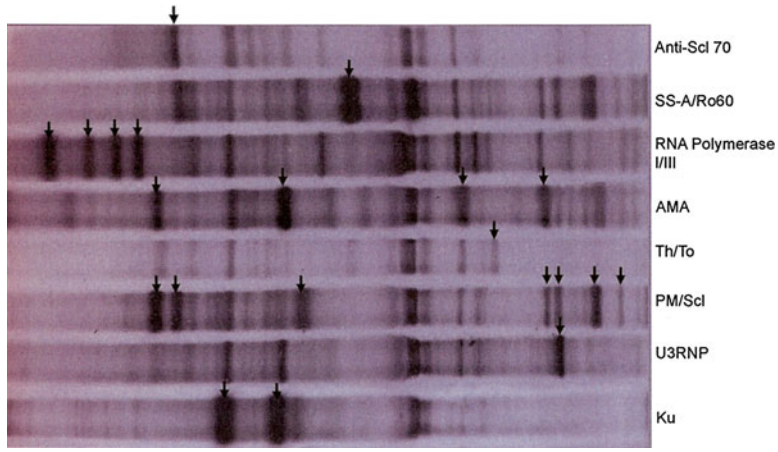

Fig. 15.3 An autoradiograph illustrating a selection of autoantibodies, including the main SSc-specific autoantibodies (anti-Scl 70, RNA polymerases, Th/To, PM/Scl, U3RNP, Ku) detected by immunoprecipitation. These may be found where RP is associated with autoimmune rheumatic disease. *Arrows* identify the position of the bands corresponding to the respective radiolabelled autoantigen-autoantibody complex that have separated according to their molecular weight (electrophoresis)

double-stranded DNA [dsDNA] titer) once they have been identified, or can be used for specific antibody detection (e.g., anti-β2 glycoprotein-I [β2-GP-I] and anti-cardiolipin [aCL]). Its method is not dissimilar to IIF but in the place of FITC, the secondary antibody is conjugated with an enzyme. An enzyme-specific substrate is then added which changes color on binding [9]. Spectroscopy is used to quantify the strength of the color change allowing estimation of quantification of autoantibody concentration from a standard curve generated with known concentrations of antigen. Up to 35 % of clinically relevant ANA results may be reported as falsely negative [10–13] and disease-specific autoantibodies may also be missed due to failure of the relevant autoantigen to be included in the assay system. Therefore a negative autoantibody by ELISA may be unduly reassuring.

Immunoblotting

This is a semiquantitative technique where antigens are separated by electrophoresis on a polyacrylamide gel according to their molecular weight and transferred to a nitrocellulose strip. An adaption more widely used is a line blot where commercially derived autoantigens are individually placed at specific positions on a membrane strip. Human serum to be tested is applied to the strip and any autoantibodies present in the sera bind to the autoantigens at their set positions. Any bound autoantibodies are then detected by a secondary anti-human antibody conjugate [14].

Immunoprecipitation

Immunoprecipitation (IP) is a sensitive method of identifying autoantibodies and has the advantage of identifying autoantibodies that are otherwise difficult to detect using routine methods. It requires use of radioactive material, is more costly, and thus is more commonly used for research purposes [15]. IP uses radiolabelled autoantigens mixed with human sera, separation by polyacrylamide gel electrophoresis according to molecular weight, and detection of autoantigen by autoradiography (Fig. 15.3).

Table 15.1 The prevalence of Raynaud's phenomenon and autoantibody positivity in autoimmune rheumatic disease

	Prevalence of RP (%)	Prevalence of autoantibodies (%)
Systemic sclerosis	>95	>90
SLE	10–44	>95
Polymyositis/ dermatomyositis	25–29	80–90
Primary Sjogren's syndrome	13–33	50–80
Mixed connective tissue disease	85–94.5	99
Rheumatoid arthritis	10–15	30–50

Autoantibodies and Raynaud's Phenomenon Associated with Autoimmune Rheumatic Disease

RP is common in ARD and these diseases are often associated with specific autoantibodies (Table 15.1) [16–19]. Autoantibody testing can aid the early identification of those patients with or at risk of developing future ARD. In the absence of other clinical features of ARD, the presence of RP in conjunction with autoantibodies is sometimes termed autoimmune RP. The presence of autoantibodies increases the likelihood of developing ARD. Patients with RP referred to one secondary unit had an overall risk of 14 % of developing an associated ARD [20]. The risk increased to 30 % if the ANA was positive (i.e., autoimmune RP) [20] and fell to 7 % if the ANA was negative [21]. A meta-analysis of ten articles reviewing a total of 639 patients demonstrated that 1/3 of patients initially classified as autoimmune RP differentiate to SSc within 5 years of presentation [22].

Systemic Sclerosis

RP occurs in more than 95 % of patients with SSc and is often the earliest manifestation of the disease [23]. The initial observation of antibodies directed to the nucleus and nucleolus in the sera of patients with SSc provided both evidence of autoimmunity and an early diagnostic marker in SSc [24, 25]. In their landmark paper of 1968, Rothfield and Rodnan identified the presence of ANA in 60 % of patients with SSc [26]. By the late 1980s, novel cellular substrates and refined serological techniques had increased the prevalence of ANAs in the Pittsburgh cohort to 76 % [27]. More recent work has reported the prevalence of ANAs in SSc in more than 90 % of cases [28, 29]. There remain a small proportion of patients with SSc (~5–10 %) who are negative for ANAs using standard techniques of identification such as IIF, immunoblotting, and ELISA. Novel mutually exclusive SSc-specific autoantibodies continue to be identified in SSc and there are likely to be other, as yet, unidentified autoantibodies in the small percentage of otherwise ANA-negative SSc [30].

The major SSc-specific autoantibodies are ACA, anti-Scl70, anti-Th/To, anti-RNA polymerase (anti-RNA Pol), and anti-fibrillarin (U3RNP). Additional rarer SSc-specific autoantibodies such as anti-U11/U12-RNP and anti-Nor-90 have also been identified [31, 32]. The major SSc-specific autoantibodies are typically mutually exclusive and each antibody predicts a well-characterized clinical phenotype [28].

The presence of SSc-specific autoantibodies (and/or abnormal nailfold capillaries) provides important prognostic information for the progression to definite SSc. Indeed, such is the importance of autoantibodies that they receive weighting in the 2013 ACR/EULAR classification criteria for SSc [33] and have been included for previous classification criteria for "early" and "very early" SSc in the absence of skin or internal organ manifestations of SSc [34–36]. Patients with RP in conjunction with positive anti-Scl 70 or ACA have a 63-fold increased risk of progression to ARD including SSc compared to those who are ANA negative ($p = 0.000009$) [37]. In this small prospective study of patients with RP, ten developed features of an evolving ARD over a mean follow-up of 4 years [37]. All ten patients had either ACA or anti-Scl 70-positive sera at baseline (100 %) compared to 13 (25 %) of the remaining 53 clinically stable

patients [37]. In a large secondary care cohort, ANA positivity gave a hazard ratio of 9.70 (2.11, 44.48) ($p=0.003$) for progression to SSc compared to ANA-negative RP [38]. The presence of ACA further increased the risk by a hazard ratio of 3.94 (1.74, 8.94) ($p=0.001$) compared to ANA positivity alone [38]. In a 20-year prospective study [39] of a secondary care cohort of patients with isolated RP and no clinical features of SSc, 11.5 % carried SSc-specific autoantibodies in the presence of normal nailfold capillaries. Of these, 35.4 % progressed to develop definite SSc compared to only 3.4 % of those with RP and a positive (but nonspecific) ANA [39]. None of the primary RP group (i.e., negative ANA and normal nailfold capillaries) progressed to develop SSc ($p<0.0001$) [39]. The presence of both abnormal nailfold capillaries in addition to SSc-specific autoantibodies improved the predictive value of progression to definite SSc and collectively provided an odds ratio of 50 ($p<0.0001$), a positive predictive value of 79 %, and negative predictive value of 93 %. In this study, the presence of SSc-specific autoantibodies provided an eightfold increased risk of developing SSc and the median time for progression was 4.6 years from RP onset [39].

Although the reported risk of progression seems to vary across the literature, it is clear that the presence of specific autoantibodies significantly increases the risk of progression to SSc. Conversely, less than 0.2 % of primary RP (negative ANA and normal nailfold capillaries at baseline) develop an ARD [40]. Only 0.5 % of patients with primary RP develop new autoantibodies during follow-up [40]. Thus if both autoantibodies *and* nailfold capillaries are persistently normal on two occasions the likelihood of RP progressing to an SSc is minimal [40].

RP is a clinical feature across all of the SSc antibody specificities although certain antibodies are associated with a more pronounced peripheral micro-vasculopathy and the formation of digital ischaemic lesions such as digital ulcers (DU) [7, 41–46]. Anti-Scl 70, anti-RNA polymerase III, ACA, U1RNP, and U3RNP are all independently associated with a higher risk of severe RP with DU and digital necrosis in SSc [41]. Anti-Scl 70 is associated with a higher frequency of severe RP (57 % of anti-Scl 70-positive SSc develop digital ulceration compared to 32.2 % of anti-Scl 70 negative) [41]. Anti-RNA polymerase III and anti-Scl 70 are associated with younger age at onset of RP and a shorter duration from RP onset to the first episode of DU than ACA. DU occurs up to 5 years earlier from the time of RP onset in anti-Scl 70-positive compared with ACA-positive SSc [41, 47]. Despite this, patients with ACA are more likely to require surgical digital amputation (14.6 % ACA positive compared to 7.9 % anti-Scl 70) [41]. The *titer* of ACA may also be relevant and has a positive association with severe RP [8].

The frequency of antiphospholipid antibodies (aCL and β2-GP-I) in SSc has been reported to be as high as 20–41 % [48]. The presence of antiphospholipid antibodies is associated with more pronounced peripheral microvascular dysfunction in SSc, reflected as both abnormal nailfold capillaries and the presence of digital pitting [48].

Autoantibodies associated with severe peripheral vascular complications in SSc (e.g., ACA, U3RNP, APLA particularly β2-GP-I) are also associated with a higher prevalence of other vascular complications in SSc including pulmonary arterial hypertension (PAH) [49–52].

PMScl and U1RNP can be found in SSc or as part of an overlap syndrome (with myositis and/or SLE). Both are typically associated with symptoms of RP, particularly when the clinical phenotype closely resembles SSc (discussed later).

Mixed Connective Tissue Disease

Anti-RNP autoantibodies (in particular U1RNP) are the hallmark of MCTD and historical diagnostic criteria included their presence as a major criterion [53]. Patients often display characteristics of several ARDs that feature in this overlap syndrome (SSc, SLE, myositis, and RA). In a review of 91 patients with MCTD, RP was the most common feature occurring in 94.5 % of patients [54].

Myositis

RP is present in about 25 % of patients with idiopathic inflammatory myositis, which is less common than in either SSc or MCTD [19] (Table 15.1). The frequency of RP increases to 38 % in association with Jo-1 [55] or the anti-synthetase syndromes. In contrast, patients with myositis with anti-signal recognition particle autoantibodies (SRP) tend to have fewer extra-muscular features including RP [56]. In this small study of 12 patients only 1 had RP in association with SRP [56].

Systemic Lupus Erythematosus

RP occurs in approximately half (40–49 %) of SLE patients [57, 58]. Whilst SLE-specific autoantibodies are associated with different systemic manifestations (e.g., the relationship between anti-dsDNA and renal disease) there does not seem to be an association of SLE-specific autoantibodies with either the frequency or severity of RP. Approximately 5.6 % of SLE patients carry ACA, and these patients have a high prevalence of RP symptoms (75 % ACA-positive patients versus 33 % ACA negative) [59].

The presence of either RP or antiphospholipid antibodies in SLE is independently associated with other vascular complications such as PAH [60]. However, in contrast to SSc, there appears to be a negative association between anti-cardiolipin antibodies and RP in SLE [61].

Primary Sjogren's Syndrome

RP occurs in 13–30 % of primary Sjogren's syndrome (PSS). In a study of 320 patients with PSS, RP preceded the onset of sicca symptoms in 45 % of cases [62]. The identification of ANA, anti-/Ro, and anti-La is more common when RP was present [62]. Similar to in SLE, the presence of ACA in PSS is associated with a higher prevalence of RP symptoms (75 versus 18 %) [63] and RP typically represents a more prominent symptom [63–66]. In prospective studies, a quarter (23 %) of ACA-positive patients initially classified as PSS progress to SSc [63–65, 67, 68]. ANCA are not commonly identified in PSS; however, one cross-sectional study identified RP symptoms in 44 % of ANCA-positive PSS compared to only 8 % of ANCA-negative PSS ($p=0.01$) [69].

Vasculitis

There are no reported associations between specific autoantibodies and the prevalence or severity of RP occurring in vasculitis.

Autoantibodies in the Pathogenesis of Raynaud's

There is some evidence that autoantibodies may not just be markers of rheumatic disease but may contribute to pathogenesis. Autoantibodies may contribute to tissue damage in systemic autoimmune rheumatic disease through complement activation [70], inducing opsonization and stimulation or inhibition of cellular receptors [71]. Endothelial injury and dysfunction are thought to contribute to the pathogenesis of RP, particularly in SSc [72]. Autoantibodies such as ACA and anti-Scl 70 are highly specific markers in SSc but there is no compelling evidence to suggest that they have a role in pathogenesis [44].

The identification of anti-endothelial cell antibodies (AECA) provides possible evidence for a direct pathogenic role of antibodies in vascular dysfunction in SSc. AECA have been identified in up to 86 % of patients with SSc and are associated with increased frequency of RP with digital ulceration [73–75]. The *titer* of AECA is also positively associated with an increased incidence of severe RP ($p<0.01$) [74], which suggests a pathogenic relationship. AECA titer is similarly associated with occurrence of other vascular complications including PAH ($p<0.001$) [74] and vascular damage on nailfold capillaroscopy [73, 76]. Endothelial dysfunction with resultant increase in endothe-

lial cell markers and adhesion molecules is considered a core pathogenic phenomenon in SSc [77–82]. A dose-dependent increase in cell adhesion molecules is seen in vitro when healthy human endothelial cells are exposed to AECA in SSc serum [83] suggesting that AECA are functional antibodies. AECA have been shown to activate antibody-dependent cell-mediated cytotoxicity and endothelial cell apoptosis, which is thought to encourage fibroblast differentiation and thus collagen deposition [84, 85]. AECA are also thought to further activate coagulation pathways exacerbating the vascular insult in SSc [86]. The identification of AECA is limited as they are not readily detectable using routine methods of autoantibody detection.

AECA have been identified in other ARDs including MCTD and are associated with prominent vascular symptoms including RP [87]. Studies have reported a higher prevalence of AECA in MCTD than in SSc (77 % MCTD versus 36 % SSc) [88, 89]. Increased levels of AECA have been found in patients with MCTD deemed to have "active" versus "inactive" disease [88]. Sera from patients with higher AECA levels induce over-expression of endothelial E-selectin [88].

Higher levels of AECA have been detected in PSS with RP compared to without RP ($p<0.01$) [90]. Similarly in a study of AECA in SLE, higher AECA levels were detected in those with RP than those without; however, results did not reach significance [91].

The identification of antibodies directed towards platelet-derived growth factor receptor (anti-PDGFR) in SSc has generated significant interest and may be relevant to RP pathogenesis because of the potential ability of anti-PDGFR to generate reactive oxygen species [92]. The high reported prevalence of anti-PDGFR antibodies has been limited to a few studies and has yet to be widely replicated [92–94]. Nonetheless, such studies raise the possibility of the presence of additional autoantibodies in ARD, which may contribute to RP but which existing cellular substrates and methods of antibody detection have yet to identify.

The presence of ACL antibodies in SSc may indirectly contribute to the pathogenesis of RP by inducing platelet activation, stimulation of endothelial cells, and inhibition of protein C activation resulting in micro-thrombosis [95].

The identification and confirmation of pathogenic autoantibodies in RP would be of significant clinical value with potential for targeted therapies that may reduce the morbidity of both sequelae of severe RP such as digital ulceration and other vascular complications of ARD such as PAH. However, the timeline for such work to migrate from bench side to bedside is lengthy and unlikely to be of clinical value in the near future.

Conclusion

Autoantibodies are important tools in the classification of RP, and help predict the risk of progression to a defined ARD. Autoantibodies such as ACA are associated with RP irrespective of the major clinical phenotype (e.g., SLE or PSS) and future work elucidating the exact mechanisms leading to expression of such autoantibodies may provide novel treatment strategies for vascular dysfunction in ARD. The identification of autoantibodies with a potential direct pathogenic role is an exciting development and offers fascinating insight into the possible associations between autoimmunity and vascular disease in RP.

Expert Opinion

Autoantibody investigations should be used as part of an initial clinical assessment of RP where there are additional clinical features that raise suspicion of an associated ARD (Fig. 15.4). Where RP occurs in conjunction with high-titer ANA or disease-specific autoantibodies at any titer, but without a definite diagnosis of ARD, patients should be monitored for disease progression and to identify systemic ARD involvement at an early stage. Screening for subclinical systemic involvement of ARD can be tailored

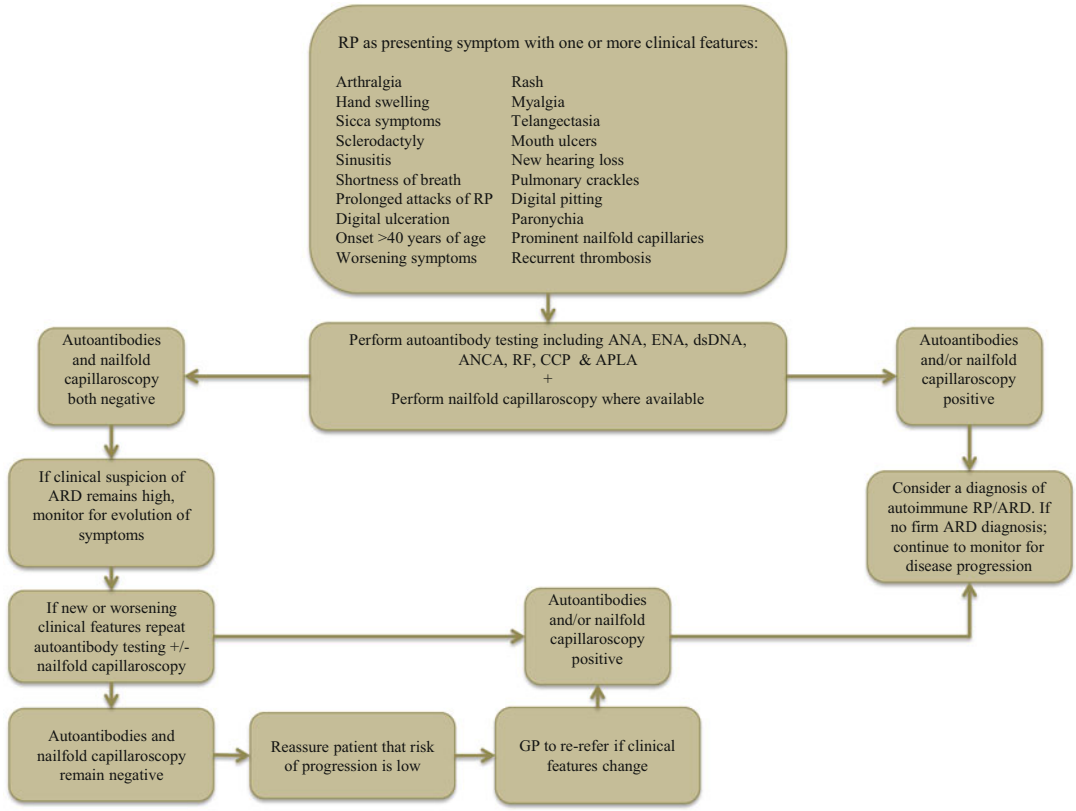

Fig. 15.4 Algorithm for autoantibody testing in patients where RP is the presenting symptom

depending on autoantibody specificity and their associated clinical manifestations. Monitoring should include a clinical assessment, urine dipstick testing, blood pressure, and consideration of echocardiography and pulmonary function tests where indicated. If baseline autoantibody investigations are negative but clinical suspicion of ARD remains high then repeat autoantibody testing may be warranted especially if new or worsening clinical features occur.

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Systemic Vasospasm

16

Laura K. Hummers

Abbreviations

SSc	Scleroderma
RP	Raynaud phenomenon
ECG	Electrocardiogram
DLCO	Carbon monoxide
CGRP	Calcitonin gene-related protein
MINC	Myocardial infarction with normal coronary arteries

Key Points

1. In scleroderma (systemic sclerosis SSc) there is clear evidence supporting vascular defects in the heart, lungs, kidneys and other vascular beds; however, the evidence of a cold-induced abnormal systemic vascular response beyond Raynaud phenomenon is limited.
2. Many studies have documented evidence of abnormal cardiac perfusion in patients with scleroderma even amongst those without overt cardiac disease or symptomatology.
3. Studies to date have not clearly linked cold-induced perfusion changes as a trigger for scleroderma renal crisis.
4. The current data suggest that pulmonary vasospasm is not cold-induced and Raynaud phenomenon per se does not appear to be a direct contributing factor to the development of pulmonary hypertension.
5. Raynaud phenomenon is linked by epidemiological studies to other disorders including migraine headache and perhaps variant angina.
6. The concept that migraine headache or variant angina is linked to a generalized vascular defect and Raynaud's phenomenon is not founded in a defined physiological mechanism.

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Introduction

Raynaud phenomenon (RP) is thought to be an exaggerated vasoactive response to environmental temperatures and emotional stress. Abnormal vascular reactivity is also the presumed mechanism underlying several common and uncommon disorders such as migraine headaches, pre-eclampsia, and variant angina. While epidemiologic studies (case reports, case series, and some controlled studies) have linked RP and these conditions, there is yet to be any clearly defined systemic vasoreactivity syndrome. Raynaud phenomenon is also a hallmark feature of systemic sclerosis (SSc), a disease with components of both vasospasm and structural small vessel disease that may lead to tissue ischemia of the digits. Whether other organ systems in patients with SSc also have a component of vasospasm as

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either an inciting event or contributing factor to damage is yet to be clearly defined. This chapter first examines the possible role of vasospasm in SSc outside of the peripheral circulation and RP in playing a role in the pathogenesis of SSc renal crisis, pulmonary hypertension, and cardiac disease. This chapter then examines the evidence that may exist linking RP with systemic vascular disorders.

Box 16.1 Systemic vasospasm

Vasospasm in Systemic Sclerosis outside of peripheral circulation	Cardiac Renal Pulmonary Pregnancy/placenta Central nervous system Penile
Systemic vasospasm	Migraine Coronary syndrome X Variant angina Preeclampsia

Systemic Vasospasm in Systemic Sclerosis

Coronary Perfusion

Cardiac manifestations of SSc are quite prevalent, but rarely overtly clinically manifest. Small subsets of patients have symptomatic cardiac disease and it is this patient population that is at a higher risk for mortality [1]. In addition to primary cardiac complications in SSc, such as cardiomyopathy, other manifestations of SSc may secondarily lead to cardiac dysfunction. For example heart failure may result from dramatic hypertension that accompanies SSc renal crisis and right heart failure is typically the final consequence of pulmonary arterial hypertension. Myocardial dysfunction has been associated with other vascular complications including digital ulcers. There is an inverse relationship seen with calcium channel blocker use and heart dysfunction [2], suggesting the vasodilator properties of the calcium channel blocker prevents heart disease; thus giving evidence that vasospasm is playing a role in the subsequent myocardial injury and dysfunction.

Many studies have documented evidence of abnormal cardiac perfusion in patients with SSc, even amongst those without overt cardiac disease or symptomatology [3]. The cardiac perfusion deficits are typically not in a territory of involvement of larger epicardial vessels. However, these studies cannot differentiate vascular disease as a result of vasospasm from small vessel perturbation or the progressive underlying vasculopathy. In addition, other recent studies suggest possible macrovascular complications of the coronary circulation with the presence of coronary epicardial vessels pathology [4]. One possibility for cardiac perfusion abnormalities is the presence of coronary arterial/arteriolar vasospasm either in epicardial vessels (similar to variant angina) or smaller vessels (as in cardiac syndrome X) [5]. Several studies have examined whether the introduction of cold stimulus may cause or augment perfusion abnormalities amongst patients with SSc. Cold pressor testing (cold water immersion of the hand) if often used and coronary perfusion is measured by various methods before and after exposure. In one early study, amongst ten patients with SSc and evidence of heart failure, cold pressor testing did not lead to changes in ST segments on electrocardiogram (ECG) or change in ejection fraction on echocardiography but no direct or indirect measures of perfusion were obtained [6]. Another study found evidence that 10/13 patients with SSc without overt cardiac disease had transient decreases in myocardial perfusion measured via thallium scintigraphy and 12/13 with changes in left ventricular systolic function with segmental areas of hypokinesis after cold challenge procedures [7]. This study did not demonstrate ECG changes of ischemia nor did patients develop chest pain, suggesting that this effect was likely subclinical. Subsequent studies have also found high prevalence of cold-induced thallium defects. In one study of 63 unselected patents with limited systemic sclerosis, 64 % demonstrated cold-induced thallium defects [8]. This study, interestingly, also noted similar prev-

alence of thallium abnormalities amongst those with primary Raynaud phenomenon (57 %). Others have noted an association with the presence of cold-induced perfusion defects and measures of Raynaud severity; again implying a direct or indirect mechanistic link [9].

Once perfusion abnormalities were appreciated, other investigations were done to assess the anatomic changes in the coronary circulation. Coronary angiography in unselected SSc patients without overt cardiac disease demonstrated ectatic coronary arteries in 3/9 patients with diffuse SSc and 0/5 with limited cutaneous disease [10]. One patient demonstrated vasospasm during the angiography (but not cold induced). 7/14 patients had tortuous vessels and 3/14 had areas of stenosis (although one had risk factors for coronary artery disease). Another study did demonstrate higher frequency of atherosclerosis in smaller coronary arteries compared with controls [11]. There are other case studies demonstrating coronary artery vasospasm during routine cardiac catheterization, but there is yet to be an angiographic study clearly directly demonstrating "coronary Raynaud's" as a significant contributor to the perfusion abnormalities seen in SSc.

If it is assumed that cold induced coronary Raynaud's or any episodic coronary vasospasm exists, the question remains whether this has any clinical consequence. This was examined in a prospective study of 51 patients who underwent baseline evaluation for "cardiac Raynaud" and follow up measures of left ventricular function at a mean duration of 7 years after baseline studies [12]. This study demonstrated that 29 %(15/51) of patients, all of whom had no clinical cardiac disease with negative stress tests, had evidence of cold-induced perfusion abnormalities demonstrated by myocardial contrast echocardiography; 8/51 had evidence of severe cold-induced changes (>4 SD more than controls). Amongst those with severe cold-induced perfusion changes, there was significantly lower ejection fraction and left ventricular volume at follow up and persistent evidence of cold induced reductions in mean blood flow and volume by perfusion studies. In multivariable analysis, severe "cardiac Raynaud" was the only independent predictor of these outcomes in the left ventricle. Those with severe cold-induced changes in blood flow were noted to have significantly longer disease duration than those without but otherwise there were no other significant difference is disease subtype and demographic features. Interestingly there is compelling longitudinal observational data that the use of calcium channel blockers is associated with a significant protective effect with regards to long term left ventricular function [2]. Whether the mechanism of this effect is via reducing vasospasm and therefore decreasing ischemia–reperfusion injury remains to be seen. Other studies have demonstrated reversal of perfusion defects in the acute setting with treatment with calcium channel blockers [13]. Calcium channel blockers alternatively may also have other effects some as well including a direct impact on myocardial contraction [11].

Renal Vascular Bed and Scleroderma Renal Crisis

It has been observed by several experts that SSc renal disease occurs more commonly in the colder months of the year (personal observation/communications). This observation and other data have prompted investigation into the possibility of a cold induced renal vasospasm or "renal Raynaud's phenomenon" as the trigger for scleroderma renal crisis. Data supporting the concept of "renal Raynaud's" dates back for decades. It was first suggested in 1956 by Sokoloff et al. and further investigated by Cannon et al. who demonstrated that cold pressor challenge led to changes in renal cortical blood flow [14, 15]. Early histopathologic evidence of small and medium sized vessels structural abnormalities are seen in patients with SSc including those with no history of renal dysfunction, hypertension, proteinuria, or elevated renin levels [15]. However, the relationship of these vascular changes to the development of a clinically important renal crisis is still not evident. Renal Doppler ultrasonography also has demonstrated increased vascular resistance among patients with SSc without clinical evidence of renal disease compared to normal controls [16]. This

and other studies suggest that changes in blood flow correlate with disease duration and others with nailfold capillary abnormality severity [17, 18]. Taking all these study data, we can conclude that, similar to what occurs in the heart, there is prevalent subclinical vascular disease in the renal vascular bed, but it is unclear that there is a direct link of "renal Raynaud's" and the development of the life-threatening renal crisis of scleroderma.

The evidence supports that patients with SSc have subclinical vascular thickening and reduced reserve in flow in the kidney. The cold-responsiveness in renal blood flow has been examined by several groups as well. Cold water exposure to the hand was able to reduce glomerular filtration rates in a small sample of patients with SSc who were without overt renal disease [19]. Cannon et al. demonstrated decrease in ^{133}Xe washout after exposure of the hands to cold [15]. Kovalchik et al. demonstrated elevated renin levels in response to cold. Interestingly, this was more prominent amongst those with more vascular changes seen on renal biopsy [20]. Neither finding, however, seemed to predict future renal dysfunction [19]. Patients with early SSc without renal disease had measures of renal vascular resistance (by pulsatility index, a measure of renal arterial resistance) and renin levels after cold immersion which demonstrated increase compared to controls; however, this was not statistically significant [21]. Therefore, studies to date have not clearly linked the possible cold-induced perfusion abnormalities to clinical manifest renal disease or "renal Raynaud's" as a trigger for scleroderma renal crisis. One cannot conclude that cold induced renal vascular vasospasm does not occur because this question has been insufficiently investigated to date.

Pulmonary Artery Vasospasm as a Contributor to Pulmonary Hypertension

Several single case reports demonstrating evidence of cold-induced increase in pulmonary artery pressure measured during invasive procedures suggest that vasospasm may play a role in the development or progression of pulmonary hypertension [22–24]. There is some evidence that hypoxia-induced vasoconstriction occurs as demonstrated a decrease in pulmonary vascular resistance with oxygen therapy in patients with fibrotic lung disease [24]. This implies that hypoxia secondary to fibrotic lung disease may in turn contribute to vasoconstriction [25]. One study using a measurement of pulmonary perfusion by ^{81}M Krypton infusion demonstrated a decrease in perfusion after hand cold exposure in four of eight patients with SSc [26]. Multiple studies of the effect of cold exposure pulmonary circulation have examined changes in diffusing capacity for carbon monoxide (DLCO) as an indirect measurement of pulmonary vasoreactivity. There have been varied results from these investigations despite very similar methodologies. This was first investigated by Wise et al. in 1982 who demonstrated no change in DLCO with cold exposure (hand and total body cooling) among nine patients with SSc and an increase in the DLCO in five patients with either lupus or primary Raynaud [27]. The investigators interpreted these findings to reflect an abnormal ability to redistribute blood flow in the lung and thus no increase the DLCO occurred due to underlying structural vascular disease in patients with SSc. This was subsequently investigated in patients with SSc, primary Raynaud and healthy controls by measurement of (DLCO) after cold pressor testing [28]. This study did not demonstrate decreases in DLCO after cold exposure in any group, but the primary Raynaud group did have an increase in DLCO which was not seen in healthy controls or scleroderma patients. Gastaud et al. similarly studied four groups (primary Raynaud, SSc without Raynaud, other connective tissue disease with Raynaud, normal controls) before and after cold exposure to the hand for 2 min [29]. In this study, patients with SSc showed a decrease in DLCO after cold exposure while the patients with primary Raynaud increased the DLCO. Fahey et al. studied five controls, seven connective tissue disease patients with Raynaud, and five with primary Raynaud. DLCO decreased in primary Raynaud group, at 15, 45, 120 min after cold exposure. In those with

connective tissue disease and Raynaud's the DLCO was low at baseline but the DLCO did not decrease with cold exposure [30]. It is unclear why there is such disparity in these studies. More often, those with primary Raynaud were found to have increase in DLCO and this may be related to increase sympathetic tone and heart rate after cold exposure leading to an increase in pulmonary blood flow. Alternatively, induction of Raynaud's may shift blood from the skin centrally and increase blood flow. Patients with underlying structural disease of the pulmonary vessel would then have an inability to increase blood flow and the DLCO would remain low or unchanged. Another study did not examine cold pressor testing, but did note improvement in DLCO in patients with SSc without pulmonary hypertension after acute administration of nifedipine and this effect was more pronounced in those with lower DLCO [31].

Shuck et al. more directly studied the possibility of pulmonary artery vasospasm by performing cold challenge during right heart catheterization in four patients with SSc and pulmonary fibrosis, and four with limited SSc (without lung fibrosis), none of whom had pulmonary hypertension. Patients underwent hand cold water challenge during right heart catheterization. No change in mean pulmonary artery pressure of pulmonary vascular resistance was noted even with increases in aortic pressure and systemic vascular resistance [32]. A later study in those with proven pulmonary hypertension also failed to demonstrate changes in hemodynamic parameters after cold exposure (mean pulmonary artery pressure and pulmonary vascular resistance) in a group of 21 patients with SSc [33].

It appears that the propensity of the data suggest that pulmonary vasospasm is not triggered by cold exposure to the hands and that Raynaud's phenomenon per se and does not appear to be a likely contributing factor to the development of pulmonary hypertension. The studies however to not exclude the possibility of vasoconstriction playing a role in progression of pulmonary vascular disease; also acute provocation studies may be insufficient to totally exclude a role for cold exposure.

Vasospasm in Other Vascular Beds

There are several case reports of transient cerebrovascular ischemia among patients with SSc. One case demonstrated transient global amnesia in a patient with SSc and history of concurrent headaches and Raynaud attacks [34]. Another case demonstrated hemiplegic migraine in a patient with CREST syndrome [35]. This patient's migraines began concurrently with her other SSc symptoms except for Raynaud phenomenon which had been present for 15 years prior. Cerebral perfusion defects were seen in 9/12 patients with systemic lupus with Raynaud, 4/7 patients with lupus alone and 3/9 patients with SSc with Raynaud [36]. Upon cold provocation, two more patients with SLE and Raynaud developed cerebral perfusion defects; none of the lupus patients without Raynaud developed defects. Two of the three patients with abnormal baseline perfusion had worsening perfusion with cold exposure among the patients with SSc, but no new defects were noted in the 6/9 patients with SSc with normal baseline studies. Another study suggested that SSc patients with radiographic evidence (CT or MRI) of cerebral vasculopathy on retrospective analysis had a higher frequency of other vascular manifestations of scleroderma including pulmonary hypertension and SSc renal crisis [37].

Men with SSc have a high prevalence of erectile dysfunction [38]. This is presumed to be related to changes in the microvasculature of the penis. One study evaluating skin temperature of the penis suggests that baseline penile temperature is lower among SSc men than in controls and that recovery of flow with cooling is also slower amongst men with SSc [39]. There are no studies clearly linking acute episodes of cold-induced vasoconstriction to erectile dysfunction, however.

Scleroderma and Pregnancy

There are numerous case reports of SSc renal crisis occurring in the setting of pregnancy in patients with SSc. Pathologically, renal crisis and

eclampsia are virtually indistinguishable. The etiology of preeclampsia is related to vascular insufficiency in the placenta, leading to a cascade of regulatory angiogenic mediators which to a generalized endothelial dysfunction with multiple end-organ manifestations (headache, seizures, renal dysfunction). There is also known epidemiologic associations between preeclampsia and antecedent and subsequent vascular disease. Women with preexisting vascular disease, such as hypertension, systemic lupus, and renal insufficiency have a higher risk of subsequent preeclampsia. Interestingly, those with preeclampsia also have a higher rate of future development of SSc [40]. Patients with SSc had an OR of 2.6 for prior hypertensive complications of pregnancy and OR of 3.9 for prior pregnancy complicated by intrauterine growth restriction. A direct link between Raynaud and preeclampsia has not been investigated, but hand-cooling of pregnant women led to increases in blood pressures and this effect was more pronounced in those with a history of preeclampsia [41].

Coexistence of Disorders of Abnormal Vascular Reactivity

Migraine and Raynaud

Migraine headache and Raynaud phenomenon have been linked epidemiologically in several large studies. This has previously been hypothesized to be related to altered vasomotor reactivity with vasodilation the proposed cause of migraines and exaggerated vasoconstriction in Raynaud phenomenon. However, it is now believed that migraine pathophysiology is not primarily a disorder of vasodilation. As discussed below, the complex series of events that lead to migraine seem to involve cortical spreading depression and trigeminal neurovascular sensitization.

Despite new insights into pathogenesis, there is evidence of an epidemiologic connection between the migraine headache and Raynaud's phenomenon. Both seem to be the most prevalent in young women with Raynaud occurring in as many as 10 % of young women in their teens and twenties and migraines occurring in about 12 % of women. Both have a familial component, although likely to be polygenetically influenced. de Trafford et al. surveyed 1,000 patients with primary Raynaud and found that 7 % more were being treated for migraine compared to controls [42]. Another study surveyed migraine patients compared to healthy controls and found that 26 % of migrainous patients had Raynaud's phenomenon compared to 6 % of controls [43]. Raynaud's phenomenon was more common in those with classic migraine than common migraine (33 % vs. 22 %). Leppert et al. surveyed 3,000 Swedish women, and found that 19 % noted symptoms compatible with Raynaud's, 79 % of which had been given a definite diagnosis [44]. Among those with Raynaud, there was a higher number with recurrent headaches (although not specifically migraines). O'Keeffe et al. studied 41 patients with Raynaud's and healthy controls matched for age and sex, and found the prevalence of migraine was higher in those with Raynaud's than in those without (58.5 % vs. 24.4 %) [45].

Migraine and Scleroderma

The prevalence of migraine was assessed in a series of 191 patients with connective tissue disease [46]. Migraine symptoms were assessed by mailed questionnaire and classified as classical or common migraines. Migraine was diagnosed in 46 % of Sjögren's syndrome, 32 % of SSc, 12 % of rheumatoid arthritis, and 11 % controls. The presence of Raynaud (assessed by questionnaire) across groups was associated with migraine.

This data all seem to suggest and epidemiologic link between Raynaud phenomenon and migraine headache. The exact pathologic mechanism remains unclear. It had been presumed that the shared susceptibility between the two disorders was one of generalized abnormal vasoreactivity. However, current concepts of migraine pathogenesis (see below) have downplayed the role of vasodilation raising the possibility that this link may have another basis. While epidemiologic studies are suggestive of some genetic

susceptibility to Raynaud phenomenon, large-scale genetic studies are lacking (see Chap. 3 for more details). However, there are some genetic susceptibility genes associated with migraine headaches. There are as many as 12 genes identified as possible susceptibility genes with at least one having a fairly clear possible mechanistic implication. Further work in this area likely deserves attention. In addition, further more detailed studies looking for confounding factors (such as medication use) should be undertaken.

Migraines as a Disorder of Vasoreactivity?

Much has changed about what is known about the pathophysiology of migraine headaches in the past decade. Previously thought to be a condition of pain directly related to vasodilation, it seemed likely that a relationship between Raynaud and migraine would be explained by a fundamental underlying abnormality in vasoreactivity. Migraine headaches had been postulated to be caused by dilation of dural and extracranial vessels. Recent evidence, however, points to a complex series of cerebral abnormalities that lead to the constellation of symptoms leading to migraine headaches. Current concepts regarding the pathophysiology of migraine are based mainly on cortical spreading depression, trigeminal nerve activation, and changes in the trigeminal vascular system. In fact, vasodilation as a primary cause of the headache component of migraines was recently refuted by magnetic resonance angiography (MRA) evidence. Amin et al. performed MRA on 19 patients during spontaneous unilateral migraine attacks [47]. They noted that the circumference of cranial vessels (including carotids, temporal, meningeal, middle cerebral and basilar arteries) in the affected and unaffected side of the brain, before and after the migraine and before and after sumatriptan administration. They found that there were no differences in circumference of extracranial vessels with a migraine attack or after successful treatment with sumatriptan. There were some changes in intracranial vessels comparing attack-free and attack days (middle cerebral and internal carotid intracranial portion) and on the pain versus non-pain side, but these mild changes did not improve with successful administration of sumatriptan. Interestingly, the non-dilated extracranial vessels did constrict with sumatriptan administration. All extracranial vessels on the pain side were numerically greater on the pain versus the non-pain side however. This would be compatible with current beliefs that there is some secondary vasodilation that occurs but is likely not the primary etiology of the headache component of migraine.

Part of the problem of the purely vascular theory of migraine is that changes in vessel diameter were insufficient to explain the multitude of symptoms induced by a migraine including premonitory symptoms, aura and postmonitory symptoms. The pulsatile nature of the pain in migraine headaches was an early leading reason to assume the vascular hypothesis was correct. In fact studies did suggest that changes in the amplitude of pulsations occurred during migraine attacks [48]. More recent studies, however, have shown that the pulsation sensation during a migraine do not correlate with peripheral pulse [49].

A circumstantial role of vasodilation as part of the etiology of migraine comes from the effects of medications to both induce and treat migraine. For example, all known medicinal migraine triggers are vasodilators. In fact, this is the main mechanism from a research standpoint used to induce migraine headache. Many of the medicines that we use to treat Raynaud phenomenon are nonselective vasodilators with effect exerted on the vascular smooth muscle (nitrates, dihydropyridine calcium channel blockers) and are known inducers of headache, but not specifically migraine. The mainstay of acute therapy for migraine headaches are the serotonin 5-HT 1B/1D agonists (known as the triptans). Serotonin is released from brainstem serotonergic nuclei. Tricyclic antidepressants (block serotonin reuptake; agonists) are effective in migraine prophylaxis. Selective serotonin reuptake inhibitors are not effective for migraine prophylaxis, but interestingly may have benefit for Raynaud phenomenon. Triptans also have other non-vasoconstricting effects. They may stabilize

perivascular sensory nerves, or may impede the signal of the first synapse of the trigeminal nerve, thereby downregulating pain signaling. Calcitonin gene-related protein (CGRP) is a neuropeptide that is expressed in trigeminal ganglia nerves and is potent vasodilator that can induce vasodilation of extracranial vessels. CGRP can induce migraines experimentally and blood levels are elevated during migraine attacks and decrease after treatment with triptans. CGRP interacts with two receptors on medium and large artery vascular smooth muscle cells to mediate vasodilation. However, this neuropeptide also plays a role in transmission of pain signals from the trigeminovascular complex to the thalamus and cortex [50]. Activation of small pseudounipolar sensory neurons originating from the trigeminal ganglion and cervical dorsal roots project and converge at the nucleus caudalis; pain signals move to the thalamus and sensory cortex and from there to other regions of the brain. Sensitization of all order neurons in this pathway cause increase nociception and likely lead to the hyperalgesia, allodynia and sensitivity which are part of migraines. The stimulation of the trigeminal ganglion may result in release of several vasoactive peptides including substance P, CGRP and neurokinin A. This release leads to neurogenic inflammation and vasodilation and plasma protein extravasation. The vasodilation in this model is an epiphenomenon of the larger process and thought not to be the primary mediator of pain.

The conclusion from these studies is that migraine is not simply due to abnormal vasodilation but is a complex process involving neurotransmission, neuropeptides, and vasoreactivity. The concept that migraine headache is linked to a generalized vascular defect or Raynaud's phenomenon is not founded in known physiological mechanism, but rather associations has been made by epidemiological surveys. There may be other explanations, however, for a mechanistic connection that have not been well explored to date such as the role CGRP may be playing in Raynaud's phenomenon. Studies have demonstrated a relative decrease in CGRP-staining neurons in the skin of patients with Raynaud phenomenon [51].

Variant Angina

Variant angina is defined by the presence of transient ST segment abnormalities, accompanied by angina symptoms in the presence of normal coronary arteries. The exact prevalence is unknown, but is more common in younger individuals (<50), in women and in smokers. The angina results from localized spasm of a major coronary artery resulting in temporary high grade obstruction which is thought to be due to vascular smooth muscle hyperreactivity and appears to be unrelated to demand (symptoms often occurring at rest). Possible mechanisms for the hyperreactivity include imbalance of vagal and sympathetic tone as patients more often have signs of autonomic instability such as heart rate variability. Other potential mechanisms implicated include this similar to those considered to occur in SSc such as endothelial dysfunction, impaired flow-mediated dilation, and increased release of vasoconstrictors such as endothelin and serotonin. Cardiac syndrome X also occurs in those with normal major epicardial vessels, but presumed to have small vessel disease but during provocation at cardiac catheterization fail to show vasospasm as is seen in patients with variant angina. One study evaluated patients with myocardial infarction with normal coronary arteries (MINC) (presumably due to the cardiac syndrome X) compared to those with coronary artery disease for the presence of migraine, infection and Raynaud's phenomenon; as possible contributing factors [52]. Migraine and Raynaud's phenomenon was assessed by a simple (non-validated) questionnaire. This study found that those with MINC had higher migraine scores than those with coronary artery disease but Raynaud scores were similar in both groups.

Although there are little more than case reports of co-occurrence of Raynaud, variant angina and migraine, a general arterial hyperreactivity is proposed it those patients who have Raynaud's, migraine, and variant angina. Koh et al. investigated this in a population of Korean patients, where the incidence of coronary artery vasospasm is higher than in western populations [53]. They studied patients with proven variant angina.

Migraine was not found more often among those with variant angina compared to no heart disease (but higher than those with coronary artery disease). Raynaud's prevalence was similar between groups. This study concluded that variant angina, was likely not part of a more systemic vasospastic disorder. O'Keeffe et al. again studied patients with primary Raynaud's, and found that migraine was present in 61 % of patients and 23 % of controls and chest pain present more commonly in those with Raynaud's as well (47 % vs. 16 %) [54]. Non-migrainous headaches were more common in healthy controls. Chest pains were more frequently reported among those with Raynaud's and migraines than those without migraine (60 % vs. 28 %). Chest pain in this study was by symptoms including those who were diagnosed with musculoskeletal or nonspecific chest pain so the exact nature of the findings with regard to possible coronary vasospasm is unclear. Thallium defects induced by cold were assessed in 13 subjects with angiographic evidence of coronary artery spasm, 8 of who had Raynaud's phenomenon and 6 patients with migraine headache. 11/13 patients have transient myocardial perfusions defects upon cold stimulation compared with none of the controls with coronary artery disease.

Expert Opinion

Raynaud phenomenon is a cardinal feature of SSc that leads to symptoms in the vast majority of patients and significant morbidity in many with as many as 50 % of patients developing tissue ischemia and damage. Some have postulated have postulated that a similar process of vasospasm ultimately leading to tissue damage may be involved in other major organ dysfunction. While there is clear evidence supporting microvascular (and perhaps macrovascular) defects in the heart, lungs, kidneys and other vascular beds in SSc, the evidence of a cold-induced vasoreactive process is limited. It is still possible, however, that vasospasm may be playing a role in induction of events that may contribute to pathology in these organs. It is difficult to prove definitively as these two events may be significantly separated in time or pathology related to the events is subclinical. Among those with all types of Raynaud phenomenon, there appears to be an epidemiologic link to other disorders including migraine headache and perhaps variant angina. It is likely, however, that this overlap between disorders is not purely based on a single inherent defect in vasoreactivity. The nature of this association is not been fully elucidated and deserves further examination now that underlying mechanisms (particularly in migraine) are better understood. Other potential reasons for the links between disorders may be related to common mediators such as vasoactive neurogenic peptides. This further understanding may lead to improved management strategies with time.

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Clinical Outcome Measures in Raynaud's Phenomenon

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Abbreviations

RP	Raynaud's phenomenon
RCS	Raynaud's condition score
VAS	Visual analog scale

Key Points

1. Currently the most commonly reported outcome measures in clinical trials of RP are frequency and severity of attacks, and the Raynaud's Condition Score (RCS). These outcome measures are recorded via patient diaries.
2. Some commonly used outcome measures have poor reliability: patient and physician overall assessment, and duration of RP attacks.
3. Outcome measures differ between trials, making it difficult to make comparisons between trials.
4. Placebo response rates are high, and may contribute to many trials being "negative."
5. Using a combination of outcome measures may reduce the placebo response, and increase the likelihood of detecting differences between placebo and active treatments. This approach requires validation.
6. Studies are required to validate physiologic outcome measures (thermography, laser Doppler methods) and to compare these to patient-reported outcomes.

At present, there are no licensed therapies for Raynaud's phenomenon (RP) in the USA and strikingly few in other parts of the world; for example nifedipine is approved in the UK. This is surprising in that Raynaud's phenomenon is common, occurring in an estimated 10 % of the population as primary Raynaud, but also has high clinical impact and unmet medical need as in the Raynaud's phenomenon occurring in the setting of connective tissue disorders. While firm guidelines and standards for approval of candidate therapies have not been published, several major past efforts in drug development based on patient-reported outcomes have been endorsed by regulatory agencies.

Raynaud's phenomenon is extraordinarily heterogeneous in clinical expression and impact in all domains of clinical assessment including attack frequency, severity, and symptoms. This is perhaps not surprising given the wide range of pathophysiologic mechanisms but may reflect other issues not easily controlled in the setting of clinical trials. Just as a patient with angina can control the occurrence of chest pain by reducing physical activity, the typical patient with Raynaud can accommodate by

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lifestyle changes that minimize exposure to cold. While it is tempting to consider Raynaud as a disorder of peripheral thermoregulation related to vascular integrity and reactivity, therapeutic studies of Raynaud have been consistently plagued by high placebo response in all patient-reported measures. While this suggests a strong influence of stress and psychologic status, it also calls into question the validity of the current panel of clinical outcome measures.

Various clinical outcome measures have been used in clinical trials of RP. The majority of clinical trials in patients with RP have used a daily Raynaud's diary for patients to record details about their RP attacks. This approach has high face validity in that it permits measure of the individual patient response in the setting of varied geography, weather, and lifestyle. However the specific clinical outcome measure used in these diary-based trials to assess response for agents varies. A PubMed search for randomized clinical trials in RP from 2001 through November 2013 identified 20 RCTs, each varying in the outcome measures used. In these 20 studies, 5 used the Raynaud's Condition Score, 11 assessed the decrease in frequency in attacks, 6 assessed the decrease in duration of attacks, 8 assessed severity of attacks, 3 assessed attack symptoms, and 1 looked at patient and physician global assessment on a visual analogue scale (VAS; Table 17.1). Individual outcome measures have shown poor reliability or a great deal of variability (Table 17.2). Reliability is used to describe the overall consistency of a measure. A measure is said to have a high reliability if it produces similar results under consistent conditions. Reliability assesses true change but also accounts for measurement error that is inherent in any measure [1]. At a group level, a coefficient of ≥0.70 (which equates to a measurement error of 30 %) is considered satisfactory [2]. In patients who participated in three large RCTs of primary and secondary RPs [3], poor reliability was seen during the screening phase of the study. One might reasonably expect minimal variability in the measures during a period of observation (typically 2 weeks) without any intervention. Poor reliability was consistent for patient and physician VAS for RP and the duration of attacks, all of which have a coefficient

Table 17.1 Outcome measures in randomized clinical trials 2001–2013. The second column provides number of trials that used the outcome measure as primary measure and third column provides number of trials that used the outcome measure as secondary measure

Outcome measure	Primary outcome measure (number of trials)	Other outcome measures assessed (number of trials)
Frequency of attacks	11 [7, 8, 16–24]	5 [25–29]
Duration of attacks	6 [7, 8, 16, 17, 20, 22]	4 [18, 25–27]
Severity of attacks	8 [7, 17, 19, 21, 22, 26, 29, 30]	1 [28]
RCS	5 [7, 8, 16, 20, 25]	1 [18]
Attack symptoms	3 [7, 31, 32]	3 [17, 18, 33]
Physician global assessment	1 [7]	2 [8, 17]
Patient global assessment	1 [7]	2 [8, 17]

Table 17.2 Intraclass correlation analysis in placebo patients from three clinical trials. Adapted from references [3, 7]

Variable	All patients ($n=249$)	Systemic sclerosis RP ($N=132$)	Primary RP ($N=117$)
Patient assessment of RP on a VAS	0.47	0.49	0.46
Physician assessment of RP on a VAS	0.54	0.52	0.57
Attack symptoms:	0.76	0.78	0.72
Pain during the attack of RP on a VAS	0.78	0.79	0.76
Numbness during the attack of RP on a VAS	0.77	0.81	0.70
Tingling during the attack of RP on a VAS	0.77	0.76	0.79
Average attacks/day	0.79	0.75	0.86
Duration of the attacks in minutes	0.61	0.63	0.61
Raynaud's condition score (RCS)	0.70	0.74	0.65

Attack symptoms are the highest (most bothersome) of the pain, numbness, or tingling during RP attack

of <0.70. This may be related to poor performance of the outcome measures or large variability inherent to populations with RP.

Patient-Reported Outcomes

Patient-reported measures are typically captured using daily diary to reduce the day-to-day variability seen in RP. Data is collected daily using electronic diaries or paper and pencil on daily basis for 1 or 2 weeks. Electronic diaries have found to be reliable and valid when compared to paper diaries [4].

Raynaud's Condition Score (RCS): RCS is a daily self-assessment, graded on a scale of 0–10 based on the patient's perceived impact of the frequency, duration, and severity of their RP (Fig. 17.1). This measure was developed by investigator consensus on the eve of a large-scale trial and was felt to offer an omnibus measure of patient perception of the impact of environmental cold and its impact on daily activity and quality of life. This score is a subjective measure of the impact of RP and incorporates the daily frequency, duration, and severity and impact of RP attacks on a scale of 0–10. Validation of its utility as a measure of outcome was post facto [5]. The majority of studies using RCS average the daily values over 1–2 weeks. All diary methods are considered to suffer from poor adherence to patient-driven data collection and recall bias. Minimally important difference estimates have been reported for RCS and range from 14 to 15 points (0–100 scale) for improvement [6].

Frequency of attacks: The frequency of attacks is the mean number of attacks per day, typically averaged on a weekly or biweekly basis. Patients are typically asked to record the number of attacks they have daily in a diary. The average attack frequency from the first week is usually compared to the average number of attacks during the final week of the study.

Duration of attacks: The average duration of attacks is another patient-recorded outcome where daily averages are generally used to calculate weekly averages. Duration of attacks can often be difficult for patients to record since in some cases, their attacks can persist throughout the day whereas in other cases, attacks can last for only seconds. A severe attack may also be perceived as lasting longer by the patient based on the degree of discomfort.

Symptoms during an attack: These are assessed based on pain, tingling, numbness, and attack symptoms as defined below:

- *Pain*: The degree of pain for each attack is recorded on a visual analog scale (VAS) or on a Likert scale and can be recorded on either a 0–10 or 0–100 scale.
- *Tingling*: The tingling per attack is recorded on a visual analog scale (VAS) or on a Likert scale and can be recorded on either a 0–10 or 0–100 scale.
- *Numbness*: The numbness per attack is recorded on a visual analog scale (VAS) or on a Likert scale and can be recorded on either a 0–10 or 0–100 scale.
- *Attack symptoms*: Gladue et al. recently proposed taking the highest average value of pain,

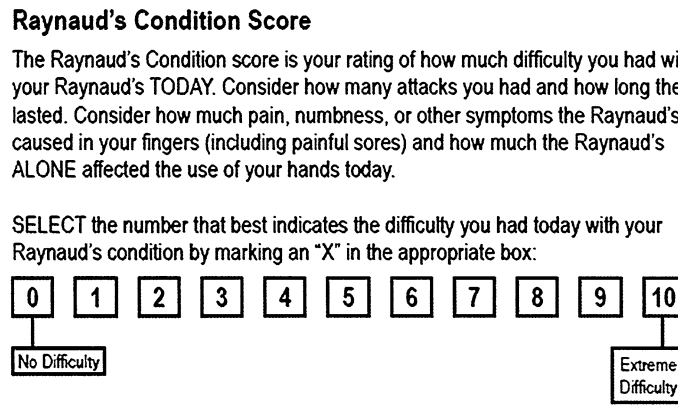

Fig. 17.1 Raynaud's condition score

tingling, and numbness over the period of assessment and terming it as a single collective parameter (attack symptoms) as they had high correlation coefficients, 0.77–0.78 [3]. Currently, this awaits prospective validation in a trial of an active agent.

Patient visual analogue score: A patient VAS of global assessment of RP has been used in many trials; however depending on the trial it may include different parameters. In some cases, the patient VAS has been used to assess either RP disease activity and/or assess the severity of the RP, whereas other times the patient VAS has been used to assess the overall burden of RP, which also takes into account not only the severity of RP but also the interference with daily life, similar to the intent of the Raynaud Condition Score. Patient VAS can be recorded on a 0–10 or 0–100 scale. Patient VAS is associated with a high degree of variability both within patients and between patients (Table 17.2) and can be associated with recall bias.

Physician-Reported Outcomes

Physician VAS: The physician VAS of global assessment of RP has been utilized in many trials and can either assess the severity of RP disease severity focusing on the actual Raynaud's attacks [7] or the overall burden of RP and influence on one's daily activities [8]. Physician VAS can also be scored on a scale of 0–10 or 0–100. The physician VAS is a subjective assessment that assesses the change in RP for a given patient. It relies on the patient giving an accurate account of the change in their RP that can be reproducibly and consistently assessed by the physician. Data regarding intra- and inter-observer variability are lacking.

Variability of Individual Outcome Measures

Gladue et al. evaluated the placebo data from 249 patients pooled from three clinical trials in RP [3]. All trials used all six outcome measures (patient and physician VAS, attack symptoms, attack frequency, duration of RP attacks, and the RCS) and the percent improvement between the run-in period and the treatment week. Figure 17.2 shows the percent of patients with a given percent improvement in the outcome measure. As can be seen the placebo response rate is consistently high among individual outcome measures. This may relate to outcome measures used or inherent variability associated with RP. As an example, the placebo rate is the improvement in outcomes without any intervention, which can be influenced by lifestyle changes or weather or by the inherent effect of placebo for the syndrome. When the placebo rate is high it is difficult to detect improvement from an active therapeutic agent. In addition, no study to our knowledge excludes outliers in reported attack symptoms,

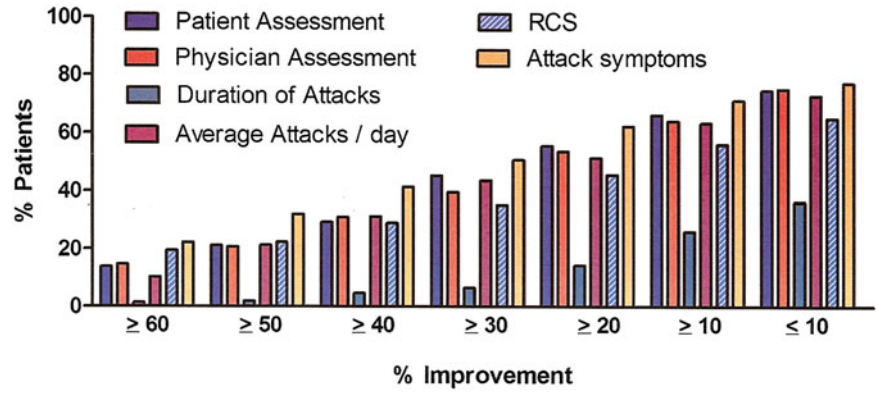

Fig. 17.2 Placebo response rate of outcome measures [3]

Outcome Measure	Definition (Scale)
1. Raynaud Condition Score	Subject daily assessment of difficulty with RP (0-10 or 0-100) assessed daily and averaged over 1-2 weeks
2. Patient Assessment of RP	Subject assessment of overall RP (0-10 or 0-100) during clinic visit
3. Physician Assessment of RP	Physician assessment of overall RP (0-10 or 0-100) during clinic visit
4. Attack Symptoms	Highest average value of pain, tingling or numbness (0-10 or 0-100 for each VAS) assessed daily and averaged over 1-2 weeks
5. Duration of attacks	Duration of attacks (in minutes) captured daily and averaged over 1-2 weeks
6. Average attacks/ day	Average number of RP attacks captured daily and averaged over a 1-2 weeks

Fig. 17.3 Composite index of six outcome measures for RP

which can dramatically affect the analysis. Use of a defined blinded placebo run-in to exclude "placebo responders" prior to randomization could be employed to assure a more consistent response during the subsequent comparison with active agent.

Use of a Composite Index

Composite index: The variability in parameters utilized in clinical trials prompted Gladue et al. to assess a composite index in an effort to standardize outcome measures to assess therapeutic effect in clinical trials for RP [3] (Fig. 17.3). In this case, six outcome measures were combined, including the RCS, frequency and duration of attacks, attack symptoms, and patient and physician VAS of global assessment of their RP. In this study, the placebo response rate for an individual outcome measure ranged from 92.8 % showing >10 % improvement in at least one core set measure to 38.5 % showing an improvement of >60 % in at least one core set measure. Our group hypothesized that an *X* % improvement (ranging from 10 to 60 %) in at least *x*/6 variables (where *x* is 2–6 variables) would decrease the placebo response rate such that the activity of new candidate agents could be better assessed [3]. Both increased standard for percent improvement and combination of core set items decreased the placebo response rate. Our analysis showed that 78 % of patients had an improvement in individual core set items by ≥30 % for one of the six core set measures, 53 % for two of six, 39 % for three of six, 26 % for four of six, 13 % for five of six, and 2 % for six of six measures, respectively (Fig. 17.4) [3]. By combining core set items, the decrease in placebo response rate allows for detection of a change by an active agent. This composite index can be thought of as analogous to the ACR 20 [9] index used as a standard to assess the response to new agents in rheumatoid arthritis. Combination of core set items together in the index decreases the placebo response rate and increases the ability to discriminate active vs. placebo groups, a crucial attribute in order to detect the response of new treatments. This composite has yet to be field tested in a trial comparing placebo to active treatment.

Patient-Reported Outcomes vs. Physiologic Outcomes

Physiologic measures including laser Doppler, thermography, and laboratory values have been occasionally used in small trials in RP. Thermography and laser Doppler appear to be useful to detect improvement in blood flow, frequently in response to a repetitive and controlled cold stimulus [10–12], and are very useful to explore physiologic action of a drug. Such studies can offer proof of concept that a candidate agent

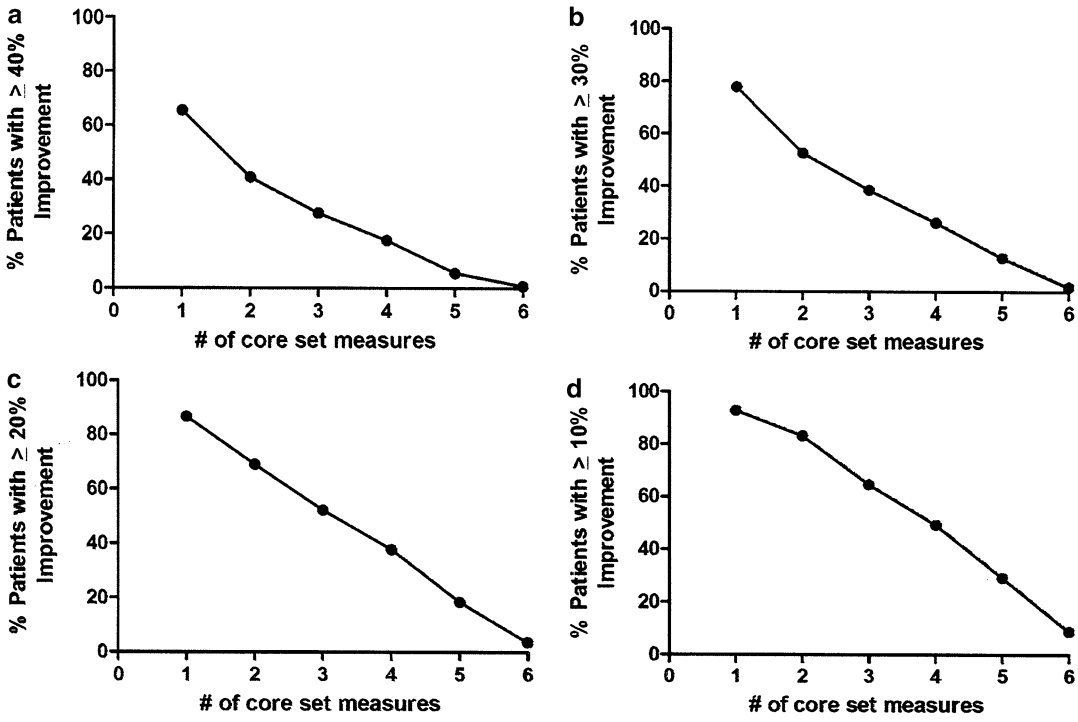

Fig. 17.4 Percentage of patients showing improvement when assessing 1–6 core set measures. Plots show improvement over the range of ≥10 % to ≥40 % (**a**–**d**), as assessed against the number of core set measures included in the analyses [3]

has consistent physiologic benefit and might also influence dose selection prior to a clinical trial. Larger studies are needed to further validate and compare to currently accepted patient outcomes. The current climate in regulatory drug approval would regard measures of physiologic response as a "biomarker" while not recognizing same as a relevant clinical outcome. In addition a standardized protocol is necessary to validate them. If they prove to be sensitive to change, they may be a better measure than the subjective measures that have high variability. Standardization of apparatus and measurement protocol across multiple clinical centers would be a daunting challenge in late-phase clinical development. Laboratory biomarkers have been shown to be associated with RP particularly ICAM-1, VCAM-1, soluble E-selectin, VEGF, t-PA, and endothelin-1 and may be a marker for effective treatment and in small studies have decreased in association with treatment; however larger studies are needed to evaluate their sensitivity to change [13–15].

Authors' View

Individual core set measures to assess activity in clinical trials have shown a large degree of variability in trials. This variability often results in a high placebo response rate [3] and may be responsible for negative trials. This is evident in the discordant results seen in the laboratory-based measures vs. clinical trials [3, 7, 10]. Clinical trials using an outcome measure that results in a high placebo response make it difficult, if not impossible, to detect differences between placebo and an active agent. Published trials have generally assessed a reduction in the frequency and severity of RP attacks as the primary outcome measure; however no trials have used a combination of variables to assess outcome. Analysis of three trials shows poor reliability of patient and physician global assessment of RP and duration of attacks. Physician assessment is also a difficult measure to assess the severity of RP. In addition, patient and physician overall assessment of RP is associated

with recall bias. RCS, frequency of attacks, and symptoms have acceptable reliability but have a high placebo response rate with RCS and the frequency and severity of attacks, the parameters most commonly used in RP trials. This variability has resulted in different trials on the same active agent resulting in mixed outcomes. For example in two trials looking at tadalafil for the treatment of RP, one study [8] showed efficacy of tadalafil as add-on therapy in the treatment of RP, whereas another study [16] showed no significant improvement. As such, a standardized set of outcome measures is needed in order to accurately compare RCTs in RP as successfully as in rheumatoid arthritis and other rheumatic diseases.

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18 Design and Reporting of Randomised Controlled Trials for Raynaud's Phenomenon

Jack Wilkinson

Key Points

1. RCTs play a crucial role in the identification of safe, effective treatments for Raynaud's phenomenon, but must be well designed.
2. RCTs for Raynaud's phenomenon are usually either of parallel group or crossover design.
3. Trials should be reported in sufficient detail to enable independent replication, in adherence to the CONSORT guidelines.
4. The seasonality of Raynaud's phenomenon has to be taken into account when designing trials.
5. Primary and secondary outcomes must be clearly defined, and subgroup analyses should be kept to a minimum and specified before the trial begins.

Introduction

If safe, effective treatments for Raynaud's phenomenon are to be identified, randomised controlled trials (RCTs) are sure to play a crucial role in the process. It is imperative that trials are designed and conducted so as to answer clinically important research questions, and that this is done in a manner that is both ethical and scientifically valid. Scientific validity is a prerequisite for ethical research, as failure to meet these standards represents a waste both of patients' time and of resources which could have been spent on more worthwhile projects. In this chapter, I shall expound some of the key features of RCTs and discuss the important methodological issues in the design and conduct of trials for Raynaud's phenomenon, using recent examples from the literature. RCTs in patients with Raynaud's phenomenon pose particular challenges, including the influence of season (temperature) on symptoms, and heterogeneity between and within different subgroups of patients.

Trial Design

"Trial design" may refer generally to the methodological features of an RCT or more specifically to the type of trial that a given study can be classified as [1]. This chapter as a whole concerns trial design in the former, broader sense. In this section, the narrower meaning is discussed. Trials for RP usually adopt either a parallel group design (e.g. [2, 3]) or a crossover design (e.g. [4, 5]).

Parallel Group Design

In a parallel group design, patients are randomly allocated either to receive an experimental treatment or to a control group. The randomised

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allocation is performed to ensure that the characteristics of the patients in each arm of the study are similar. If there are systematic differences between the study arms, then any differences in outcome may not be wholly attributable to the intervention. Alternatively, such confounding due to group imbalances may mask or attenuate a treatment effect, causing promising interventions to be overlooked. The balancing of study arms in a parallel design is therefore crucial in order to preclude spurious estimates of the effect of the treatment. However, simple random allocation does not guarantee the balance of characteristics between study arms, particularly for small trials. Investigators may therefore wish to implement a stratified randomisation procedure, whereby patients are categorised according to one or more factors that are believed to be associated with the study outcome variables and are then randomised to receive either treatment or control in blocks. This prevents large imbalances between the groups in relation to the stratification factor/s; at most the imbalance will be half the size of the block. As an example, investigators may wish to achieve similar numbers of smokers in each arm of a trial for Raynaud's phenomenon, due to the effects of smoking on the vasculature. This could be achieved by stratifying by smoking status. Prior to randomisation, a patient's smoking status is established, and the patient is randomly allocated to the treatment or control arm using a randomisation list for smokers or non-smokers. At the analysis stage, adjustment should be made for the stratification variable using regression methods. Such an approach may be preferable to the exclusion of smokers from the study, as the latter strategy has an impact on the generalisability of the findings.

In addition to details of the randomisation procedure employed, trial reports should present separate summaries of the baseline characteristics for each arm of the study cohort so that a reader may judge to what extent the randomisation has been successful in the balancing of potential confounders [1]. Tests of statistical significance of differences in baseline characteristics between groups are to be avoided, as they are inappropriate for two reasons. Firstly, any differences between randomised groups *must* be due to chance, making the test redundant. Secondly, there may be a substantive confounding effect even if no significant difference between groups is found, making the test uninformative [6]. Whichever method of randomisation is employed, it is imperative that the randomisation list is concealed from the persons entering patients into the study, or else the allocation procedure will not be truly random. The steps taken to ensure allocation concealment should also be described in the trial report.

Patients in the control arm may receive either a placebo or an active treatment. In a parallel-group trial of losartan for Raynaud's phenomenon (including both patients with primary Raynaud's phenomenon and those with systemic sclerosis-related Raynaud's phenomenon), Dziadzio et al. [7] used the calcium channel blocker nifedipine as a comparator drug. The use of an active control brings several potential advantages: it allows for a direct comparison to be made between an experimental and an established treatment; it may help to maintain the blinding of participants and investigators to the treatment allocation; it may be considered more acceptable from an ethical perspective to treat patients with an active drug rather than mere placebo, and this may be more acceptable to patients considering whether or not to participate. A benefit of the increased acceptability of using an active comparator is that investigators may then be more inclined to include patients with more severe symptoms, knowing that they will not be given placebo and thereby withheld treatment. These are precisely those patients for whom there is greatest need to identify effective treatments, so it is vital that they are included in trials. Problems with interpretation may arise however when no evidence of superiority is found from a direct comparison of experimental treatment versus active comparator. In such circumstances, it cannot be said that either treatment has been shown to have an effect. A common but misguided approach in this situation is to declare an effect to have been demonstrated in one or both groups on the basis of within-group changes. This reasoning cannot be justified, as a fundamental principle motivating the status of the RCT

as a gold standard in research is that effectiveness of a treatment can only be declared on the basis of a direct comparison between randomised groups [8]. Investigators may therefore wish to include a placebo group in a trial, either as the sole comparator arm or alternatively as a third arm in addition to the experimental treatment and active control groups. The inclusion of a placebo arm may be recommended for several reasons [9]. The placebo arm acts as an internal standard, and a comparison between treatment and placebo arms serves to provide a direct assessment of the effect of the treatment over and above non-specific placebo effects. The inclusion of a placebo arm also enables investigators to distinguish adverse events attributable to the experimental treatment from those spontaneous events related to the disease.

Crossover Design

In an "AB/BA" crossover design, all patients recruited to the study receive both the experimental treatment "A" and the control "B", which may be active or placebo (e.g. [5]). The order in which these are received is randomly allocated, so that a participant may undergo a period of A followed by a period of B, or else this sequence will be delivered in reverse. The two periods are separated by a washout phase, which must be of sufficient length to ensure that there are no persisting effects of the intervention delivered in the first period upon commencement of the second. Failure to include a sufficient washout phase in the design of a crossover study will compromise the investigators' ability to make a valid inference relating to the effect of the experimental treatment, as carryover effects from the first period will obfuscate and potentially interfere with any effects in the second. These effects cannot be isolated at the analysis stage, so it is imperative that they are precluded through thoughtful design [10].

Senn notes how crossover trials may further be subject to period effects, where some secular trend in the experiment means that outcomes in the second period would be higher or lower than those in the first even if no treatment was administered. In the case of Raynaud's phenomenon, this could plausibly manifest if all of the assessments in period 1 took place within a short timeframe, all of the assessments in period 2 were similarly grouped, and temperatures between the two periods of assessment were different enough to impact upon patient outcomes. Under such circumstances, it may be prudent to use one of the two methods described by Senn to adjust for period effects at the analysis stage. In practice, patients will usually be recruited into the study and assessed at different times, so that some participants will have completed period 2 before others have begun period 1. This means that a period effect may be apparent for some patients (e.g. those for whom temperatures were substantially different between treatment periods) but not others. Senn notes that although such interaction effects might add to the variability in the results, they should not prevent a valid assessment of the treatment effect. Advantages of the crossover design arise from the fact that each patient acts as their own control. Consequently, treatment effects are evaluated on the basis of within-patient comparisons, removing the effects of confounding and reducing the required sample size. The removal of sources of between-patient variability is particularly useful in a condition as heterogeneous as Raynaud's phenomenon.

Placebo Effects/Blinding

When a treatment is administered, a patient and their clinicians may expect to see beneficial effects. These expectations may translate into the patient reporting that they feel better, even if there is no objective physiological improvement to their condition. We refer to this and related phenomena as "placebo effects". When we talk of the effectiveness of a treatment, we are referring to any therapeutic effects over and above these non-specific placebo effects. A direct evaluation of the effect of an intervention therefore requires a randomised comparison with a placebo arm (e.g. [2]). The value of the comparison with placebo rests on the ignorance of the participant

and the investigators regarding treatment allocation. To this end, it is preferable that participants and investigators are blind to the allocation in the study. Should the treatment allocation of patients become apparent, there is scope for both patients and investigators to alter their behaviour in a manner that will introduce bias to the study and impact upon the assessment of the treatment effect. Where the comparator is an active drug, a double-dummy design may be used to maintain blinding. Here, each patient is given two tablets (or whatever is the method of administration) resembling the two treatments. Only one of these is active, the other is placebo. A problem in clinical trials of Raynaud's phenomenon is that patients may "guess" they are on active treatment because they experience vasodilatory side effects, thus negating the advantages of blinding. For example, in an RCT of crossover design, all 18 patients completing the study were able to state correctly whether they were receiving placebo or sildenafil [11].

The scenario where both investigators and patients are blind to the treatment allocation has historically been referred to by describing a study as "double-blind". Given the tendency for modern trials to require the collaboration of multiple investigators performing different roles including the allocation of patients, the administration of treatment and the assessment of outcome, only some of whom may be blinded, this designation is no longer particularly informative, and may have run its course [12]. Given the considerable inconsistency in how this term is used, authors are instead encouraged to explicitly report the blinding status of all personnel who could feasibly introduce bias into the study [1].

The outcomes typically used in trials of Raynaud's phenomenon include frequency of attacks [13], Raynaud's Condition Score [5], duration of attacks [2] and (in studies of systemic sclerosis-related digital vasculopathy) numbers of digital ulcers and ulcer healing [3]. Patient-reported outcomes may be particularly susceptible to placebo effects. Taking steps to ensure adequate blinding is therefore of particular importance in trials of Raynaud's phenomenon. For early-phase trials, it may be preferable to use more objective measures of mechanistic improvement, such as thermography, laser Doppler imaging [14], and finger systolic pressure measurements [15]. However, these non-invasive methods require further validation before they can be widely used as outcome measures (Chap. 13).

One proposal to deal with the high-level of placebo response in trials of Raynaud's phenomenon is to include a placebo run-in period where all patients are given a placebo for some period prior to allocation to a study arm. Placebo responders are then withdrawn from the study. The use of a placebo run-in may be criticised on ethical, theoretical and empirical grounds. Firstly, Senn [16] notes that the use of a placebo run-in requires the deception of study participants so that all believe that they are taking an active treatment. The wilful deception of patients may be difficult to justify. Secondly, in the absence of a randomised "no placebo" group during the run-in, there is nothing to distinguish placebo response from natural changes over time. It is unrealistic to suppose that patients' conditions will remain static in the absence of placebo effects; consequently it is likely that the use of a run-in will lead to the unwanted exclusion of those patients who show improvement for reasons unrelated to placebo response. There are clear implications for the generalisability of the findings of the trial. Ethical and theoretical considerations aside, it can be noted that in other clinical areas where a strong placebo response is usual (such as in trials of interventions for depression), inclusion of a placebo run-in period does not appear to have any impact on placebo response [17, 18].

Seasonality/Study Duration

In the discussion of crossover trials for Raynaud's phenomenon above, it was noted that differences in temperature between treatment periods may obfuscate the effect of the experimental treatment. In fact, the seasonal variation in the condition also has implications for trials of parallel design. If patients were to join the trial at different times throughout the year there would be

scope for differences in patient outcomes according to the season when their assessment took place, regardless of any treatment effect (or lack thereof). This would be of particular concern if there was systematic imbalance with respect to the timing of outcome assessments between the treatment arms. For this reason trials are often completed within a single winter season, and so trial duration is usually short. For parallel group trials, duration has usually been in the order of 4–6 weeks [2, 19–21]. If the concern of the study is more broad ranging than short-term safety and efficacy in Raynaud's phenomenon, then a longer duration is likely to be required. Indeed, because Raynaud's phenomenon is a long-term condition, there is a good rationale for long term trials.

An example of such a longer term study was a four-arm trial investigating the effectiveness of each of the calcium-channel blocker nifedipine and temperature biofeedback for the treatment of Raynaud's phenomenon in comparison to control arms receiving placebo tablets or electromyographic feedback [22]. The investigators incorporated a longer follow-up while controlling for seasonal period effects by allowing some flexibility in the timing of the outcome assessment; the primary outcome was measured in a winter month approximately 1 year post-randomisation, so that the median follow-up time was 13.5 months. As a result of this flexibility, the duration of treatment will have varied amongst the patients. Provided that the durations did not systematically differ between the study arms however (so that, for example, patients in the nifedipine arm were not followed up for longer than the placebo tablet arm), this variation will not have introduced bias to the estimate of treatment effect. In fact, this variation in treatment duration may contribute to the general applicability of the results, as the situation more closely reflects what is observed in clinical practice than would a short-term trial conducted under tightly controlled experimental conditions.

Where outcome assessment occurs under controlled laboratory conditions, the effect of ambient temperature is likely to be of lesser concern. Ambulatory studies of clinical effectiveness may seek to address whether treatment efficacy as demonstrated in a laboratory setting translates to general benefit to patients in their daily routines, and may use a patient-reported outcome such as Raynaud's Condition Score. It is for the latter trials that seasonal effects may be of particular concern. In practice, monitoring devices are often employed to record the ambient temperatures experienced by patients during the study. If the number of participants is sufficient, it may be possible to distinguish treatment effects from temperature effects at the analysis stage using regression techniques.

Analysis of Trials

The conclusion made from a trial in relation to the effectiveness of a treatment should be based on the analysis of the primary outcome, which should be clearly designated in the trial protocol before the study begins. The CONSORT statement recommends that the primary outcome is described with considerable specificity; the measurement to be taken, the timepoint when the assessment will occur, the mathematical summary of the measurement that will be compared between treatment groups (such as the mean or median), the statistical test to be applied and the rationale for these decisions are to be stated both in the protocol and in the trial report [1]. Consequently, the selection of the primary outcome is likely to require considerable deliberation. However, the rewards for prior and precise specification of the primary outcome are great, minimising the possibility of arriving at false positive results due to the testing of multiple hypotheses (some of which may be informed by the data themselves, introducing a circularity to the whole enterprise) and reducing the scope for misleading conclusions based on selective reporting of those analyses that showed the most promising results. It is preferable for just one outcome to be specified as "primary". Certainly, the number of primary outcomes should be kept to a minimum.

Modern trials typically report multiple outcomes, and it is important that primary and secondary outcomes are clearly delineated. For example, in a parallel group trial of modified-release sildenafil compared to placebo for

Raynaud's phenomenon, Herrick et al. [2] named the mean percentage change from baseline to week 4, analysed using an analysis of covariance (ANCOVA), as the primary outcome. The weekly attack rate, mean Raynaud's condition score, mean RP pain score and mean duration of RP attacks were listed as secondary outcomes. Analyses of secondary outcomes should be further delineated into those which were prespecified in the protocol and those which were not. The latter will to some extent be conditional on the data that were observed in the study. There is a degree of triviality to any analysis that tests a hypothesis against the same dataset that was used to generate it, and so these post hoc analyses should be viewed as exploratory or hypothesis-generating. In a parallel group study of bosentan versus placebo for the treatment of digital ulcers, Matucci-Cerinic et al. [3] clearly stated which of the presented analyses were post hoc, allowing the reader to adjust their interpretation of those results accordingly. This is the correct approach.

Much attention is paid to the *p*-values generated from the analysis of trial data, although in general there is much misunderstanding around the concept of statistical significance. When interpreting the results of a trial, it is important to note that "statistical significance" does not imply that a treatment effect is large enough to represent any practical clinical significance, or even that the effect is real. The clinical significance of a treatment effect cannot be deduced from a *p*-value. Instead, investigators should look to the estimate of the treatment difference and its 95 % confidence interval, which together give the estimated size of a treatment's effect compared to the control intervention and the range of values in which the true treatment effect could reasonably lie [23]. Clinicians may then use their judgement to decide whether or not the effect is large enough to warrant a change in practice, taking the degree of uncertainty in the estimate into account. When deciding whether or not a statistically significant result is likely to represent a true treatment effect, clinicians may find the analogy with diagnostic testing of a patient to be useful [24]. The *p*-value of a study represents the probability that the observed data (or data more extreme than these) would have been observed if the null hypothesis of no treatment effect is true. This can be construed as the probability of a false positive result, so that a small *p*-value (by convention $p<0.05$), indicates that the result is unlikely to have occurred if the null hypothesis holds. Analogously, when a patient receives a positive result from a diagnostic test, the false positive rate of the test indicates the probability that the result is erroneous (so that the patient does not, in fact, have the disease). The diagnostic test does not directly tell the clinician the probability that the patient has the disease. Instead, the clinician must combine the positive test result with knowledge about the characteristics of both the patient and the disease to make a judgement about the likelihood that the patient does in fact have the condition. Browner and Newman give the example of a young woman with several soft breast masses, who receives a positive test result for breast cancer. Even if the false positive rate of the test was low (5 %, say), this would not suffice to make a diagnosis of breast cancer, as the likelihood of breast cancer in this case would a priori be low. Just as the test does not directly report the probability of disease, so the *p*-value does not directly indicate the probability that the study hypothesis is correct. Investigators may combine the low *p*-value with their understanding of the plausibility of the study hypothesis to make a judgement about its likelihood. Just as the diagnosis of breast cancer may become more credible if a second test is also positive, so the truth of the study hypothesis may be seen as more probable once it is replicated in a second study. Just as a surprising diagnostic test result may warrant cautious scepticism, so should an unexpected finding of a trial warrant cautious scepticism; the more unexpected the effect, the greater the need for independent replication to confirm the result.

Where the *p*-value is larger than 0.05, a treatment effect has not been demonstrated. A common fallacy is to conclude that it has been shown that there is no treatment effect. This does not necessarily follow; all that has been demonstrated is that the study did not have sufficient power to detect any effect that might be present. Powerful studies are therefore particularly informative in

the case of a null result, in the same way that a sensitive diagnostic test is informative when the test result is negative: it is unlikely that a negative result would obtain if the disease were present or the study hypothesis were true. The confidence interval for the treatment difference is again useful in this scenario. If the interval is narrow and centred near to the value representing no treatment effect (which will be zero if the treatment effect is being represented by a difference or 1 if represented by a ratio), then it can be used to exclude the possibility that the treatment has clinically significant effects, provided that any values that would be notable from a clinical perspective lie outside of the confidence limits. Studies with greater power will have narrower confidence intervals, representing a more precise estimate of the effect.

Subgroup Analysis

Trials for Raynaud's phenomenon may include patients with a variety of demographic and disease characteristics. A common scenario is for a trial to include both patients with primary and secondary Raynaud's phenomenon [5, 25]. Given that the secondary form of the disease is generally more severe, it would be desirable for the proportion of patients with secondary Raynaud's to be similar in each study arm. An analogous situation arises in trials restricted to patients with secondary Raynaud's, where treatment arms may be imbalanced with respect to the specific diagnoses. Accordingly, it would be appropriate to stratify by the form of the disease when randomising patients to treatment groups as described in the discussion of parallel group trials above. Where a trial does contain identifiable subgroups of patients, a natural matter of interest for the clinician is whether or not the treatment was more or less effective in some of these subgroups compared to others. In practice, the analysis of subgroups in clinical trials is often problematic.

One of the main difficulties lies in the fact that the overall sample size in the trial is selected to ensure that the study has adequate power to detect an overall treatment effect. Given that the power calculation is based on the full cohort, a study may have only limited power to explore differences in treatment effects between smaller subgroups. As discussed in the previous section, failure to detect a difference as a result of underpowering cannot be construed as a demonstration that there is no difference, so subgroup analyses are often uninformative. Where there is an interest in determining the effect of a treatment for patients with a specific diagnosis, it would be prudent to consider designing a trial containing only patients with that diagnosis. Alternatively, a trial may include multiple subgroups of patients, but the numbers of each should be carefully considered to ensure that the study has sufficient power to investigate these differences.

As the number of analyses performed becomes large, the probability of obtaining false positive results becomes substantial. Accordingly, it is preferable that the number of subgroup analyses be kept to a minimum, if any are performed at all. As mentioned earlier, any subgroup analyses should be specified in the protocol before the trial begins, where they should be justified either on a priori grounds or on the basis of results from previous relevant studies. As with other data-driven analyses, post hoc subgroup analyses should be given relatively little weight; at best, they may be useful for generating hypotheses for future studies. All subgroup analyses that are performed must be reported, and it must be made clear which of these were and were not pre-specified. This allows readers to distinguish those findings which are the product of clinical prediction from those which are the product of fishing the dataset; the latter are more likely to be spurious. Where subgroup analysis is performed, the appropriate statistical approach is to perform a test of interaction between treatment and subgroup in a regression model. The statistical significance of the interaction term indicates that there is evidence of a differential effect of treatment between subgroups.

A common fallacy in relation to the analysis of subgroups is for it to be proclaimed that a treatment was most effective in those patients who were worst off at the start of the study, where the worst patients are defined as those having the poorest baseline measurements of the study

endpoint. However, it is known that those patients who have the most extreme measurements on one occasion will tend to have measurements closer to the population average on a subsequent occasion regardless of any treatment effect, a phenomenon known as *regression to the mean*. Even if the treatment is not effective, the impression will be given that those who were worst at baseline improved the most. Investigators should be wary of endorsing this conclusion whenever a similar scenario obtains. A direct comparison with the randomised control group is required to protect against regression to the mean.

The Role of Pilot Studies in the Design of RCTs

There is considerable inconsistency in how the term "pilot study" is used. Although it would be incorrect to indicate that a consensus has been reached on what constitutes a pilot study, it is clear that it is distressingly common for investigators to adopt this designation inappropriately. A pilot study only makes sense as a precursor to a subsequent main trial; it may reproduce all or part of the protocol intended for use in the main trial on a smaller scale, with the purpose of investigating the integrity of those aspects of the protocol under rehearsal. However, Arain et al. [26] found that only 8 out of 90 pilot studies identified by an earlier review of seven major medical journals [27] led to subsequent main trials. This is symptomatic of an unfortunate trend for investigators to conduct so-called pilot studies that are intended to stand alone, but are nonetheless too small to grant reasonable levels of power to detect realistic treatment effects. Such underpowering in a clinical trial removes the ability to answer the research question, undermining the motive for conducting the study in the first place. "Pilot studies" of this sort are therefore methodologically incoherent and cannot be ethically justified.

Pilot studies are useful for assessing the suitability of various aspects of a trial protocol, including recruitment, allocation concealment, randomisation, delivery of treatment and outcome assessment. They serve as an opportunity to identify features of the protocol that do not function as intended, allowing modification of the main trial as required. The pilot also provides useful information which may be needed in the design of the main trial, such as the variability in the study endpoint and the rate of attrition, both of which are needed in the calculation of the required sample size.

Although the design and conduct of a pilot study represents the expenditure of additional resources which could have been used in the main trial, the investment is likely to be worthwhile. The alternative strategy of proceeding directly to the main trial might result in flaws in the study design going unrecognised until the study is underway. The consequences for the validity of the trial may be severe.

A related (but separate) issue is the proof-of-concept, early phase study, designed to investigate whether or not an emerging treatment is sufficiently promising to be put to the test in a later phase trial. The proof of concept studies may be single-dose. Lack of effect in early phase studies obviates the expense of a longer study involving larger patient numbers [28]. Early phase studies should be sufficiently powered to detect effects of plausible sizes, although the outcomes may be physiological measurements reflecting improvement relatively early in the causal pathway from treatment administration to clinical improvement. The matter of whether or not this mechanistic improvement translates into notable clinical benefit to the patient may then be addressed in subsequent larger studies using patient-reported outcomes. It may be worth summarising several characteristics that distinguish early phase studies from pilot studies, as the distinction often goes unrecognised. Pilot studies are preparatory, whereas early phase studies are investigational. Pilot studies should not be used to determine whether or not a subsequent main study should occur, unless there is some indication that the intervention is harmful or that the orchestration of the main study protocol is not feasible. By contrast, the results of early phase studies may indeed determine whether or not subsequent studies are justified. Pilot studies may

precede main studies of any phase, including early phase proof-of-principle studies. They may be most important for larger, later phase studies however, as it is for these that there is most at stake should the trial design turn out to be flawed.

Systematic Reviews/Meta-analysis

A systematic review typically addresses RCTs of a specific intervention or family of similar interventions in a particular patient group, and summarises the evidence relating to effectiveness and safety. The quality of the included trials represents a crucial component of the review. Each study is subjected to a rigorous critical appraisal whereby various aspects of the study design are assessed in order to identify potential sources of bias. Many of the elements to be considered have been discussed in this chapter: the adequacy of the method of randomisation of patients to treatment groups; the concealment of the allocation schedule; the blinding of personnel and participants. In practice, the tasks of summary and appraisal may be precluded by the poor quality of trial reports, particularly where the trials were not recently published. Review authors are encouraged to contact the investigators to obtain missing information, although the likelihood of success in this endeavour is perhaps lowest for historical trials, which are precisely those trials that tend to lack detail. Although the general quality of reporting in trials has improved over the past two decades, persistent problems of missing or inaccurate information, selective reporting or emphasis of outcomes and the failure to report negative trials still serve to undermine the evidence base. Trialists are encouraged to report all studies regardless of the results and to do this according to the CONSORT statement [1], thereby enabling the interpretation and appraisal of individual trials and supporting the synthesis of evidence in systematic reviews.

A systematic review may or may not include a *meta-analysis*, whereby estimates of treatment effect obtained from the individual trials are combined to give an overall estimate of the treatment effect with a confidence interval expressing the degree of uncertainty in the estimate. Trials are given more or less weight in the meta-analysis according to the precision with which the study estimated the treatment effect. In practice, this results in larger studies receiving more weight in the analysis than smaller studies. A meta-analysis may or may not be appropriate in any given review. If the protocols of the included studies display considerable variety in terms of control groups, concomitant medications and participants, then the review authors should consider whether this disparity precludes the meaningful pooling of results. This *clinical heterogeneity* should be assessed on the basis of judgement and cannot be discerned on the basis of any statistical test [29]. Where meta-analysis is deemed appropriate, it must be interpreted in the context of the full review, noting the assessment of the value of the trials when taken together as a body of evidence. Readers may, of course, agree or disagree with this assessment; the methods employed in the review are themselves open to critical appraisal and must be described in detail to facilitate this.

Several of the methodological points made here in relation to the design of trials are applicable to the design of systematic reviews by analogous arguments. A primary outcome should be specified ahead of the review, to preclude selective reporting and multiple testing. Subgroup analyses are often inconclusive and may be misleading. Furthermore, subgroup analysis in systematic reviews usually consists of the meta-analysis of subgroups of trials rather than subgroups of patients. This raises additional concerns to those already discussed. Most notable is the fact that patients have not been randomly allocated to randomised trials but rather to treatment arms within randomised trials. As a result, comparisons between subgroups of trials are not guaranteed to be based on groups of otherwise similar patients and are prone to confounding.

In a recent example, Ennis et al. [30] reviewed trials of calcium channel blockers for the treatment of primary Raynaud's phenomenon. The authors concluded that calcium channel blockers were at best minimally effective for reducing the frequency of Raynaud's attacks. The pooled

estimate (95 % CI) for the difference in mean number of weekly attacks for calcium channel blockers compared to placebo was 1.72 (0.60–2.84), indicating that patients taking a calcium channel blocker may experience between 0.6 and 2.8 fewer attacks per week on average compared to a patient taking placebo. The authors noted that the findings of the review were limited by the generally poor quality of outcome reporting in the included studies, of which 6 of 7 were published in 1991 or earlier. In particular, the frequency of attacks was the only outcome which was both common to and commensurable between the studies. Another recent example is a systematic review of phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon [31]. The authors included six trials in the review and reported on three outcomes (Raynaud's condition score, daily attack frequency and daily attack duration). The authors found statistically significant but modest effects of treatment compared to placebo for all three. The authors judged the risk of bias in the included studies to be low. In particular, they noted that the crossover trials in the review used washout periods of 1–2 weeks, which was deemed to be appropriate for the purposes of preventing carryover effects. A final example is a review of oral vasodilators for primary Raynaud's phenomenon [32]. In this case, the authors concluded that the poor methodological quality of the eight included studies limited the value of the results and that there was no evidence that vasodilators were effective.

Expert Opinion

Although it is true that RCTs may provide high quality evidence about the effectiveness of treatments for Raynaud's phenomenon, poorly designed and conducted trials do not. Methodological rigour is necessary to ensure the validity of the results. Trials should be reported in sufficient detail to enable independent replication and inclusion in systematic reviews, in adherence to the CONSORT guidelines. Challenges of RCTs in Raynaud's phenomenon include seasonality, the heterogeneity of the condition, and the placebo effect. The thoughtful use of pilot studies may improve the quality of trials by highlighting unanticipated difficulties and providing information about recruitment rates, attrition and the variability of the outcome that can be used to inform the study design.

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Non-drug Approaches to Treating Raynaud's Phenomenon

19

Linda Kwakkenbos and Brett D. Thombs

Abbreviations

RP	Raynaud's phenomenon
RCT	Randomized controlled trials
EMG	Electromyography

Key Points

1. Reducing exposure to triggers that provoke Raynaud's events is one of the most effective intervention strategies for patients with both primary and secondary RP.
2. Education about the cause and precipitating factors of Raynaud's events is the foundation of any treatment program for RP.
3. Avoiding exposure to cold and maintaining whole body and digital warmth is the most important non-drug therapy.
4. While definitive studies are lacking, avoidance of vasoconstricting drugs and smoking cessation is recommended.
5. Although emphasized by many health care providers and patients, the nature of the association of emotional stress and RP remains to be elucidated.
6. There is not currently trial evidence to support the idea that behavioral treatments are effective in reducing the number or severity of attacks in RP.
7. A number of complementary and alternative medicine treatments have been tested for RP management, but none have demonstrated effectiveness from well-conducted trials, and they are not recommended.

Raynaud's phenomenon (RP) attacks are thought to be triggered or aggravated by a number of factors, including changes in environmental temperature, trauma to the fingers, smoking, some medications, and emotional distress [56, 19]. The first step in treating RP typically involves lifestyle modification to reduce exposure to potential triggers. Reducing exposure to triggers is probably one of the most effective treatment strategies. In fact, noninvasive interventions to reduce the frequency of attacks for patients with primary RP, may be enough to provide considerable symptom relief without the need for drug therapy [24, 69].

To be able to understand how to reduce or prevent exposure to triggers patients should be educated about RP and possible precipitating factors for episodes. A clear understanding of why RP is occurring reduces anxiety and thus

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provides reassurance to the patient. Patients can adapt strategies that enable them to recognize specific circumstances that lead to attacks in their own lives. Education about RP and possible triggers should be done face-to-face by the treating physician and can be reinforced by a specialized nurse [41] or through patient organizations. Additionally, informational flyers describing the disease may help improve patients' knowledge, as well as using high-quality information that can be found on the internet [69]. To help identify individual factors that precipitate attacks, patients should be encouraged to keep a diary of activities and register when attacks happen. This method provides valuable insight that can encourage obvious lifestyle changes to avoid precipitating circumstances. Providing general patient education or guidance on identifying personal triggers have not been formally tested to determine the degree to which these strategies are effective in reducing the frequency or severity of RP attacks. Nonetheless, good patient education is a core component of patient-centered care and is known to improve outcomes in many conditions where it has been studied [66, 65].

Non-drug approaches to treating RP, in addition to or as part of patient education, could potentially include: (1) avoiding exposure to cold and maintaining whole body and digital warmth; (2) avoiding medications that may trigger attacks; (3) smoking cessation; (4) behavioral interventions to manage emotional stress; and (5) other approaches, such as laser therapy or acupuncture. In this chapter, possible non-drug approaches to treating RP that have been suggested or tested are discussed. As a part of this, evidence from existing randomized controlled trials (RCTs) is presented (Table 19.1), along with an assessment of the quality or risk of bias of each trial (Table 19.2).

Our descriptions of RCTs are focused on outcomes directly relevant to RP attacks, and risk of bias ratings done using the Cochrane Risk of Bias tool, a standard evaluation system for RCTs [32]. The Cochrane Risk of Bias tool is used to evaluate the design and execution of individual RCTs and identify factors that could influence the validity of published results from RCTs. Domains of the Risk of Bias tool include randomization sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; handling of incomplete outcome data; selective outcome reporting, and other possible sources of bias. Based on evidence that study sponsorship and author–industry financial ties are associated with outcomes [59, 60], we evaluated the risk of bias from this factor as well. See Table 19.3 for descriptions of Risk of Bias domains. In addition to bias, in evaluating RCTs, we considered the sample size of the RCTs. It is increasingly well documented that results from small, substantially underpowered trials are highly imprecise. Due to publication biases, very small trials that are published often report large and statistically significant effects that are false positives and do not replicate in larger, well-conducted studies, whereas very small studies with negative findings are typically not published [38, 39].

Avoidance of Cold Exposure and Maintenance of Whole Body and Digital Warmth

Cold exposure and sudden temperature changes are considered the most important triggers for RP attacks (e.g., [56, 70]). Circumstances that can trigger an attack include seasonal temperature changes and situational changes in temperature, such as putting one's hands in a refrigerator or freezer, entering an air conditioned environment or the frozen food section of the supermarket, or going swimming in cool water [56, 69]. Thus, maintaining body warmth and avoidance of cold and sudden temperature changes are important ways to prevent attacks and potentially reduce severity and duration when an attack occurs. There are no RCTs that have investigated the effect of cold avoidance on symptoms of RP, generally, or specific strategies [55], but common sense and anecdotal reports suggests that taking measures to reduce cold exposure will contribute to reducing attacks with very little harm in applying

Table 19.1 Characteristics and outcomes of randomized controlled trials of non-drug treatments for Raynaud's phenomenon compared to usual care, waiting list, or sham interventions

First author, year, country	Study funding source	Treatment group	Control group	Core inclusion criteria	Number of patients randomized/ analyzed	Mean age (years)	Females (%)	Primary outcomes	Key secondary outcomes
Behavioral approaches									
Büttner, 1991, Germany [6]	NR	Biofeedback three times per week for 5 weeks	Hand exercises three times per week for 5 weeks (placebo intervention)	RP	Tx: NR/10	35–59	NR	*Number attacks pre-post*	*Duration of attacks*
								Tx = 4.8–3.4	Tx = reduction from 17 to 15 min
					Control: NR/10			*Control 3.9–3.1*	Control = reduction from 28 to 21 min
								P = NS	*P* = < 0.05 for difference between groups before and after intervention
Freedman, 1983, USA [18]	NHLBI	1. Temperature biofeedback in 10 biweekly sessions	Sham frontalis EMG bio-feedback in 10 biweekly sessions	Primary RP	Tx (1): NR/8	20–65	Overall: 88	*Decrease in attack frequency*	None
					Tx (2): NR/8				
					Tx (3): NR/8				
					Control: NR/8			Tx (1): 93 %	
		2. Temperature biofeedback under cold stress in 10 biweekly sessions						Tx (2): 67 %	
								Tx (3): 33 %	
		3. Autogenic training in ten biweekly sessions						Control: 17 %	
								P < 0.05 for 1 and 2, but not 3, versus control	
Freedman, 1984, USA [17]	NHLBI	1. Temperature biofeedback in ten biweekly sessions	Sham frontalis EMG biofeedback in ten biweekly sessions	RP secondary to systemic sclerosis	Tx (1): NR/8	NR	Overall: 92	*Decrease in attack frequency*	None
					Tx (2): NR/8				
					Control: NR/8			No significant differences	
		2. Autogenic training in ten biweekly sessions							

(continued)

Table 19.1 (continued)

First author, year, country	Study funding source	Treatment group	Control group	Core inclusion criteria	Number of patients randomized/ analyzed	Mean age (years)	Females (%)	Primary outcomes	Key secondary outcomes
Guglielmi, 1982, USA [26]	Rehabilitation Services Administration	Skin temperature biofeedback	1. Sham biofeedback (EMG relaxation of forehead muscles) 2. No treatment	RP, not taking vasoactive medication or medication for Raynaud's	Tx: 12/12 Control (1): 12/12 Control (2): 15/12	Tx: 33 Control (1): 34 Control (2): 34	NR	*Total attacks in 5 months* Tx: 225 Control (1): 204 Control (2): 254 *P* = NS	None
Raynaud's Treatment Study Investigators, 2000, USA [57]	NIH	Temperature biofeedback with suggestions for warmth imagery and passive volition delivered in ten 1-h sessions over 5–10 weeks[a]	Sham (frontalis muscle Surface EMG biofeedback) delivered in ten 1-h sessions over 5-10 weeks[a]	Primary RP with ≥2 attacks per day during previous cold season	Tx: 81/81 Control: 74/74	Tx: 44 Control: 46	Overall: 70[b]	*Daily attacks at 1 year*[c] Tx = 0.23 Control = 0.16 *P* = 0.38	*Daily attacks at 2 months*[c] Tx = 0.12 Control = 0.15 *P* = 0.57
Sporbeck, 2012, Germany [63]	Physiomed Elektromedizin AG	Biofeedback three times per week for 4 weeks	Waiting list	RP secondary to systemic sclerosis	Tx: NR/8 Control: NR/10	Tx: 50 Control: 59	Tx: 88 Control: 90	*Scleroderma VAS RP item at 4 weeks* Tx = NR Control = NR *P* = 0.021 (favors Tx)	*Scleroderma VAS RP item at 12 weeks* Tx = NR Control = NR *P* = 0.093 (favors Tx)
Surwit, 1978, USA [67]	NIMH	Autogenic relaxation training or autogenic relaxation training with biofeedback during six biweekly sessions	Waiting list	Primary RP	Tx: NR[d]/15 Control: NR[d]/15	23–54	100	*Number attacks pre-post* Tx = 32 % reduction Control = 10 % reduction *P* = NS	*Attack intensity* Greater reduction in Tx group *P* = NS

Other approaches									
Al-Awami, 2004, Austria [1]	NR	Low level laser therapy every other day for ten sessions total	Sham level laser therapy every other day for ten sessions total	RP for 2 years or more with average of ≥4 episodes per week, age 18–65	Tx: NR/24	Median age:	Tx: 67	*Daily attacks at 6 weeks*	*Daily attacks at 3 months*
					Control: NR/23	Tx: 45	Control: 91	Tx = 3	Tx = 3
						Control: 46		Control = 5	Control = 6
								P = 0.007	*P* = 0.02
								Severity attacks (0–10) at 6 weeks	*Severity attacks (0–10) at 3 months*
								Tx = 1	Tx = 0
								Control = 4	Control = 4
								P = 0.02	*P* = 0.04
Appiah, 1997, Germany [2]	NR	Acupuncture with seven treatments over 2 weeks	No treatment	Age 18–60 years, primary RP	Tx: NR/17	Tx: 46	Tx: 71	*Daily attacks*[e]	None
								Tx = reduction from 1.4 to 0.6	
					Control: NR/16	Control: 42	Control: 69	Control = reduction from 1.6 to 1.2	
								P = NS	
Hahn, 2004, Germany [27]	NR	Acupuncture weekly for 8 weeks	Sham acupuncture weekly for 8 weeks	Secondary RP	Tx: NR/11	Tx: 47	Tx: 91	*Daily attacks*	*Duration attacks*
									Tx = reduction from 15 to 12 min
								Tx = reduction from 1.9 to 1.4	Control = reduction from 31 to 16 min
									P = NS
					Control: NR/8	Control: 41	Control: 75	Control = reduction from 2.8 to 1.8	*Severity attacks (0–5)*
									Tx = reduction from 2.6 to 2.1
								P = NS	Control = reduction from 3.0 to 3.0
									P = NS

(continued)

Table 19.1 (continued)

First author, year, country	Study funding source	Treatment group	Control group	Core inclusion criteria	Number of patients randomized/ analyzed	Mean age (years)	Females (%)	Primary outcomes	Key secondary outcomes
Hirschl, 2002, Austria [33]	NR	Low level laser therapy for 30–40 min in five sessions per week for 3 weeks	Sham laser therapy for 30–40 min in five sessions per week for 3 weeks	Primary RP	Crossover design: 18 (15)	53	80	*Daily attacks* (1–5)[f] Tx = 0.67 Control = 0.72 $P = 0.520$[g]	None
Hirschl, 2004, Austria [34]	NR	low level laser therapy for 30–40 min in five sessions per week for 3 weeks	sham laser therapy for 30–40 min in five sessions per week for 3 weeks	primary RP and not taking vasoactive medication	Crossover design: 50 (48)	46	79	*Intensity of attacks* (1–5)[f] Tx = 2.3 Control = 2.8 $P < 0.001$[g]	*Daily attacks*[f] Tx = 1.6 Control = 2.0 $P = 0.001$[g]
Ko, 2002, Canada [43]	Thermoflow	Ceramic-impregnated gloves for 3 months	Placebo gloves for 3 months	Age ≥ 18 years, "Pal" questionnaire criteria for RP	Tx: 49/30 Control: 44/30[h]	Tx: 52 Control: 54	Tx: 67 Control: 87	*Pain VAS*[e] Tx = 50.8 Control = 57.9	None
Sporbeck, 2012, Germany [63]	Physiomed Elektromedizin	Deep oscillation three times per week for 4 weeks	Waiting list	RP secondary to systemic sclerosis	Tx: NR/10 Control: NR/10	Tx: 53 Control: 59	Tx: 80 Control: 90	*Scleroderma VAS RP item at 4 weeks* Tx = NR Control = NR $P = 0.055$ (favors Tx)	*Scleroderma VAS RP item at 12 weeks* Tx = NR Control = NR $P = 0.081$ (favors Tx)

EMG = electromyographic; NHLBI = National Heart, Lung, and Blood Institute; NIH = National Institutes of Health; NIMH = National Institutes of Mental Health; NR = not reported; NS = not statistically significant; RP = Raynaud phenomenon; Tx = treatment; VAS = visual analog scale

[a]Trial also included separate sustained-release nifedipine versus placebo comparison

[b]Included all four trial arms

[c]Geometric means adjusted for baseline values and clinical center. Intent to treat analysis used to include all randomized patients

[d]A total of 32 patients were randomized, of which data were reported for 30

[e]Appears to be a statistically significant different, although no between groups results were reported, and these could not be calculated because the number of patients included in means was not reported

[f]Data presented here for third of 3 weeks of treatment

[g]*P* value for multiple assessments over 3-week period

[h]Trial report described a regression approach to imputation for missing data, but not possible to determine if imputed data presented

Table 19.2 Assessment of risk of bias in randomized controlled trials of non-drug treatments for Raynaud's phenomenon

	Cochrane risk of bias tool domains							
Trial, year, country	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment[a]	Incomplete outcome data	Selective outcome reporting	Study funding and author–industry financial ties[a]	Other sources of bias
Behavioral approaches								
Büttner, 1991, Germany [6]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Freedman, 1983, USA [18]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Freedman, 1984, USA [17]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Guglielmi, 1982, USA [26]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Raynaud's Treatment Study Investigators 2000, USA [57]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Sporbeck, 2012, Germany [63]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Low risk	Low risk
Surwit, 1978, USA [67]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk	Low risk
Other approaches								
Al-Awami, 2004, Austria [1]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Appiah, 1997, Germany [2]	Unclear risk	Unclear risk	High risk	High Risk	Unclear risk	Unclear risk	Low risk	Low risk
Hahn, 2004, Germany [27]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Hirschl, 2002, Austria [33]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Hirschl, 2004, Austria [34]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
Ko, 2002, Canada [43]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk
Sporbeck, 2012, Germany [63]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	High risk	Low risk

[a]Additional domain added to standard Cochrane Risk of Bias tool [59, 60]

Table 19.3 The Cochrane tool for assessing risk of bias

Domains	Definitions
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
Blinding of participants, personnel and outcome assessors	*Assessments should be made for each main outcome (or class of outcomes).* Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Incomplete outcome data	*Assessments should be made for each main outcome (or class of outcomes).* Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.

Other sources of bias: State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry. Was the study apparently free of other problems that could put it at a high risk of bias? **Study funding and author–industry financial ties*: State the funding source(s) of the trial, or indicate if the trial funding source was not reported. State whether any trial authors disclosed financial ties and/or employment by industry, or if author–industry financial ties or affiliation were not reported

*Additional item added to Cochrane Risk of Bias tool based on (1) Roseman M, Turner EH, Lexchin J, Coyne JC, Bero LA, Thombs BD. Reporting of conflict of interest from drug trials in Cochrane reviews: A cross-sectional study. *BMJ*. 2012;345:e5155 and (2) Roseman M, Milette K, Bero LA, Lexchin J, Turner E, Coyne JC, Thombs BD. Reporting of conflicts of interest in meta-analyses of pharmacological treatments. *JAMA*. 2011;305(10):1008–1017

them. The assumed benefits in this case outweigh the risks so clearly that evidence seems unnecessary, similar to the effectiveness of parachutes; although the effectiveness of parachutes among people who jump from airplanes is not rigorously evaluated in any RCT, few people would debate their benefit [62].

Cold avoidance and maintaining body warmth can be accomplished in many different ways. Patients should, whenever possible, avoid situations with rapidly changing temperatures, such as suddenly moving from a hot environment into an air-conditioned room. Maintaining general body warmth could be accomplished by dressing appropriately, for instance by wearing thermal underwear, layered clothing, and a hat when going outside. Winter gloves, chemical hand warmers, and heavy wool socks may also help. Avoiding sitting motionless in cool breezes or cold environments is also recommended [56, 69].

The hands are most vulnerable to cold exposure. Although toes may also be involved in RP, these are generally more protected from temperature changes by socks and shoes [56]. There is some evidence from observational studies that warming the hands before cold exposure (e.g., holding them in warm water for 5–10 min) may increase blood flow, and may normalize vascular responsiveness to cold [23, 22]. When attacks occur, placing the hands in warm water, holding the hands on a bottle with warm water, using chemical hand warmers, or placing the hands in another warm place (such as the axilla) may help terminate the attack. Additionally, rubbing the hands together or rotating the arms in a whirling or windmill pattern may help to restore the blood flow in the fingers and terminate the attack [69].

A number of different kinds of gloves have been proposed for patients with RP to reduce the likelihood of attacks, including, for instance,

battery-heated gloves, gloves knotted with silver thread, and gloves that enable the use of touchscreens. There has been only one RCT that has examined the specific effects of using specialized gloves. In that study, ceramic-impregnated Thermoflow gloves were compared with "placebo" cotton gloves with similar appearance, odor and texture in a trial sponsored by the producer of the gloves [43]. The study included 93 patients recruited from newspaper advertisements who scored at least 4 on the "Pal" checklist for RP, but who were not evaluated otherwise to confirm the diagnosis. As shown in Table 19.1, of the 93 patients randomized, pre-post results for per-protocol analyses of 30 patients using the impregnated and 30 control patients were conducted, but groups were not directly compared. The authors reported that there were significant improvements in subjective measures of pain and discomfort and in objective measures of temperature, grip, and dexterity in the treatment group versus placebo. However, they reported that there was too much missing data for information directly relevant to RP attacks to be evaluated. Thus, it remains to be elucidated whether these ceramic-impregnated gloves are more effective than a good pair of less expensive gloves.

Although wearing gloves to prevent cold exposure may appear to be a suggestion that is easily implemented, some patients may be reluctant to do so because of social implications of wearing gloves inside (e.g., in a grocery store or air-conditioned office), or when it is relatively warm outside (e.g., during spring or summer). The hands are a part of the body that cannot easily be hidden and that are used across many different social situations. Thus, people with RP may have concerns about their appearance from the symptoms themselves or about how they present themselves to others if they use gloves in situations where this would not normally be expected. These concerns about appearance may lead to an acute fear of negative evaluation and social anxiety [61], which, in turn, can lead to avoidance of social situations where attention may be given to physical appearance. Support may be indicated for patients who are hindered by these concerns, for instance by referring them to interventions focusing on teaching techniques that help to effectively anticipate and manage the reactions of others and to increase patients' confidence and self-esteem in social settings.

Avoidance of Vasoconstricting Drugs (Also See Chap. 10)

Patients should be advised to avoid medications that may worsen vasospasm, if possible [56, 69, 70]. There are no formal studies to define which drugs in fact have a significant impact on RP. However, some drugs derive their therapeutic benefit by causing vasoconstriction and should therefore be avoided. For example, the goal of over-the-counter drugs for nasal decongestion is to constrict blood vessels in the nasal mucosa. The two most commonly used agents are phenylephrine and pseudoephedrine. Phenylephrine can cause powerful vasoconstriction of digital arteries (see Chaps. 4 and 5). However, it is extensively but variably metabolized in the gut, and it is unclear if it can attain sufficient blood levels to cause vasoconstriction [11, 40, 29]. Other drugs that are recommended to be avoided include amphetamines; some migraine remedies containing ergotamine or serotonin-receptor agonists; medications used to treat attention deficit disorder, such as methylphenidate, dextroamphetamine–amphetamine, and atomexetine; diet pills; and herbs containing ephedra. In fact, one case–control study that included 64 patients with RP reported a significant association between the presence of RP and past or current use of attention deficit hyperactivity disorder stimulants (methylphenidate and dextroamphetamine) and provides preliminary evidence of an adverse effect of CNS stimulant medications in these patients [20].

Avoiding caffeine containing products is also often recommended. The potential effects of caffeine on the cardiovascular system are complex, and include the potential to directly constrict smooth muscle, activate or inhibit endothelial cells, and increase sympathetic activity. Acute caf-

feine consumption is reported to increase blood pressure and cause vasoconstriction in cerebral, coronary, central, and forearm vascular systems [51, 31, 58, 47, 9, 53, 42]. The effect of caffeine is dependent on the amount ingested and potentially on whether the individual is a naïve or chronic consumer, with desensitization occurring in some individuals [51, 58, 47, 42]. It also depends on the context, with most caffeine delivery occurring through drinking coffee, which contains hundreds of biologically active compounds, some of which may have beneficial effects [51].

The prevalence of RP is higher in females compared to males. Indeed, estrogen can increase cold-induced vasoconstriction in the cutaneous circulation (see Chap. 5). A possible negative influence of estrogen use in patients with RP is suggested by the finding that postmenopausal women using unopposed estrogens have a higher prevalence of RP [13]. Generally, it is recommended to avoid estrogen replacement in patients with severe RP.

It was initially thought that nonselective beta-blockers could cause RP [45]. There were reports of patients treated for hypertension who showed increased symptoms of RP [72]. The Framingham Study suggested the use of beta-blockers accounted for 34.2 % of secondary RP [73]. However, other studies found that beta-blockers did not have any negative effect on microcirculation [74, 75], nor on Raynaud's symptoms [76]. It was also suggested that the newer selective beta-blockers (metoprolol) improved blood flow [77]. Subsequent studies suggested that beta-blockers did not induce vasoconstriction in patients with RP [14]. Interestingly, a clinical trial that investigated calcium channel blockers given alone or in conjunction with beta-blockers found that patients on combined therapy had improved Raynaud's symptoms [8]. Thus, using selective beta-blockers when needed for other conditions like hypertension is not contraindicated.

As reviewed in Chap. 10, there are other drugs that either cause or aggravate RP. These include interferons, cocaine, polyvinyl chloride exposure, and chemotherapeutic drugs including cisplatin, bleomycin, or gemcitabine [78].

Patients should avoid:

- Smoking
- Ergotamine
- Methylphenolate
- Dextroamphetamine
- Amphetamine
- Atomexetine
- Diet pills
- Ephedra
- Caffeine
- Interferons
- Nonselective beta-blockers
- Decongestants with sympathomimetic drugs

Smoking Cessation

Cigarette smoking is well known to contribute to vascular disease in the general population (e.g., [50]). In RP, the evidence on the effect of smoking on disease severity is contradictory, which may be due to differences in modeling of smoking behavior, and the lack of controlling for relevant confounders [35]. Early studies did not find an association between smoking and the age of onset of RP [54] or the frequency of attacks [52]. A more recent study from 2007 found that RP was more prevalent in men who were smoking, but not women [68]. A recent 2011 study, on the other hand, found that smoking was associated with substantially worse symptoms of RP among 606 mostly female (87 %) patients with scleroderma [36]. Moreover, the study showed that the association between smoking and symptom severity dropped rapidly as cessation time increased beyond 1 year, suggesting that there may be relatively little delay in the response to smoking cessation on RP symptoms.

No RCTs have assessed whether smoking cessation improves RP outcomes. However, there is evidence that cigarette smoking reduces digital blood flow in regular smokers [21], which is supported by evidence from recent observational data on the link between smoking and RP. Thus, smoking cessation is emphasized in the education of RP patients [56, 19, 70, 35, 30]. Recent meta-analyses on the effectiveness of brief

(<10 min), simple advice from physicians to quit smoking on medical grounds have shown that the rate of quitters is low, although a brief encouragement increases the rate of patients who quit smoking by approximately 50 % from the unassisted quit rate of 2–3 % [3, 64]. Providing follow-up may produce additional benefit. Specific interventions, such as nicotine replacement therapy, the antidepressant bupropion, and referral to counseling if patients are amenable result in higher rates [71]. Thus, it seems beneficial to systematically identify patients with RP who are smokers and offer them advice as a matter of routine, including specific smoking cessation services.

Behavioral Interventions to Manage Stress and Emotion

Following the early description of Maurice Raynaud [79] that attacks are often precipitated by emotional stress, there have been long-lasting beliefs that stress can trigger RP attacks, as is also reflected in the diagnostic criteria for Primary Raynaud's [70]. There is limited systematic evidence, however, on the degree that emotional stress reactions may indeed be associated with RP attacks, and results of studies investigating this association are often indirect or anecdotal (e.g., [49, 25]). Existing studies tend to be limited by small sample sizes, differences in methods of provoking an emotional reaction (e.g., sounds, visual stimuli), settings (e.g., laboratory, natural environment), and outcome measures (e.g., indirect measures such as arterial pressure or finger temperature versus direct measures, such as frequency of attacks) [12, 16]. Some studies have found no association of stress with RP attacks or an opposite effect, reporting an increase in blood flow (less vasospasm) in patients with RP compared to healthy controls as a reaction to emotional stress [28, 37, 7, 10, 46]. One report, based on 313 patients from the Raynaud's Treatment Study [57], reported that there is a small but statistically significant relationship between trait anxiety, but not acute stress, and the frequency of attacks, although only above a temperature of 40 F [5]. Other studies in patients with primary RP report a reduced habituation of cardiovascular components of the alerting response to acute emotional stress caused by auditory stimuli compared with healthy controls [12]. Additionally, two other studies have reported that scenes specifically stressful for patients with RP (i.e., scenes related to cold) caused a significant reduction of finger temperature in RP patients but not healthy controls, whereas temperature changes in scenes related to warmth, general stress, and neutral scenes did not affect RP differently than controls [15, 48].

The association of emotional stress and RP, although emphasized by many health care providers and patients based on their clinical and lived experiences, remains to be elucidated. Studies that would effectively track and dissect the potential influence of stress and anxiety on attacks, however, are difficult to conduct and would require large samples with long-term and detailed follow-up (e.g., diary measures). The largest study to date on the topic [5] found that trait or ongoing anxiety, rather than situational stress, is associated with attack frequency. Treatments for anxiety, among patients with a high level of ongoing anxiety, are often effective [4]. For patients with RP, treatment of an anxiety disorder could potentially affect RP symptoms, in addition to reducing anxiety. To date, however, behavioral treatments that have been used to address RP symptoms have been designed to attempt to improve the capacity of patients to manage acute stress episodes, rather than treat defined mental health conditions, such as anxiety disorders.

A number of behavioral approaches have been suggested for acute stress management, and thus to be potentially beneficial for the treatment of RP, including autogenic training (a form of relaxation), classical conditioning, and temperature biofeedback. Almost all existing RCTs that have compared behavioral approaches to sham or usual care for managing RP symptoms are studies that have tested temperature biofeedback. Temperature biofeedback is a method used to support relaxation training. Stress leads to reduced blood flow to the body's extremities, and relaxation can increase the blood flow. Thus, in

temperature biofeedback for RP, finger temperature data is provided to patients to help them learn to relax by monitoring their internal states and changing temperature.

As shown in Tables 19.1 and 19.2, however, the majority of biofeedback trials have included very small numbers of patients and has generally been of low quality [6, 18, 17, 26, 63, 67]. Reported results have been mixed, and a 2009 meta-analysis concluded that temperature biofeedback was not more effective than sham electromyography (EMG) biofeedback for addressing RP [44]. One well-conducted RCT [57] (see risk of bias ratings in Table 19.2) randomized 313 patients with primary RP to sustained-release nifedipine ($n=77$), placebo ($n=81$), temperature biofeedback ($n=81$), and a sham biofeedback paradigm ($n=74$). For the biofeedback comparison, patients in the intervention group received temperature biofeedback with suggestions for warmth imagery and passive volition delivered in ten 1-h sessions over 5–10 weeks. Patients in the sham biofeedback control arm received frontalis muscle surface electromyographic biofeedback, which is used to treat conditions such as muscle pain and tension headaches, but would not be expected to influence RP. Patients who received temperature biofeedback experienced only non-substantial and non-statistically significant reductions in the number of attacks compared to patients in the sham group (Table 19.1). Patients in the trial who received sustained-release nifedipine, on the other hand, experienced substantial reductions in attacks and the trial investigators concluded that temperature biofeedback was not more effective than a sham procedure and was inferior to nifedipine treatment [57]. Thus, there is currently no trial evidence to support the idea that behavioral treatments are effective in reducing the number or severity of attacks in RP.

Over-the-Counter Agents and Other Non-drug Approaches (See Chap. 20)

A number of complementary and alternative medicine treatments have been tested for RP management. A 2009 meta-analysis reported that trials of dietary supplements, such as antioxidants, essential fatty acids, ginkgo biloba, L-arginine, and glucosaminoglycans, have generally been of very low quality and have not demonstrated effectiveness [44].

As shown in Tables 19.1 and 19.2, there have been two very small RCTs of acupuncture [2, 27]. However, both were of poor quality, and neither found that acupuncture influenced RP episodes. There have been three trials of low-level laser irradiation treatment [1, 33, 34]. Two were small trials [1, 33]. The third RCT randomized 98 patients in a crossover design and found a relatively small, but statistically significant effect on attack severity and frequency [34]. In all trials, the treatment was intensive, either every other day for a total of ten sessions [1], or five times per week for 3 weeks [33, 34]. In the crossover trial, the effect of treatment did not appear to last once patients crossed from the active laser treatment to the sham laser [34]. Thus, a concern is that the treatment, if effective, would be too resource intensive for the amount of benefit and would have to be ongoing.

Author Recommendations

- Patients should be educated about RP and possible precipitating factors for episodes.
- To help identify individual factors that precipitate attacks, patients can be encouraged to keep a diary of activities and register when attacks happen.
- Maintaining body warmth and avoidance of cold and sudden temperature changes are important ways to prevent attacks and potentially reduce severity and duration when an attack occurs.
- Patients should be assisted to avoid medications that worsen vasospasm, if possible.
- Physicians should systematically identify patients with RP who are smokers and offer them advice as a matter of routine, including specific smoking cessation services.
- Psychological and behavioral treatments that focus on defined mental health problems, such as depression and anxiety disorders, should be provided to RP patients with these problems.

There is not currently trial evidence, however, to support the idea that behavioral treatments are effective in reducing the number or severity of attacks in RP. Given the cost and time intensiveness of these interventions, along with the lack of evidence of effect, recommendations to manage RP via behavioral intervention are not warranted.

- A number of complementary and alternative medicine treatments have been tested for RP management, but none have demonstrated effectiveness from well-conducted trials and they are not recommended.

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Drug Treatment of Raynaud's Phenomenon

20

Janet E. Pope

Abbreviations

ACE	Angiotensin-converting enzyme
AEs	Adverse events
CAMs	Complementary and alternative medicine
CCBs	Calcium channel blockers
CGRP	Calcitonin gene related peptide
CTD	Clinical trial data
EULAR	European league against rheumatism
EUSTAR	EULAR scleroderma trials and research
5HT	5-Hydroxytryptamine
MCTD	Mixed connective tissue disease
NO	Nitric oxide
PAD	Peripheral vascular disease
PDE5	Phosphodiesterase 5
RCS	Raynaud's condition score
RCTs	Randomized clinical trials
RP	Raynaud's phenomenon
SCTC	Scleroderma clinical trials consortium
SERM	Selective estrogen receptor modulator
SSc	Scleroderma
SSRI	Selective serotonin reuptake inhibitors
VAS	Visual analog scale
WMD	Weighted mean difference

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Key Points

1. Drug therapy should be started in patients with severe RP not controlled by non-pharmacologic methods or in those patients in whom specific treatment of an underlying process is not effective.
2. Drug treatment will likely not stop all Raynaud's events, but the goal should be to decrease the frequency severity, duration, and complications of the attacks.
3. The dihydropyridine calcium channel blockers are the most studied drugs used and are considered the first line prescription treatment for RP.
4. There is evidence albeit weak to support the use of several other options including phosphodiesterase 5 inhibitors, angiotensin II inhibition, topical nitrates, and selective serotonin reuptake inhibitors.
5. Intravenous prostacyclins such as iloprost can be effective for RP for several months after a peripheral intravenous delivery. Prostacyclin is used in severe RP not responding to oral vasodilators.
6. Complementary and alternative medicines (CAMs) are popular among the general population, but there is little evidence for their benefit in treating RP.

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Introduction

This chapter provides data and expert opinion for the pharmacological management of Raynaud's Phenomenon (RP). Chapter 23 will then provide case examples to provide practical guidelines for specific clinical situations. It is important to note that the majority of people who experience primary RP will not need drug treatment. The severity of RP is worse in patients with secondary RP with a risk of tissue injury; for example those patients with RP associated with connective tissue disease, especially for those with systemic sclerosis (SSc; scleroderma). Therefore, these patients often need specific treatment with vasoactive drugs. As discussed in Chap. 6, the foundation of therapy for RP is non-drug management. Keeping the whole body warm with hats, mittens, layered clothing, avoiding sudden changes in temperature, cool humidity, and cold breezes, use of chemical warmers for hands and feet are also recommended for all patients with RP. Stress management (see Chap. 19) and smoking cessation can also help decrease attacks. Removing drugs (see Chap. 19) that could aggravate RP is also potentially helpful. Although these non-drug recommendations are felt by experts in the field to be helpful, randomized studies to define the most effective warming techniques and other strategies are mostly lacking.

Drug therapy should be started in patients with severe RP not controlled by non-pharmacologic methods or in those patients that the specific treatment of an underlying disease process or causative factor is not effective. The severity of RP is defined by the impact of the attacks on quality of life. Frequent Raynaud's events with cold hands, bothersome skin color changes or repeated uncomfortable episodes with numbness, discomfort, or decreased hand or finger function has an impact on normal quality of life and thus warrants intervention. Patients with evidence of significant ischemia–reperfusion that threatens tissue injury should also be treated with drug therapy. The risk and benefit of drug intervention needs to be carefully assessed by a comprehensive evaluation including a full understanding of comorbid conditions. When treating any patient with RP, the goals of intervention need to be clearly understood by the both patient and physician. Treatment will likely not stop all events but should decrease the frequency, severity, and duration of attacks. Other goals would include decreasing pins and needle sensations and numbness, decreasing pain, stopping interference with daily activities and preventing complications such as digital ulcers. The Raynaud's Condition Score is a useful patient generated scale that can be used to monitor treatment effect (see Chap. 17). This scale simply asks the patient to rate their RP from 1(mild) to 10(severe) and can quickly be administered at a clinical encounter. Clinical trial data (CTD) supports that the usual treatment effect with current drugs is about a 30 % reduction at most [1] (see Fig. 20.1).

Treatment Approach

Indications for Drug Therapy

- Severe RP that is impacting quality of life despite non-pharmacologic therapy.
- Raynaud's events with signs of ischemia–reperfusion injury that threatens digital tissue.
- Recurrent digital ulcers in a patient with secondary RP.
- History of digital loss associated with secondary RP.

Most people who have primary RP will not need pharmacologic treatment, but if they do, calcium channel blockers (CCB's) are usually used first. The dihydropyridine calcium channel blockers are the most studied and are first line prescription treatment, particularly nifedipine. Although not as well studied in randomized clinical trials (RCTs) other drugs in the dihydropyridine class (nicardipine, amlodipine, felodipine) are also effective. Studies of CCBs have shown that these drugs will decrease the frequency of attacks. They do not work in every case and there may have side effects such as hypotension,

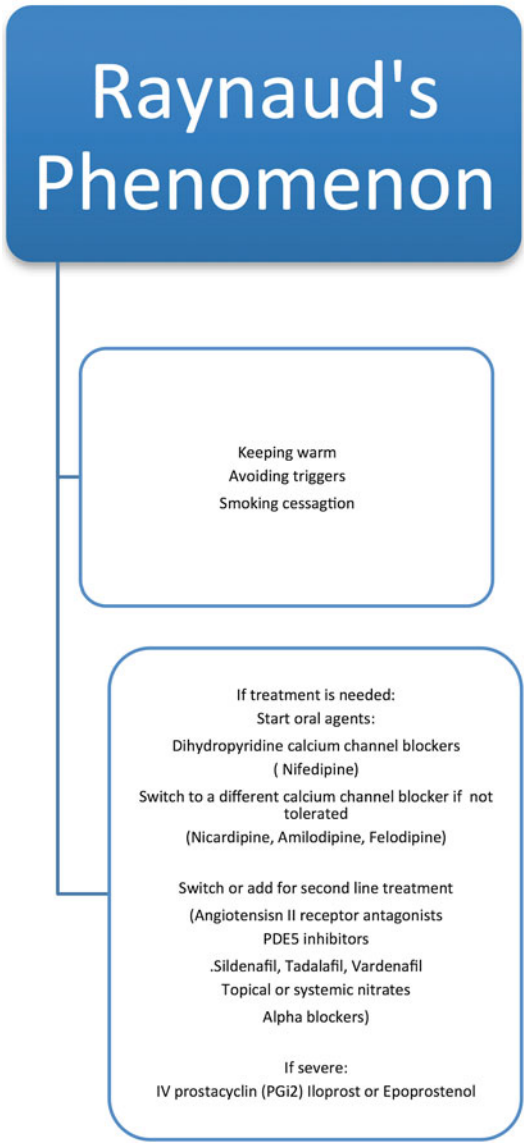

Fig. 20.1 Treatment of Raynaud's phenomenon (RP)

lightheadedness, flushing, headaches, and peripheral edema that limit their use. If patients tolerate the dose of a CCB but do not obtain benefit, the dose can be increased to tolerance or maximum benefit. It is the author's opinion that a higher dose of a calcium channel blocker is more effective than lower doses. This view is based on clinical experience in that no RCTs at higher doses have been systematically done. If one calcium channel blocker is not tolerated or ineffective at a higher dose, then switching to another calcium channel blocker or another vasoactive medication class can be tried. There is clinical trial evidence to support the use of several options (see Specific Drugs below) including phosphodiesterase 5 (PDE5) inhibitors, angiotensin II inhibition (losartan), topical nitrate, and selective serotonin reuptake inhibitors (SSRI) drugs (fluoxetine). Many older drugs once used for treatment of RP (alpha blockers such as prazosin; the adrenergic neuron blocker guanethidine or the monoamine transport blocker reserpine) have fallen out of favor because they often cause significant hypotension including intolerable postural hypotension.

A meta-analysis of drug treatment of secondary RP provides evidence that best support s the use of either a CCB or the intravenous administration of the synthetic prostacyclin, Iloprost. The authors of this analysis considered that the data for other treatments was sparse, negative, or conflicting [2]. Most of the objective data providing evidence for drug therapy are from studies in secondary RP in patients with scleroderma (SSc). Indeed, among patients with connective tissue diseases, SSc patients often suffer with the most severe RP and are at risk of digital ulcers or digital loss.

Guidelines from the European League against Rheumatism (EULAR) and EULAR Scleroderma Trials and Research group (EUSTAR) state that in patients with SSc-related Raynaud's attacks, dihydropyridine-type CCBs, usually oral nifedipine, should be initially considered for RP treatment [3]. In cases with more severe RP then consider intravenous iloprost [3]. Iloprost is approved and available in Europe for treatment of SSc related RP. Experts from the US based Scleroderma Clinical Trials Consortium (SCTC) also start with a CCB, but would in severe RP add a PDE5 inhibitor and then if this combination is not effective consider moving on to an intravenous prostanoid [4] (see Fig. 20.2). This approach is based on the evidence that PDE5 inhibitors seem to work as shown in both in the clinic and in published RCTs. The PDE5 Inhibitors also provide a simpler oral administration; in addition, intravenous iloprost is not available in the USA. Other prostanoids such as the prostacyclin epoprostenol is available for the treatment of pul-

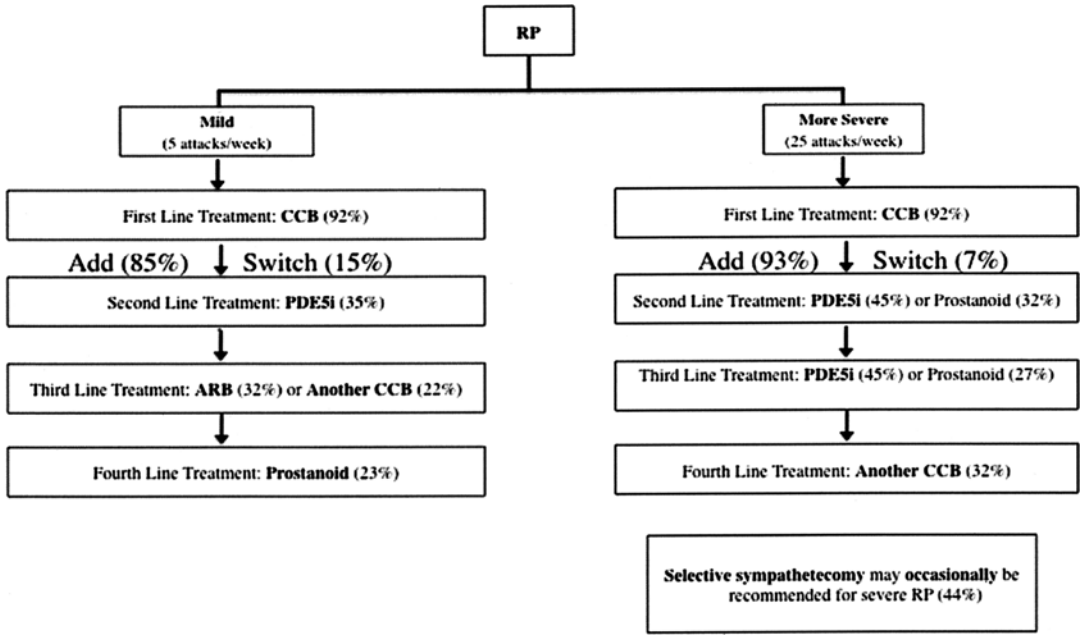

Fig. 20.2 RP treatment in systemic sclerosis expert consensus (*Treatment of Systemic Sclerosis* (*SSc*) *Complications*: *What to Use when First-Line Treatment Fails. A Consensus of SSc Experts. Semin Arthritis Rheum 2012 Aug;42(1):42–55*)

monary hypertension but is not FDA approved for the treatment of RP. However, it is an option and can be used in complicated and severe cases. It should be noted that botulinum toxin locally injected is reported in uncontrolled case series to be helpful [5]. It is an option in cases not responding to other traditional agents (see Chap. 22).

Specific Drugs

Drugs Used for Treatment of RP

- Dihydropyridine type calcium channel blockers.
- Phosphodiesterase 5 (PDE5) inhibitors.
- Prostanoids (PG12, PGE_1).
- Alpha adrenergic receptor blocker.
- Nitrates (nitroglycerin).
- Angiotensin H receptor blockers (ARB).
- Selective serotonin reuptake inhibitor (SSRI).
- Botulinum toxin.

Many different drug therapies have been suggested for treatment in RP. For many of these, the evidence base for their use is weak, in part reflecting the difficulty in mounting clinical trials in RP. This section describes the different drugs and groups of drugs used in patients with RP, and the evidence base for their use.

Calcium Channel Blockers (CCBs) (Table 20.1)

Calcium Channel Blocker (CCB)

- Use an extended release dihydropyridine class of a CCB.
- Expect a 30 % reduction in number of attacks in 2–4 weeks on initial treatment with a CCB.
- If tolerated but benefit not achieved, then increase the dose because higher doses are likely to improve severity of RP.

Table 20.1 Tips for RP treatment with CCBs

• If a patient needs treatment, usually a dihydropyridine calcium channel blocker (CCB) is prescribed
• First: nifedipine ex. As needed 10 to 30 mg a day and increasing if needed to long acting (XL) to max of 90 mg daily
• Next: an alternative dihydropyridine CCB – Nicardipine, amlodipine, felodipine
• Long acting drugs are usually better tolerated
• However, short acting CCBs may be considered when an outdoor activity that precipitates RP is to be undertaken
• If, the drug is tolerated and efficacy is not obtained then the dose can be increased
• Treatment goals include: – Reducing the frequency of attacks – Reducing the severity of attacks – Reducing the duration of attacks
• Clinical trial data support mostly the first two treatment possibilities
• CCBs may cause orthostatic hypotension and many people with primary RP are young women and have normal to low blood pressures
• Side effects of calcium channel blockers include hypotension, flushing, peripheral edema, and headache

The first line drug treatment for RP is from the dihydropyridine class of calcium channel blockers (CCBs). Calcium channels enable activator calcium to enter smooth muscle cells and initiate constriction (or vasospasm). There are meta-analyses to evaluate evidence for the treatment of RP with CCBs. The trials reviewed often included both primary and secondary RP (mostly patients with scleroderma) making the measured outcomes reasonably generalizable to the various populations of patients with RP [6, 7]. Usually the response to treatment is blunted in the subset of patients with secondary RP compared to primary RP; especially among patients with SSc. Many trials are small, use low doses of medications, were of short duration and most use a crossover design with the potential problem of having a significant crossover effect. The crossover effect especially occurs when the study patients do not return to baseline status at time of the second treatment period is started.

Most of the convincing data supporting the use of nifedipine or other drugs used in RP comes from Randomized Clinical Trials (RCTs). Meta-analyses are used to collate these data. Most of the RCTs included in published meta-analyses were small; the number of people included in each RCT with primary Raynaud's phenomenon ranged from 3 to 130 (8 RCTs included 21 people or fewer with primary Raynaud's). There are also biases in these trials. For example, if the trial included subjects with both primary and secondary RP, the meta-analysis can be biased if the randomization was not stratified by subgroups. These reviews often included RCTs with a withdrawal rate of up to 35 %. The analysis also noted that many of the included RCTs were of short duration (median 2 weeks, range 1−10 weeks) and used relatively low doses of agents such as nifedipine.

A meta-analysis compared calcium-channel blockers as a group versus placebo in primary RP [7]. The meta-analysis included for review a RCT if a subset of people with primary RP could be identified separately and their outcome assessed independently, or if >75 % of people had primary Raynaud's. Most RCTs compared a CCB to placebo, but some compared the CCB to other drugs. The meta-analysis of primary RP included 18 eligible trials (of 31 that were found) consisting of 13 RCTs comparing nifedipine to placebo, two of nicardipine, two of nisoldipine, and one of diltiazem. Eleven were crossover studies and two were parallel. It found that calcium-channel blockers as a group significantly reduced the frequency and the severity of attacks compared with placebo. The frequency of ischemic attacks were reduced by 3–5 attacks per week overall and six attacks less for nifedipine. The severity [measured on a 10-cm visual analog scale]: was reduced by 1.4 overall and 1.8 for nifedipine alone. The severity of RP was reduced by 1/3 by CCBs; a clinically relevant change.

Another meta-analysis review the experience in scleroderma related RP [6]. Five of the six RCTS of calcium-channel blockers versus placebo in SSc tested nifedipine and one compared nicardipine to placebo. The average quality score

of the studies included in the analysis was 4.2 out of 5; so the trial quality was good overall. Nifedipine was usually studied at 10–20 mg TID. The reduction in the frequency of RP attacks over a 2-week period was 8.3 attacks overall and 10.2 attacks per week for nifedipine. The severity of attacks decreased significantly for all CCBs versus placebo (three trials) and for nifedipine versus placebo (two trials) with an approximate reduction of 2.3 cm on a 10 cm visual analog scale (VAS) or a 35 % improvement compared to placebo [6]. Therefore, the evidence from several small clinical trials of CCBs for RP in patients with SSc appear to lead to significant clinical improvement in both the frequency and the severity of ischemic attacks (see Figs. 20.3 and 20.4).

Nifedipine

There were 12 trials from the meta-analysis that compared nifedipine to placebo in primary RP containing 215 subjects [7]. The doses were mainly from 5 to 20 mg three times daily; and one trial used 30 mg extended release daily. The duration of the trials ranged from 2 to 10 weeks. Overall there were statistically significant results compared to placebo in the reduction of attacks per week, severity of attacks and improvement in ischemic attacks. The analysis showed an average reduction of six attacks per week. In five trials a reduction on severity of attacks of 1.8 on a 0–10 cm VAS was demonstrated. There was also an improvement in ischemic attacks of 1 on a 5-point scale in 6 of the RCTs. More adverse events (AEs) where found when higher doses are used [8, 9]. For example, in a crossover trial of 22 patients, AEs were found in 27 % on placebo, 45 % who used nifedipine 10 mg daily and 72 % who used nifedipine at 20 mg a day. Side effects of CCBs include lower extremity edema, flushing, tachycardia, palpitations, and headaches.

There were five trials that compared the frequency of attacks of nifedipine to placebo and two for the severity of attacks in SSc associated RP [6]. There were ten less attacks over 2 weeks in the nifedipine treated patients versus placebo treated and the severity was reduced in a clinically relevant and statistically significant way; thus nifedipine had a more positive effect than in the overall calcium channel blocker group.

Nicardipine

Nicardipine was studied in some RCTs, but full data was missing and a carryover effect that may occur in crossover trials was not reported. Although nicardipine may be used to treat primary RP the reported trials included mostly secondary RP. A trial by Feri et al. in 21 subjects with primary RP used slow-releasing nicardipine at 20 mg twice a day was effective in reducing the number of attacks over 2 weeks compared to placebo [10]. A larger trial of 69 people with primary Raynaud's was of crossover design.

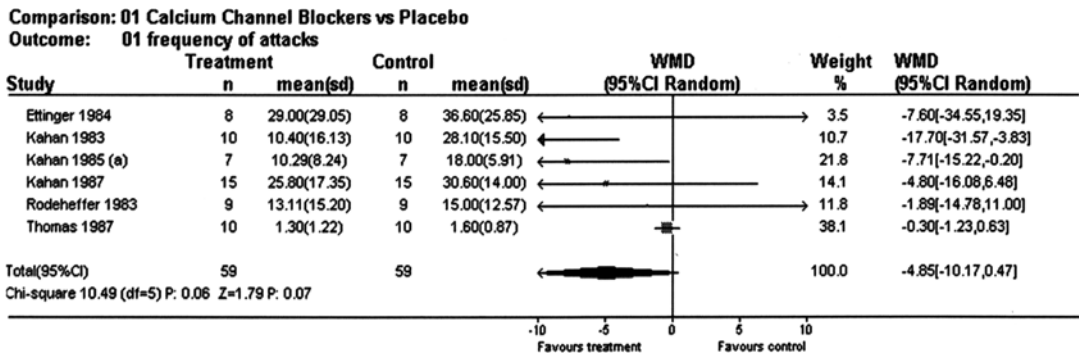

Fig. 20.3 Treatment of RP in scleroderma with calcium channel blockers: frequency of attacks. (*Data based on Thompson A*, et al. *Arthritis Rheum 2001;44:1841–7*)

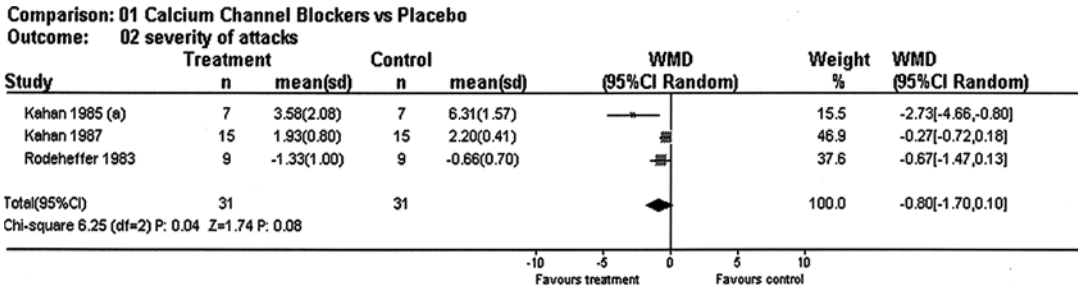

Fig. 20.4 Treatment of RP in scleroderma with calcium channel blockers: severity of attacks. (*Data based on Thompson A*, et al. *Arthritis Rheum 2001;44:1841–7*)

Nicardipine significantly decreased the frequency of attacks over 8 weeks compared with placebo (attacks/week: 4.9 with nicardipine vs. 5.8 with placebo; mean difference 0.9; $P=0.02$) and reduced overall disability (measured on a 10 cm visual analog scale; mean 2.6 with nicardipine vs. 3.3 with placebo; $P=0.018$), but found no significant difference in the severity of attacks [11].

There was a trial of 27 patients with RP (12 with primary RP and 15 with secondary RP including systemic lupus erythematosus [2], SSc [4] and rheumatoid arthritis [12]) who participated in a 4 week per treatment arm, double-blind, crossover study of nicardipine versus placebo [13]. Nicardipine significantly improved pain, decreased the number of RP attacks, and was preferred over placebo in primary RP. In secondary RP it only showed a significant effect on a reduction in the number of attacks. Twenty patients with RP were treated in random order in a crossover study with 2 weeks of nicardipine 20 mg three times daily and 2 weeks of placebo [14]. Nicardipine significantly improved the frequency and severity of RP.

Not all studies find a consistent benefit for nicardipine in RP. There are two published negative trials of nicardipine versus placebo in RP treatment. A RCT with a crossover design studied 25 people, 16 with primary RP and nine with secondary RP, found no significant difference in the frequency, severity, or duration of attacks at 6 weeks between nicardipine 30 mg three times a day and placebo [15]. In the sub-analysis of the 16 people with primary Raynaud's; the mean frequency of attacks/day was 4.4 for both nicardipine and placebo; the mean severity of attacks on a 10-point scale was 3.5 with nicardipine versus 3.7 with placebo; and the mean duration of attacks 13 min with nicardipine versus 11 min with placebo. Another negative trial reported no differences between nicardipine and placebo for the frequency and severity of RP attacks in a double-blind crossover study [16]. AEs caused more dropouts with nicardipine than placebo due to flushing, headache, and palpitations.

Amlodipine

There is one randomized crossover trial of amlodipine in the treatment of RP that is published [17]. There were 24 patients included of whom 15 had primary RP. The authors found that amlodipine significantly reduced the number of acute attacks per week from baseline at 7 weeks (from 11.8 attacks/week at baseline to 8.6 attacks/week after treatment; $P<0.001$) and reduced the severity of attacks from baseline (from a discomfort score of 7.8 at baseline to 5.1 after treatment). However, the RCT did not assess the between-groups difference in frequency and severity of attacks. It found that amlodipine was associated with ankle edema (55 % of people taking amlodipine and none in placebo), flushing, and headaches compared with placebo (10–20 % with amlodipine and none with placebo).

Felodipine

One trial compared two doses of felodipine (10 mg a day and 10 mg twice a day) with nifedipine

in 16 patients with a double-blind crossover design [18]. There were no significant between-groups differences. Although the study was underpowered to detect differences, it gives some evidence supporting the use of felodipine in the treatment of RP.

Nisoldipine

A RCT using Nisoldipine in 36 patients with primary RP in a dose of up to 10 mg/day did not find benefit [19].

Diltiazem

Sometimes a non-hydropyridine CCB drugs such as diltiazem are used for RP treatment when there is intolerability to dihydropyridine CCBs or if there is another indication for its use such as angina or hypertension. Although diltiazem is somewhat cardioselective, it has been studied in RP in two RCTs [20, 21]. The trial by Rhedda et al. was a crossover design with 30 subjects of whom 19 were classified as primary RP [20]. Diltiazem significantly reduced the number and duration of attacks over 8 weeks compared with placebo (mean reduction in attacks from baseline: 22.9/month with diltiazem versus 4.6/month with placebo; $P = 0.01$; mean reduction in duration from baseline: 444 min/month with diltiazem versus 160 min/month with placebo; $P < 0.01$). The results were reported as comparisons from baseline, removing the benefits of randomization. In addition, this analysis was not by intention-to-treat (8/30 [27 %] people withdrew from the trial). Two people using diltiazem withdrew from the trial because of adverse effects (rash or headache). In the Kahan et al. trial, there were 16 patients of whom six were primary RP and ten were secondary to CTD (7 had SSc) [21]. Diltiazem was dosed 120 mg three times a day for 2 weeks and compared to placebo in a crossover design. RP severity was assessed by a 10 cm visual analog scale (VAS). Diltiazem significantly decreased the frequency and severity of Raynaud's phenomenon as compared with placebo in primary RP, but these outcomes were not statistically significant different in secondary RP.

Verapamil

Verapamil is another cardioselective non-hydropyridine CCB and should not have much effect on the peripheral circulation. There is one trial of verapamil in RP, comparing it to nifedipine and diltiazem. Verapamil was not effective [22]. It is not recommended for RP treatment.

Summary of CCBs

The evidence from clinical trials supports the use of dihydropyridine CCBs as first line therapy in both primary and secondary RP. The author prefers nifedipine but amlodipine, felodipine, and nicardipine are other options. The non-dihydropyridine CBB diltiazem can be used, but verapamil is not recommended. When using a CCB, an extended release preparation is preferred and before using combination therapy, the dose should be increased to clinically effective outcome within dosing tolerance.

Phosphodiesterase 5 (PDE5) Inhibitors

PDE5 inhibitors are used in erectile dysfunction and also the treatment of pulmonary arterial hypertension. PDE5 degrades cyclic GMP, which is a major mechanism for nitric oxide (NO) to cause vasodilation, so PDE5 inhibitors can potentially amplify or mimic NO. The potency and selectivity of a PDE5 inhibitor will be dependent on the expression and activity of the enzyme. They have been studied in clinical trials in the treatment of severe RP with most but not all trials having positive results. A meta-analysis of PDE5 inhibitors RCTs in the treatment of RP found statistically significant decreases in the Raynaud's Condition Score (RCS) by −0.46 (−0.74 to −0.17), the daily frequency of RP attacks by

–0.49 (–0.71 to –0.28), and the daily duration of RP attacks by –14.62 (–20.25 to –9.00) min [23]. The analysis included six trials (two with sildenafil, three with tadalafil, and one with vardenafil).

Sildenafil

There are two trials of sildenafil used in severe RP, particularly associated with scleroderma. One trial published in 2005, was a crossover study in 16 patients with symptomatic secondary RP failing other vasodilator therapy. Patients were treated with 50 mg sildenafil or placebo twice daily for 4 weeks. Compared to placebo, sildenafil decreased the frequency of RP attacks (35 ± 14 versus 52 ± 18, $P = 0.0064$), the cumulative attack duration (581 ± 133 versus 1,046 ± 245 min, $P = 0.0038$), and the Raynaud's Condition Score (2.2 ± 0.4 versus 3.0 ± 0.5, $P = 0.0386$) [24]. Two patients discontinued the study due to AEs.

A double-blind, placebo-controlled randomized trial of 57 patients with RP associated with SSc who were nonsmokers received either placebo or sildenafil as a modified-release 100 mg tablet once daily for 3 days followed by modified-release sildenafil 200 mg once daily for 25 days [25]. The mean number of attacks per week improved in the placebo group from 25 at baseline to 19 and from 31 to 19 after sildenafil; the difference in attacks per week between the drug and placebo was not statistically significant. However, the percentage reduction in the number of attacks was significant. Raynaud's Condition Score (RCS) and pain were not significantly different. The frequent adverse events were headache and dyspepsia.

Tadalafil

There are three randomized trials with tadalafil in RP. One trial included patients with SSc and mixed connective tissue disease (MCTD) having at least four RP attacks per week despite being on vasodilators [26]. They were randomized to receive either placebo or tadalafil (20 mg) on alternate days as add-on therapy to their current vasodilators for 6 weeks. After a 7-day washout, patients were crossed over to the alternative treatment. Twenty-five patients were enrolled. All the patients were receiving calcium channel blockers and in addition 18 were receiving other vasodilators. During tadalafil treatment, there were significant improvements in frequency and duration of RP and the mean daily Raynaud Condition Score. All the 24 digital lesions healed during tadalafil therapy as compared with 3/13 during the placebo treatment ($P < 0.0001$). There were no serious AEs. One patient dropped out of the study.

A short trial compared tadalafil in 20 subjects with RP on two separate study days, when subjects received either placebo or tadalafil (10 mg) [27]. The study duration was too short to draw any conclusions on the efficacy of tadalafil in RP. Another trial was negative where sexual dysfunction and RP were studied in 39 women with RP secondary to SSc over 4 weeks using tadalafil 20 mg daily [28].

Vardenafil

A RCT of Vardenafil in RP was published [29]. Patients with primary and secondary RP were recruited in a double-blind, randomized, placebo controlled, crossover design study for 6 weeks to assess the efficacy and safety of vardenafil (10 mg twice daily). Treatment was switched from vardenafil to placebo or vice versa after a 1-week washout phase. Vardenafil significantly reduced the RCS by –0.45 compared with placebo ($P = 0.03$) and decreased the number (–0.51 versus. placebo; $P = 0.005$) and cumulative duration of daily RP attacks (–11.43 min versus. placebo; $P = 0.003$). The drug was overall well tolerated, but AEs included flushing, headache, dyspepsia, and dizziness.

Udenafil

Udenafil, a relatively new PDE5 inhibitor, was compared to amlodipine (10 mg/day) at a dose of udenafil of 100 mg/day. The RCT was a cross-

over design with a double blind with 4 weeks treatment prior to washout. Included in the trial were 29 patients with secondary RP associated with connective tissue diseases (most of the patients had diffuse SSc) [30]. There were no between groups differences in decreasing the frequency of RP attacks ($P=0.99$). Udenafil treatment significantly decreased pain compared to baseline, whereas amlodipine did not; but there were not significant between group differences. This implies that udenafil and amlodipine are seemingly equally effective in RP. In addition, adverse events were similar.

Summary of PDE5 Inhibitors

These clinical trials support the use of PDE5 inhibitors either alone or in conjunction with a CCB. There is no evidence to define one PDE5 agent over another and specific dosing is not fully studied. Sildenafil is preferred and a dose of 20 mg three times or 50 mg twice daily is suggested.

Other Phosphodiesterase Inhibitors

Some drugs used in peripheral vascular disease (PAD) have been tried in RP treatment. These drugs are, however, not routinely used in RP. The PAD drugs include: cilostazol and pentoxifylline: these are the preferred treatments due to effectiveness and cost for the treatment of claudication [31, 32]. *Pentoxifylline is a nonselective* phosphodiesterase inhibitor with hemorrheologic vasoactive properties that improves blood flow and is used for the treatment of peripheral vascular disease. There is one negative trial in RP comparing pentoxifylline to ketanserin. Pentoxifylline was slightly more effective, but neither drug was very effective in RP treatment [33]. In fact, in systematic reviews of claudication pentoxifylline is even thought to be relatively ineffective [31, 32]. Therefore, it is not recommended for treatment of RP. Cilostazol is a quinolinone that inhibits cellular phosphodiesterase III which suppresses the degradation of cAMP leading to inhibition of platelet aggregation and vasodilation. In a small study it was found to increase brachial artery diameter in primary and secondary RP patients [34]. However no clinically relevant RP outcomes were studied.

Prostacyclins

Prostacyclin (prostacyclin I2, PGI2) is also called epoprostenol. There are several analogs on the market including iloprost and trepostinil. PGI2 is produced in endothelial cells from prostaglandin H_2 (PGH_2) through the enzyme prostacyclin synthase. Prostacyclin is a potent vasodilator working on the systemic and pulmonary vasculature and is now used worldwide in the treatment of severe pulmonary arterial hypertension. It has many biological effects including inhibiting smooth muscle proliferation, providing endothelial cell protection and inhibiting platelet aggregation. Prostacyclins can be delivered intravenously, orally or by inhalation. However, there is little data to support the benefit of oral or inhaled prostacyclins in the treatment of RP. Intravenous iloprost and other prostacyclins are mostly used in severe RP secondary to SSc. Cisaprost and beraprost are orally delivered synthetic analogs of prostacyclin. The side effects of prostacyclins are common and may limit the ability to complete the full course of a treatment protocol. They include headaches, flushing, hypotension, gastrointestinal upset, and jaw pain.

Epoprostenol

There is one RCT of intravenous epoprostenol in 14 patients that was showed benefit by reducing the frequency and severity of RP attacks. The response lasted from 6 to 10 weeks after the infusion [35]. Epoprostenol is available in the USA and other countries. Therefore, it is an option for those who cannot obtain intravenous iloprost. These are patients with severe RP requiring treatment after multidrug failure or with threatened digital loss from severe ischemia.

Iloprost

Intravenous iloprost can be effective for RP for several months after a peripheral intravenous delivery at 0.5–2.0 ng/kg/min continuously for 6 h daily for 5 consecutive days. Intravenous iloprost is now commonly used in severe SSc associated secondary RP in Europe. There are many completed positive clinical trials supporting its use. Seven randomized trials and 332 patients were included in a meta-analysis of RP from SSc [36]. Five trials compared intravenous iloprost, one oral iloprost and one oral cisaprost. The analysis showed that Iloprost decreases the frequency and severity of Raynaud's attacks. Review of secondary or exploratory outcome found that intravenous iloprost could also heal and potentially prevent digital ulcers. Oral iloprost and other prostacyclins studied thus far do not appear as effective as intravenous iloprost, perhaps due to drug instability or poor absorption. Lower doses of intravenous iloprost may have similar efficacy to the current usual recommended dosage of iloprost [37].

Beraprost

Beraprost is an oral prostacyclin (a synthetic analog). In 125 patients with primary RP, beraprost was compared to placebo over 8 weeks [38]. There were no significant differences in the outcomes comparing beraprost to placebo. In another RCT, beraprost was found to have numerically but not statistically fewer ulcers in SSc patients. Although RP was not the primary outcome of this trial, in general the results favored beraprost but were not statistically significant [38]. Although available and used in Japan for RP, these data do not support the use of beraprost in the treatment of RP.

Treprostinil

Treprostinil may be effective for RP, but there are no RCTs. It used by subcutaneous, intravenous or inhalation delivery for the treatment of pulmonary hypertension. Nineteen scleroderma patients (84 % female, 53 % limited scleroderma) received treprostinil diethanolamine SR orally with dose titration up to 4 mg twice daily as tolerated [39]. Peak concentrations (mean maximum plasma concentration [Cmax] = 1,176 and 2,107 pg/mL) occurred approximately 3.6 h after dose administration, and overall exposure (under the plasma concentration-time curve from time 0–12 h post dose [AUC0-12] = 7,187 and 12,992 h pg/mL) was linear between the 2 and 4 mg doses. Perfusion and digital skin temperature were positively associated with log-transformed plasma concentration at the 4 mg dose ($P = 0.015$ and $P = 0.013$, respectively). This laboratory based study suggested that oral treprostinil may have benefit in patients with SSc related RP. However, treprostinil was used in a clinical trial as a stable oral preparation for the treatment of SSc digital ulcers with some early benefit but was not superior to placebo in the longer term [40].

Other Prostanoids

PGE_1 (Alprostadil) has been used for critical limb ischemia and can improve RP acutely but when the infusion is stopped, there is no long lasting benefit. It needs a central line for delivery and close monitoring. Compared to iloprost, intravenous PGE_1 is not superior to placebo at 4 weeks, so it is not indicated in the long term treatment of SSc associated RP. However, intravenous alprostadil may have similar acute benefits as intravenous iloprost in a small study of CTD associated RP [41]. It is an option for an ischemic digital crisis, but its benefit is likely not sustained [42, 43].

In one RCT of RP used a topical placebo or prostaglandin E2 analog applied daily for 6 weeks. The active agent had fewer and shorter spasm attacks and better healing of ulcers [44].

Summary of Prostanoids

The evidence supports the use of prostacyclin delivered intravenously in cases of severe RP,

especially when due to SSc. This does not exclude other clinical situations with critical ischemia or severe RP. Iloprost is the best studied, but epoprostenol is an option that is available in the USA. The dose recommended is low dose (0.5–2 ng/kg/min); infused intravenously via a peripheral vein daily for 3–5 days. It can be used once during an ischemic crisis coupled then with maintenance of an orally delivered CCB or other effective vasodilator (e.g., PDE5). Prostacyclins can also be delivered intermittently with intervals defined by clinical benefit, usually 10–12 weeks. Some decide to use it prior to severe weather or known periods of worsening symptoms. Oral prostanoids have not yet shown clinical benefit. Prostaglandin E1 is only recommended for short term therapy for acute ischemia if a prostacyclin is not available.

Other Vasoactive Drugs Used for RP

Other vasoactive treatments that may be effective include: topical or systemic nitrates; angiotensin II-converting-enzyme inhibitors; and selective serotonin reuptake inhibitors; long acting drugs are usually better tolerated than short acting preparations. Local Injection of botulinum is also being used in severe cases (see Chap. 22). These alternative agents are often used because calcium channel blockers may cause orthostatic hypotension, and are therefore poorly tolerated by many people with RP; particularly young patients with normal or low blood pressures.

Alpha-blockers, angiotensin-converting-enzyme inhibitors, and a variety of other vascular agents (see below) that have been used are disappointing and are not recommended due to significant side effects or lack of evidence of benefit. There is a meta-analysis of potential oral vasodilators in primary RP [45]. This article updated a previous meta-analysis of oral vasodilators [46]. There were 8 RCTs with less than 300 subjects studied. All compared a drug to placebo. Unfortunately, the quality of most of these trials was poor and most had a negative outcome. In fact, in an enalapril trial, it slightly increased the frequency of attacks per week. There was a significant reduction by buflomedil on the frequency of attacks per week (WMD −8.8), but no significant effect on the Raynaud's severity score. In a trial of moxisylyte, four times more subjects reduced the number of RP attacks in the moxisylyte treatment group compared to placebo. However, there was no evidence of benefit on the frequency, severity or duration of attacks in primary RP in the trials of captopril, beraprost, dazoxiben, or ketanserin. Beraprost and moxisylyte gave significantly more adverse effects than placebo. In general, there is sparse data to support benefit of oral vasodilators beyond the use of CCBs for primary RP.

Nitrates

Exogenous nitrates generate NO, so they are somewhat analogous to using prostacyclins—providing an endothelium-derived protective agent that may be diminished in SSc. Also, there is the complicating issue that some nitrates (esp. nitroglycerin) require metabolism to release NO, and the distribution of the metabolizing enzyme is not completely defined. Oral nitrates are used rarely due to their side effects. In theory, there is an advantage of a far lower dose and less side effects if topical nitrates are used. However, like the oral preparations, transdermal or topical nitrates creams or ointments may also cause side effects such as headaches, which could limit their use. There are randomized controlled trials of topical nitrates that can vasodilate blood vessels and be potentially effective in the treatment of RP. They have been found to decrease the frequency and severity of attacks in primary and secondary RP and may improve digital ulcers.

There are 7 RCTs employing various topical nitrates in RP treatment. Improved local digital blood flow was demonstrated with topical glyceryl trinitrate (nitroglycerin) [47, 48] and a nitric-oxide generating gel [49], The frequency and severity of attacks were improved with sustained-release glyceryl trinitrate patches and RP improved with nitroderm [50, 51]. The Raynaud's condition score (a patient generated severity score) but not the frequency and duration of RP

episodes was significantly different when comparing a novel formulation of topical nitroglycerin [52]. However, there was no significant improvement in RP in another trial with isosorbide dinitrate ointment [53]. Overall, these studies support the use of topical nitrates in selective cases. However, the long term use is not defined and side effects may limit their use. Topical nitrates are therefore recommended for short term use usually with a CCB. It should not be used at the same time as a PDE5 due to added sided effects.

Angiotensin II Receptor Blockers (ARBs)

The Angiotensin II AT1 Receptor Antagonist, Losartan

This drug is approved for hypertension and other conditions improved by blocking angiotensin II [54]. A RCT of RP (25 people with primary RP and 27 with RP secondary to SSc) were randomized to receive 12 weeks' treatment with either losartan (50 mg/day) or nifedipine (40 mg/day). The frequency and severity of RP attacks were compared not between groups but within treatment groups. The frequency of attacks was significantly reduced with losartan and both losartan and nifedipine reduced the severity of attacks. The trial was too small to analyze differences between groups in order to determine if losartan was superior to nifedipine. The benefit was seen more in the subgroup with primary RP; likely due to the increased severity of secondary RP. The author has not been impressed with the benefit of losartan for RP in clinical practice.

Angiotensin-Converting-Enzyme (ACE) Inhibitors

Captopril, Enalapril, Quinapril

Studies of angiotensin-converting-enzyme (ACE) inhibitors in RP have shown inconsistent results [55]. Captopril dosed at 25 mg three times a day in a crossover study compared to placebo did not improve the frequency or severity of RP attacks in 15 patients with primary RP [56]. Enalapril was ineffective in the treatment of primary RP in one trial [57], whereas in a crossover trial of primary and secondary RP, enalapril at 20 mg daily reduced in the frequency of Raynaud's attacks, especially in patients with primary Raynaud's [58]. Long term use of quinapril at 80 mg/day in a large placebo controlled trial was negative with respect to RP in patients with limited SSc or suspected SSc [59]. Overall the data does not support the use of an ACE inhibitor.

Selective Serotonin Reuptake Inhibitor (SSRI)

There is a positive trial in the treatment of RP using fluoxetine, an SSRI approved for the treatment of depression and anxiety disorders [60]. Twenty-six patients with primary and 27 patients with secondary RP were randomized to treatment with fluoxetine (20 mg daily) or nifedipine (40 mg daily) for 6 weeks. Following a 2-week washout period, each group was crossed over to the other treatment arm. The analysis was limited to within groups; no between groups differences were tested. However, the fluoxetine treated group did have significant reductions in the frequency and severity of RP attacks. These data support using a fluoxetine and perhaps another SSRI in patients who cannot tolerate a CCB or who have a low blood pressure. The SSRI may also be helpful to treat the patient with RP and a significant anxiety disorder.

Alpha-Adrenergic Receptor Blockers

Prazosin

Prazosin is an alpha-1 adrenergic receptor blocker that was one of the early drugs used for RP. A meta-analysis of two trials of prazosin for RP in patients with SSc found prazosin to be more effective than placebo [61]. Another crossover

RCT was conducted in 24 subjects including both 14 primary and ten secondary RP patients [62]. This study compared prazosin (1 mg three times a day) versus placebo. Prazosin significantly reduced the mean number of attacks over 6 weeks after crossover (attacks/day: 2.5 with prazosin versus 4.1 with placebo; $P=0.003$) and reduced the duration of attacks (21.9 min with prazosin and 29.9 min with placebo; $P=0.02$), but found no difference in the severity of attacks (measured on a 10-point scale; 4.1 with prazosin versus 4.8 with placebo; $=0.11$). Patients also significantly preferred prazosin to placebo. A randomized trial of prazosin in 15 females with primary RP at various doses was also completed [63]. At 1 mg twice daily, five out of seven of the prazosin-treated patients reported a reduction of cold-induced RP attacks. The highest tolerated dose in the prazosin-treated patients varied from 2 to 8 mg daily; side effects were more common at the higher dose. Prazosin is associated with hypotension and palpitations. The common side effects of prazosin (up to 50 % in some trials) may outweigh any benefits in treating primary RP. Because of this poor tolerance and availability of alternate treatments, prazosin is now rarely used in the treatment of RP.

Buflomedil

Buflomedil is a nonselective alpha adrenergic receptor inhibitor and smooth muscle vasodilator used to treat claudication. It is not approved in the USA. There is one randomized parallel trial of buflomedil versus placebo in 31 patients with primary RP over 6 months (16 in the buflomedil group, 15 in the placebo group). It showed that buflomedil improved the frequency and severity of attacks [64].

Thymoxamine

Thymoxamine is an alpha-adrenergic blocking drug. A randomized double-blind, crossover trial compared thymoxamine 40 mg, 80 mg and placebo in 24 patients with primary RP [65]. Rewarming was improved especially in the higher dose. However, no clinically relevant outcomes with moxisylyte (thymoxamine) were studied.

Isoxsuprine

Isoxsuprine has α-receptor antagonist with β-receptor agonist action with relaxation of the vascular smooth muscle. Oral and sublingual isoxsuprine 20 mg was compared to placebo in a double-blind randomized crossover trial in seven patients with RP [66]. The sublingual dose was superior to oral and placebo, but the study is too small to draw any conclusions for RP treatment.

Botulium Toxin A

Botox

Botulinum toxin type A could potentially reduce vasoconstriction by multiple mechanisms (Chap. 5). There are several case series published suggesting benefit in treating RP and ischemic digital ulcers [5]. There are no studies comparing Botox to placebo and it is an expensive treatment option. Botox use is reviewed in Chaps. 5 and 22. It is considered an option in patients who have failed traditional oral therapy or in patients who cannot tolerant a CCB or other oral vasodilator.

5-Hydroxytryptamine (5HT) Receptor Antagonist

Ketanserin

Ketanserin, a 5-hydroxytryptamine (5HT) receptor antagonist has been studied in primary and secondary RP. In general, possibly due to the low benefit and side effect profile, this treatment is not used for RP. A RCT in 41 subjects with primary RP with ketanserin only showed improvement in the RP severity score and not in the

frequency and duration of attacks [67]. A trial that included 222 primary and secondary RP patients found a significant reduction in frequency of RP attacks (34 % decrease) with ketanserin used at 40 mg three times a day, compared to 18 % with placebo ($P=0.011$) over 3 months [68]. However, no other outcomes (duration or severity of RP attacks) were significantly different. In a meta-analysis of SSc patients with RP, three trials of ketanserin were included with a total of 66 patients. Ketanserin treated patients were 5 times more likely to improve. However, when comparing ketanserin to placebo, the decrease in severity of RP attacks favored placebo, but the difference was not statistically significant. Side effects were 6 times more common when treated with ketanserin. The frequency of attacks did not change, but the duration of attacks decreased significantly in the ketanserin group [69]. Ketanserin is not recommended or available, but blocking 5HT receptor may have benefits and new agents should be studied. For example, saprogrelate, another 5HT receptor antagonist was reported to have benefit in several patients with scleroderma [70].

Naftidrofuryl Oxalate

Naftidrofuryl oxalate is a selective inhibitor of the 5-HT2 receptor and a prejunctional inhibitor of adrenergic neurotransmission. It also inhibits platelet aggregation. Although not often used for RP, there are studies testing it in RP. Ten patients with RP were in a double-blind 6-week crossover trial with naftidrofuryl (200 mg three times a day) versus placebo. Patients had a significant improvement with respect to their RP with naftidrofuryl, but digital flow did not increase [71]. In another RCT, 102 people (87 with primary RP) compared naftidrofuryl oxalate 600 mg daily versus placebo for 2 months [72]. Naftidrofuryl oxalate significantly reduced the duration of attacks ($P<0.05$), intensity of attacks ($P<0.001$), and reduced the impact of attacks on daily activities compared with placebo ($P<0.05$) over 2 months.

Other Vasodilators

Calcitonin Gene Related Peptide (CGRP)

Calcitonin gene related peptide (CGRP) is an endogenous vasodilator and CGRP in digital cutaneous perivascular nerves is deficient in Raynaud's phenomenon. Two small short trials of CGRP in severe secondary RP demonstrated increased blood hand flow with some sustained benefit three days after the infusion (in one trial that studied this). Clinical parameters such as the frequency and severity of RP attacks were not studied [73, 74]. CGRP is no longer available for use in RP.

Minoxidil

Minoxidil is a pyrimidine derivative that acts on arteriolar smooth muscle leading to vasodilation. Ten patients with primary RP were enrolled in a randomized double blind-controlled acute challenge crossover trial using a single application of topical minoxidil 5 % solution compared to placebo. It did not improve digital blood flow or cold tolerance [75]. The effects of repeated dosing over time or use of oral minoxidil are unknown.

Inositol Nicotinate

Inositol nicotinate (hexapol) is vitamin B3 and inositol and is a variant of niacin but with less cutaneous flushing. There are studies that suggest inositol nicotinate can improve the digital blood flow in patients with RP. However, no conclusions about its use in RP for improving relevant outcomes can be drawn [76]. Two RCTs were analyzed [77, 78]. One RCT (23 people with primary RP) compared inositol nicotinate (4 g daily) versus placebo for 84 days during the winter [77]. Compared to placebo, participants who received inositol nicotinate had fewer and shorter attacks over 84 days, but the difference was not significant.

The second RCT (65 subjects, 54 with primary RP) found that, compared with placebo, more subjects taking inositol nicotinate 2 g twice daily improved over 12 weeks (as measured by a 5-point scale); but the difference was not significant. Side effects were minor but included gastrointestinal disturbance and dizziness [78].

Other Approaches

There are several agents and treatment strategy that has potential to help patients with secondary RP. This includes treating any underlying disease process that may be aggravating or causing vascular perturbation.

Antiplatelet Therapies and Anticoagulants

Although it makes sense to give low dose aspirin to secondary RP patients such as those with severe RP in SSc, there are no data to support this. However the risk and benefit of ASA may be considered to be favorable for treating digital ulcers in SSc. There are many negative trials of antiplatelet drugs and anticoagulants in managing RP including ticlopidine [79], thromboxane synthetase inhibitors [80–83], and low molecular weight heparin [84].

Endothelin-1 Inhibitor

Endothelin-1 is a protein primarily produced by the endothelium that is a potent vasoconstrictor. Levels of endothelin-1 are elevated in SSc and it is thought to play a major role in the scleroderma vascular disease. It is used In patients with various forms of pulmonary hypertension and it is approved in Europe to prevent digital ulcers in patients with SSc. In a placebo controlled trial of bosentan in SSc associated RP, there were no significant differences between drug and placebo. Bosentan did not improve the frequency, duration, pain or severity of RP attacks. While Bosentan may prevent digital ischemic ulcers in patients with SSc is not effective in RP treatment [85].

3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase (HMG-CoA Reductase)

Stains (HMG-CoA reductase) have numerous beneficial biological effects on the vascular including improvement of endothelial function, antioxidant properties, increased nitric oxide availability, reduction of cholesterol, increase in progenitor cells, and reduction of inflammation. A trial in patients with scleroderma compared atrovastatin to placebo and demonstrated improved RP and a decrease in the number new digital ulcers in the active drug group [86]. Statins have the potential of protecting vessels from Injury and then secondarily improving RP and digital Ischemia in patients with secondary RP

Immunosuppressive Treatment

The role of immunosuppression in autoimmune diseases in treating associated RP is not studied. Certainly, an autoimmune disease or inflammatory process that is causing vascular injury and vasospasm might mimic RP. Treating the underlying disease state is always important in that the vascular consequences may respond to immunosuppression. Scleroderma is associated with an underlying vasculopathy and RP, but few studies have investigated the role of immunosuppression as treatment for SSc vascular disease. However, an unblinded randomized 1.5 year long trial in early dcSSc of cyclophosphamide (2 mg/kg daily for 12 months and then 1 mg/kg daily) compared to azathioprine (2.5 mg/kg daily for 12 months and for the next 6 months 2 mg/kg daily), where both groups received concomitant steroids for the initial 6 months was performed that suggested RP attacks were reduced with cyclophosphamide. The skin score and inflammatory markers improved with cyclophosphamide compared to

azathioprine and interestingly, so did the frequency of RP attacks [87]. The role of immunosuppression in the treatment of SSc vascular disease is an active area of research.

Complementary and Alternative Medicine (CAMs)

CAMs are becoming more popular with the public and several have been studied in RCTs, although for most CAM agents, the results have not been replicated beyond one trial. RCTs with CAMs include herbals, biofeedback, laser therapy, and antioxidants, but most of the trials have shown no difference from placebo. The mechanism of action for many CAMs is not always fully understood and occasionally some outcomes associated with the effects are inconclusive. CAMs may be an alternative for patients who do not tolerate pharmaceutical therapies or for those who prefer to use them for their own personal reasons, however, there is little evidence to support their benefit.

In 2009 a meta-analysis was published of alternative treatments including 20 trials (acupuncture, antioxidants, biofeedback, essential fatty acids, *Ginkgo biloba*, L-arginine, laser, and glucosaminoglycans) [88]. Effects were usually negative or only weakly positive. For instance, low level laser resulted in one less RP attack on average over 2 weeks versus sham [weighted mean difference (WMD) 1.18; 95 % CI 1.06, 1.29], and a change in severity of attacks (WMD 1.98; 95 % CI 1.57, 2.39; $P<0.05$). No significant differences were found in the nutritional supplements. However, one study of *Ginkgo biloba* in primary RP reduced the number of weekly RP attacks from 13.2 ± 16.5 reducing to 5.8 ± 8.3, (56 % less attacks) compared to placebo which reduced the number of weekly attacks by 27 % ($P<0.00001$) [89]. However, another trial showed that sustained release nifedipine was more effective than *Ginkgo biloba* with 50 % improvement in RP in the former and 30 % improvement in the latter group ($P<0.03$) using a 2–1 randomization to nifedipine versus *Ginkgo biloba* in primary RP [90].

A synthetic antioxidant (probucol) has been compared to nifedipine and may have some benefit, but more data are needed to draw a positive conclusion [91]. Ascorbic acid did not help RP and fish oil may have some modest benefit [92, 93]. Subsequent to publication of the meta-analysis, a negative trial was published using St. John's wort which was postulated to be beneficial due to potential properties of the plant that could alter serotonin [94]. Interestingly RP improved with St. John's wort, but the improvement was even more with placebo. This highlights that proper trial design with blinding and an identical appearing placebo is important when interpreting RP trials. A biofeedback trial was published after the meta-analysis of CAMs done. This small trial of biofeedback, or deep oscillation versus no treatment in RP associated with SSc, found a trend improvement in the two treatment groups as rated on a visual analog scale (VAS). The study was flawed because there was no blinding, thus the results may be biased [95]. A trial that compared nifedipine to biofeedback in primary RP demonstrated that nifedipine was superior and biofeedback no better than a sham procedure [96].

Modifying Natural Hormones

Cyclofenil a selective estrogen receptor modulator (SERM) is not effective for RP treatment [97]. Stanazol an anabolic steroid is ineffective in RP [98]. High doses of thyroid hormone (T3) can possibly help RP but can cause side effects such as palpitations and in the long term can possibly be associated with other hyperthyroid side effects such as low bone mass. Use of excess thyroid hormone replacement is not a recommended option [99].

Potential Agents for the Future

There are several agents that have the potential to reverse vasospasm and improve clinical RP. The most promising include agents that alter the Rho/Rho kinase pathway, known to be critical in the

upregulation of alpha 2c receptors on vascular smooth muscle and soluble guanylate cyclase stimulators, known to increase cGMP, independent of nitric oxide and thus mediate vasodilation. Studies are needed in future to evaluate these agents.

Alpha 2C-Adrenergic Receptor Antagonist

It Is known that the alpha 2C adrenergic receptor is upregulated in cutaneous vessels during cold exposure (see Chap. 4) OPC-28326 is a selective alpha-adrenergic antagonist with preferential binding to the alpha (2C)-adrenergic receptor (alpha(2C)-AR) subtype. It was studied in 13 secondary RP patients with SSc in a double-blind, placebo-controlled, randomized, 3-period crossover study of OPC-28326 (oral doses of 10 mg or 40 mg) or placebo [100]. Digital skin perfusion was improved with the drug. Side effects were more common at the higher dose. The effects of relevant outcomes to RP have not been studied. A high-potency a2C-adrenoceptor antagonist ORM-12741 was studied in the attenuation of a cold-induced reduction in finger blood flow and temperature in patients with RP secondary to SSc [101]. The area under the rewarming curve (LDI) of the right index finger (arbitrary flux units time) was lower for both 30 mg ($P=0.043$) and 100 mg ($P=0.025$) of ORM-12741 compared with placebo, indicating delayed reperfusion. This paradoxical worsening by ORM-1274 may be due to its some nonspecific inhibitory prejunctional alpha$_2$-ARs on vascular sympathetic nerves. This pre-junctional alpha$_2$-AR inhibition will augment sympathetic transmission, increase the release of norepinephrine, and promote vasoconstriction as discussed in Chap. 4.

Potassium Channel Agonist

A potassium channel opener pinacidil was compared to placebo and nifedipine in a RCT of subjects with RP. Pinacidil did was not effective in RP [102].

Rho Kinase Inhibitors

RhoA/Rho kinase pathway is important in cold-induced vasoconstriction, the function of vascular smooth muscle cells, and vascular homeostasis. Fasudil a Rho kinase inhibitor was studied in a RCT of RP secondary to SSc [103]. However, in an acute challenge of a dose of fasudil at 40 mg or 80 mg orally or placebo, there were no significant differences with respect to skin temperature recovery time and the digital blood flow after the cold challenge.

Soluble Guanylate Cyclase Stimulators

Riociguat is now approved for the treatment of pulmonary hypertension [104]. It increases cGMP which mediates vascular dilatation and potentially may improve RP. However, to date there are no studies in patients with RP reported.

Vasopressin

Vasopressin primary function is to regulate body water and to constrict blood vessels. An oral vasopressin receptor antagonist was compared to placebo in a crossover design. It seemed to improve skin temperature and attenuated the fall in hand blood pressure in response to cold, but clinically relevant outcomes for RP were not studied [105].

Summary

The usual drug treatment is oral dihydropyridine calcium channel blockers (CCBs). Nifedipine is the most studied, but others in that class may be considered such as nicardipine, amlodipine, and felodipine. Less often used are other CCBs such as diltiazem, but it may be considered if there is another reason to use diltiazem such as tachycardia, or ischemic heart disease. If the RP is not responsive to CCBs then other agents may be considered such as topical nitrates, PDE5 inhibitors,

angiotensin II receptor blockers, selective serotonin reuptake inhibitors, and if very severe, intravenous prostacyclins may be considered. There are other agents with positive data such as alpha blockers, but these are used less commonly due to side effects such as hypotension. Vasodilators used in peripheral arterial disease and drugs altering platelet function or viscosity have unknown benefits in RP. It is important to note that virtually all RP treatments are off label (i.e., drug authorities have not approved most drugs that are used in RP for this indication).

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Management of Digital Ischemia

21

Antonia Valenzuela, Rasidat Adeduntan, and Lorinda Chung

Abbreviations

ACE	Angiotensin converting enzyme
ARBs	Angiotensin receptor blockers
cAMP	Adenosine monophosphate
CCBs	Calcium channel blockers
cGMP	cyclic guanosine monophosphate
DU	Digital ulcers
ET-1	Endothelin-1
ET_A	Endothelin-1 A receptor
ET_B	Endothelin-1 B receptor
ETRA	Endothelin receptor antagonists
FDA	Food drug administration
HHS	Hypothenar hammer syndrome
MCTD	Mixed connective tissue disease
PAH	Pulmonary artery hypertension
RCT	Randomized controlled trials
RP	Raynaud's phenomenon
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
SSRI	Selective serotonin reuptake inhibitors
WHO	World Health Organization

Key Points

1. Digital ulcers are denuded areas with a defined border, loss of epithelialization, and loss of epidermis and dermis that typically occur at the distal aspects of the digits.
2. Digital Ulcers are the consequence of tissue ischemia secondary to a variety of diseases that cause injury to peripheral arteries
3. Ischemic digital ulcers are a consequence of multiple factors including ischemia–reperfusion injury with oxidative stress from recurrent vasospasm, thrombosis, and loss of vascular integrity from arterial disease.
4. Both non-drug and drug therapy need to specifically address the underlying cause of the vascular disease whenever possible.
5. Hydrocolloid membranes used as a dressing after cleansing can provide protection from repeated trauma and also accelerate DU healing and reduce pain
6. Pharmacologic agents used to treat RP either alone or in combination can prevent DU since ischemia–reperfusion injury contributes to the development of ischemic DU [also see Chap. 20]
7. Vasoactive drugs including endothelin receptor antagonists, phosphodiesterase inhibitors, prostaglandins, and statins may prevent the development of new DU in patients with scleroderma.
8. Digital sympathectomy is favored over proximal upper limb sympathectomy in treating distal circulatory problems.

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9. Critical digital ischemia is a digit-threatening event requiring emergency care to immediately define the underlying cause and to begin appropriate vascular therapy.

Introduction

Digital ischemia is the reduction in digital perfusion associated with impaired tissue viability that can frequently result in digital pitting scars, digital ulcers (DU), loss of digital pulp, and if severe, gangrene requiring amputation. Ulceration from digital ischemia typically occurs at the distal aspects of the digits, at or distal to the proximal interphalangeal joints [1]. Because the management of digital ischemia varies depending on the etiology, it is important to be familiar with the differential diagnosis (see Table 21.1).

Table 21.1 Digital ulcer differential diagnosis

Differential diagnosis	Characterization
Connective tissue diseases	Digital artery fibrosis and hyperplasia leading to vascular occlusion.
Scleroderma	
Systemic lupus erythematosus	
Mixed connective tissue disease	
Vasculitis	Inflammation and fibrinoid necrosis of vascular walls.
Arteriopathies	Insidious widespread arterial disease. Particularly within the retinal, cerebral, coronary, pulmonary, and renal circulations in addition to the limbs and digits.
Occupational diseases	Embolization to digital arteries resulting from constant force or pressure to the ulnar artery.
Paraneoplastic syndrome	Rapid ischemic onset due to impaired anticoagulant and fibrolytic pathways in the presence of cancer.
Steal phenomenon after vascular access shunts	Abnormal blood flow after radial artery shunt placement. Frequently accompanied by numbness and parathesia.
Iatrogenic after radial artery cannulation	Partial or complete vascular occlusion from indwelling catheters.
Septic shock	Decreased peripheral tissue perfusion after severe infection.
Anatomic variants	Abnormal vascular flow due to abnormal arterial anatomy.

Connective Tissue Diseases

Connective tissue diseases are chronic autoimmune diseases that can result in inflammation and vascular pathology. In one study of 50 patients with digital ischemia, connective tissue disease was the predominant underlying disease, associated with 38 % of cases [2]. Forms of connective tissue disease that can present with digital ulcers include systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD) [2]. Digital ulcers and ischemia can occur in up to 50 % of SSc patients over the course of their disease [3]. Although clearly less common than in SSc, the exact incidence and prevalence of digital ischemia are currently unknown in SLE and MCTD patients [4, 5]. SSc is characterized by cutaneous and visceral fibrosis, in addition to vascular disease that involves the arterioles and arteries of the peripheral circulation [1]. Histologically, the digital arteries in patients with SSc are characterized by intimal hyperplastic or fibrotic proliferation, resulting in extensive luminal narrowing (Fig. 21.1) [6, 7]. Digital artery thrombosis can also occur, further compromising the peripheral circulation, leading to both chronic and acute episodes of digital ischemia [8]. The majority of studies on the management of digital ulcers and ischemia summarized below have included patients with SSc.

Vasculitis

Vasculitis occurs when there is inflammation and fibrinoid necrosis of blood vessel walls [9, 10]. This leads to vessel destruction and subsequent hemorrhagic and ischemic damage [11]. In addition to affecting the larger blood vessels, inflammation can occur in arterioles, venules, and

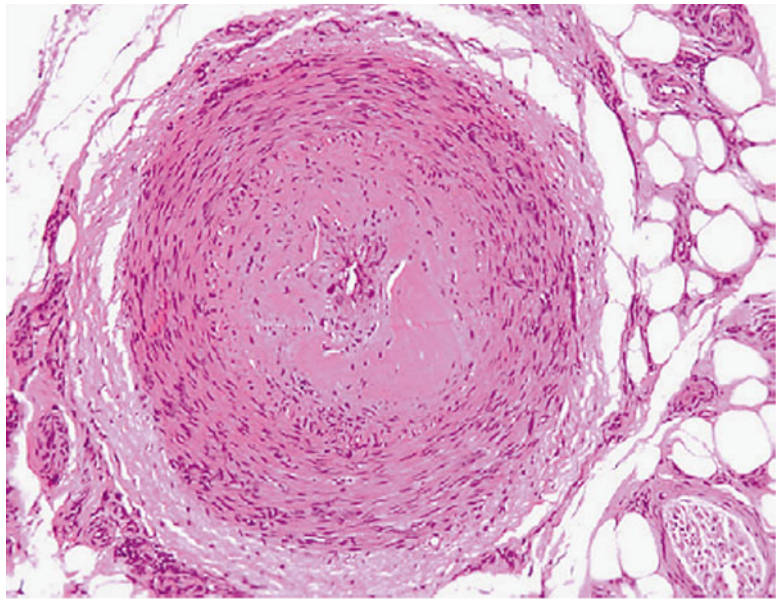

Fig. 21.1 Digital artery from a patient who has SSc (amputation specimen) showing marked intimal hyperplasia and almost complete occlusion of the lumen (Reproduced with permission from: Herrick, A. (2008). "Diagnosis and management of scleroderma peripheral vascular disease." Rheumatic Disease Clinics of North America 34(1): 89–114)

capillaries. However, digital ischemia typically occurs in association with large or medium vessel vasculitis. Primary vasculitides that can be associated with digital ischemia include giant cell arteritis or Takayasu's arteritis which affect large vessels; polyarteritis nodosa which affects medium vessels; and anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis, cryoglobulinemic vasculitis, and connective tissue disease-associated vasculitis which can affect small and medium sized blood vessels [12].

Arteriopathies

The most common cause of peripheral vascular disease is obstructive atherosclerosis of the extremities. Atherosclerosis is considered to involve an inflammatory component which may be in part immune-mediated [13]. Traditional risk factors are well known including age, gender, family history, diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking, and obesity with metabolic syndrome [14, 15]. Atherosclerotic plaque can cause stenosis or occlude peripheral vessels causing claudication with physical activity or it can cause cutaneous ulceration. Thrombosis, embolism, and vascular dissection are complications that can cause digital ulcers or peripheral skin ulcerations. In patients with other vascular diseases, underlying larger vessel atherosclerosis is a common complicating factor that must be appreciated and addressed. The prevalence of atherosclerotic cardiovascular disease has been found to be higher in patients with SSc than in the general population [15, 16]. Although the exact mechanisms are unknown, this increased rate may be secondary to the chronic inflammation, altered lipid profiles and function, development of autoantibodies, and vascular dysfunction found in SSc [15].

Fibromuscular dysplasia (FMD) is a systemic arterial disease that is noninflammatory and nonatherosclerotic [17]. FMD has an unknown etiology but has been suggested to be due to hormonal, mechanical or genetic causes [17, 18]. It typically affects the renal and carotid arteries, but can also affect the small arterial beds where it

manifests as lesions in the middle or distal arterial segments. Although uncommon, case studies have reported digital ischemia in patients with brachial artery FMD [19–21]. FMD predominantly presents in young female adults who are suffering from renal hypertension [18].

Degos disease (also called malignant atrophic papulosis) is a rare condition that can be purely cutaneous (small, white, and firm papules), or that can present as a systemic variant with cutaneous manifestations [22]. The pathogenesis is unknown [22–25]. The systemic variant has a high morbidity and can affect the nervous, ophthalmological, gastrointestinal, cardiothoracic, and hepatorenal systems. It has been suggested that the skin lesions of Degos disease are secondary to the slow occlusion of deeper arterioles [25], which can ultimately cause digital ischemia. Histologic findings in one small study noted that all patients with Degos syndrome had varying degrees of lymphocyte-mediated necrotizing vasculitis [24].

Occupational Diseases [See Chap. 9]

Blunt or penetrating injury can lead to vascular trauma and complications of digital ulcerations. Hypothenar hammer syndrome (HHS) is a condition resulting from constant pressure or vibrational force to the ulnar artery. Embolization to digital arteries from the injured ulnar artery can cause unilateral finger ischemia [26]. Occupations that require repetitive movement in which the palm is used as a hammer, such as carpenters, machinists, and mechanics, are most susceptible to digital ischemia related to injury of the ulnar artery [26–28]. The incidence of HHS in these occupations is estimated to be 14 % [29]. Symptoms associated with HHS range from mild pain or cold sensitivity to digital gangrene. It has been suggested that individuals who develop HHS may have a preexisting abnormality of their ulnar artery, making it more susceptible to digital artery embolization from traumatic injury [26]. Identifying HHS can be difficult, and it is believed to be underdiagnosed [30]. A thorough patient history for occupation, hobbies, and previous hand trauma is important to properly diagnose the disease [31].

Paraneoplastic Syndrome

Malignant disease can be associated with digital ischemia, and has been reported with a variety of cancers including those of the kidney, ovary, colon, and pancreas [32–34]. Although digital ischemia as a paraneoplastic syndrome has been reported in a number of case studies, the prevalence is unknown [32, 35–37]. Factors that may contribute to cancer-related ischemia include tumor cell infiltration, impaired blood flow due to hyperviscosity, an increase in circulating coagulant factors, and impaired anticoagulant and fibrinolytic pathways. Tumor antigen–antibody immune complexes can also cause arterial microvascular thrombosis [38]. Generally, onset is sudden and can be rapidly progressive [32]. In some cases, symptoms reduce after therapy for the primary tumor [39–41].

Steal Phenomenon After Vascular Access Shunts

If a patient has recently received shunt placement, steal phenomenon should be considered as a possible mechanism for digital ischemia. Placement of upper limb arteriovenous accesses for hemodialysis has been reported to induce hand ischemia in 1.6–8 % of hemodialysis patients [42–44]. With vascular steal, extremity ischemia can occur when significant arterial blood flow is shunted directly into the venous outflow of an arteriovenous fistula or graft but a portion of the collateral flow to the distal extremity is taken by the access [43]. Vascular steal can range in intensity. In mild cases, onset is insidious and can be delayed by a few days to a few months. Symptoms include numbness and paresthesia of one or more fingers. Pain, stiffness, and swelling of the fingers may also occur [42]. In

severe cases, there is progressive numbness and pain, accompanied by reduced sensation, ischemic ulcers, and dry gangrene of the fingers [42, 44]. Confirmation of the diagnosis is made with digital plethysmography/pulse volume recordings that document digital pressures less than 50 mmHg and augmentation of the pulse wave with fistula compression [42].

Iatrogenic After Radial Artery Cannulation

Although an uncommon complication, ischemic damage from radial artery cannulation may occur [45, 46]. Radial artery cannulation is a procedure that allows precise measurement of blood pressure, blood gases, arterial pulse contour, and cardiac output, and is particularly useful when managing critically ill patients and individuals who will be undergoing major surgery. However, indwelling catheters have been reported to create partial or complete vascular occlusion that results in ischemia and at times gangrene of a digit or hand. Autoimmune diseases, vasospastic conditions such as Raynaud's phenomenon (RP), severe arteriosclerosis or ischemic disease, and thrombotic tendency have all been identified as risk factors for cannulation complications [46].

Septic Shock

Septic shock occurs when the systemic response to infection leads to hypotension and organ dysfunction [47]. Septic shock is characterized by decreased peripheral tissue perfusion, abnormal cellular metabolism, and misdistribution of blood flow due to vessel constriction, all of which can lead to digital ischemia [48].

Anatomic Variants

Abnormal anatomic structures may influence the occurrence of digital ischemia. Variations in the arterial anatomy of the upper extremities are found in as many as 24 % of patients and are most common in the radial or ulnar artery [49, 50]. Anatomic variation can be observed by arteriogram. Anatomic arterial contribution to abnormal blood flow should be assessed prior to determining the best therapy for digital ulceration [50].

Digital Ulcers

Definition

Digital ulcers (DU) are denuded areas with a defined border, loss of epithelialization, and loss of epidermis and dermis [51]. DU do not include fissures (Fig. 21.2) or paronychia (Fig. 21.3). DU can be related to ischemic causes, from severe recurrent vasospasm related to RP and underlying vascular pathology. Other contributing factors include trauma or underlying calcinosis (Fig. 21.4). They typically present as painful sores on the fingers or toes (Fig. 21.5), but can also occur over the interphalangeal joints of the hands, or other extensor surfaces (Fig. 21.6) [52]. DU can also be partially or completely covered with crust, hyperkeratosis, or fibrin. Chronic ulcers can progress to gangrene, loss of distal tissue, or become infected and lead to osteomyelitis [52].

Pathophysiology

Ischemic DU are a consequence of multiple factors. Although the vasospasm associated with RP is reversible, recurrent and prolonged episodes may contribute to ischemic damage to distal tissues. In addition, vascular injury can result in endothelial dysfunction and abnormal vascular reactivity. For example, increased levels of vasoconstrictors (endothelin-1) and decreased levels of vasodilators (nitric oxide and prostaglandin) are thought to lead to decreased perfusion of the digits in patients with SSc. Finally, the lumen of digital arteries in patients with SSc is compromised due to thrombosis [51] and fibrosis of the intimal layer [53]. Progressive occlusion of arteries from thrombosis can occur in other diseases associated with DU.

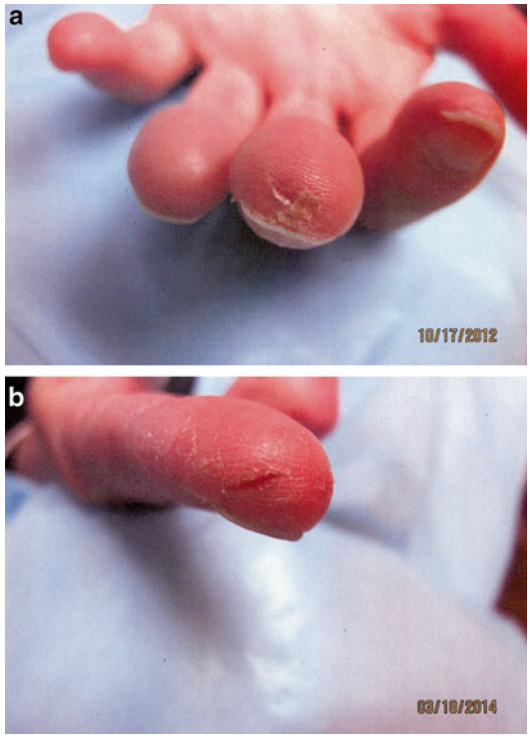

Fig. 21.2 (**a**) Dryness, scaling, and fissuring of the fingers from dehydration related to obliteration of adnexal structures; (**b**) Fissure of the skin on distal finger

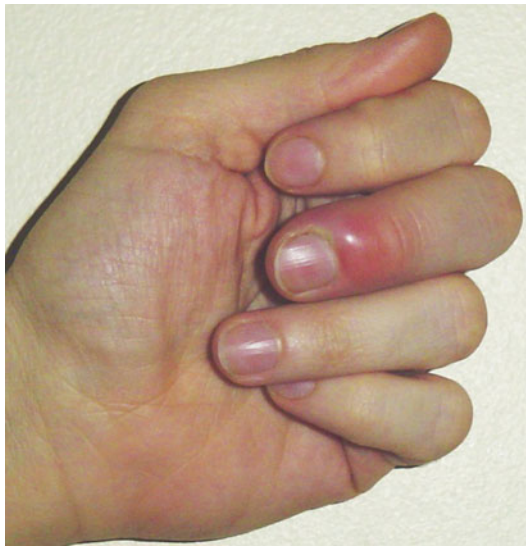

Fig. 21.3 Chronic paronychia is common due to loss of a functional barrier at the nail fold

Prevention and Treatment of DU

Although treatment with a variety of vasodilators has been shown to be effective in managing RP, DU remain a serious complication for many patients, and a uniform effective therapy is lacking [53]. Below, we will address non-pharmacologic and pharmacologic therapies targeted to treat DU, as well as surgical options. It is important to note that most of the clinical trials investigating agents used to prevent or heal DU have been done in patients with SSc. Therefore, the benefit or not of a given agent in other vascular diseases causing DU is unclear. It is also important to address the underlying cause of the vascular disease with specific therapy if possible. For example, active vasculitis may need corticosteroids or immunosuppressive therapy to control the inflammatory component of the vascular insult.

Non-pharmacologic Therapy

The management of DU includes non pharmacological modalities, including the avoidance of all inciting factors such as cold exposure, emotional distress, smoking, repeated trauma of hands, and some drugs [54], specifically pharmacologic vasoconstrictors such as smoking, cocaine, and sympathomimetics [55]. In patients with scleroderma (SSc), physical therapy is important in improving joint contractures of the digits where abnormal skin stretched over an immobile joint often leads to a trauma-induced DU [1] (Fig. 21.7).

Keeping the affected area clean is of utmost importance to promote healing and prevent infection. Also, patients should minimize trauma to their digits as much as possible. Hydrocolloid membranes such as Duoderm can provide protection from repeated trauma and also accelerate DU healing and reduce pain [56]. These dressings decrease oxygen tension and preserve moisture over the damaged area, promoting growth of granulation tissue and the epidermal and dermal layers of the skin [1]. Duoderm is a polyurethane film coated with a strong adhesive that protects skin from bacteria and serves as a barrier against

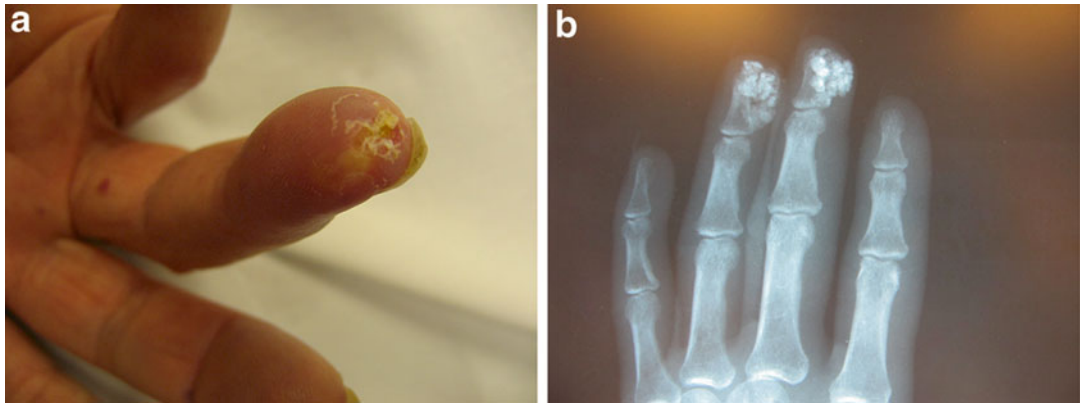

Fig. 21.4 (**a**) Ulceration over first fingertip related to the presence of calcinosis, (**b**) X-ray showing subcutaneous calcinosis in fingertip

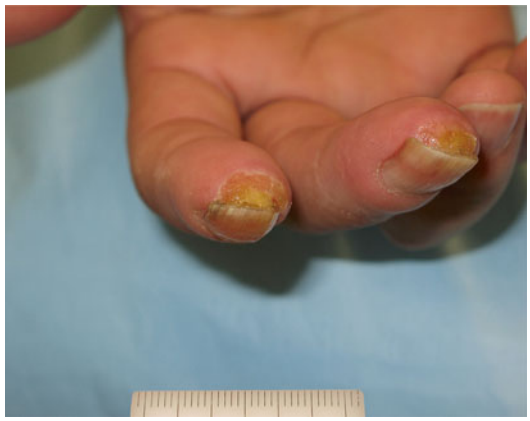

Fig. 21.5 Ulceration at fingertips

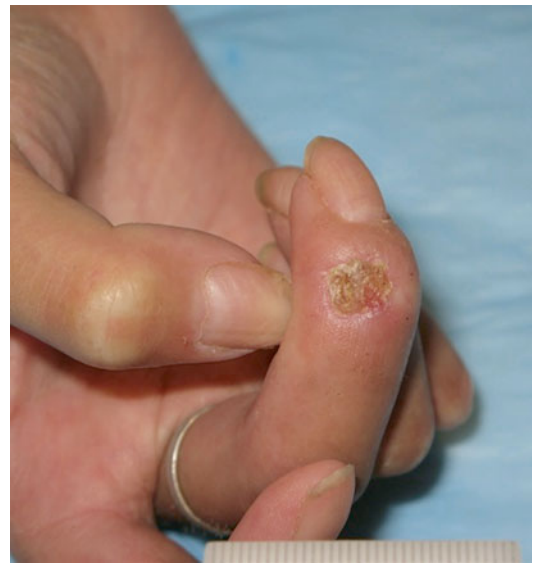

Fig. 21.6 Ulceration over the right third distal interphalangeal joint with overlying crust

further injury. We use the following approach for the application of Duoderm. First, we recommend cleaning the area over the ulcer with hydrogen peroxide 3 % or an antibacterial soap, drying, and covering with antibacterial ointment, being careful not to get the greasy ointment where the adhesive will be placed. Duoderm should be cut approximately 1/2–1 in. beyond the wound's margin and applied to the wound after peeling off the adhesive. Tape may be used around the edges of the dressing to aid keeping it in place. The Duoderm dressing should be changed and cleaned every third day, or sooner if the dressing is oozing a lot of fluid.

The removal of damaged tissue can be helpful in improving the healing potential of remaining tissue [57]. Debridement can be performed if the DU appears to be superficial and there is no deep infection or exposed bone [58]. Surgical debridement may be indicated for deeper lesions [see Chap. 22].

Pharmacologic Therapies

Optimization of Raynaud's Phenomenon (RP) Therapy

We often use pharmacologic agents to treat RP either alone or in combination for the treatment and prevention of DU since RP contributes to the

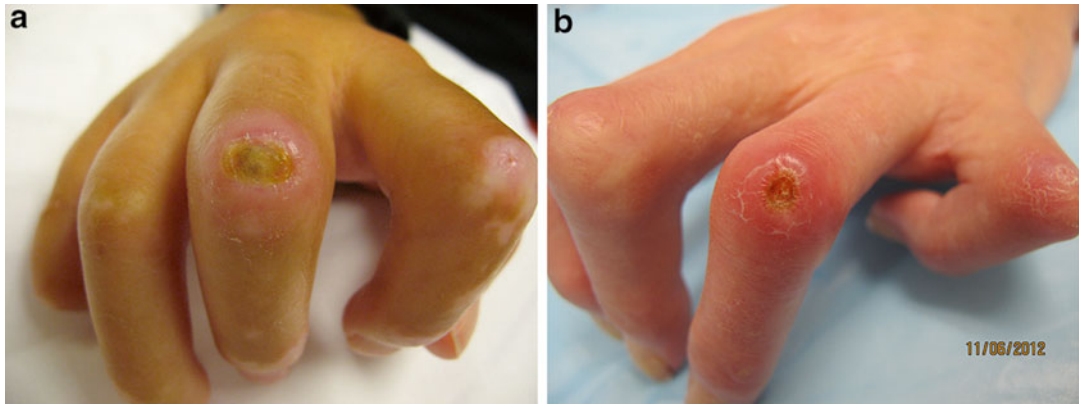

Fig. 21.7 (**a**) A traumatic ulcer over the proximal pharyngeal joint in the middle finger, (**b**) A traumatic ulcer over the proximal pharyngeal joint in the ring finger

development of ischemic DU, and the majority of validated outcome measures used in DU clinical trials are borrowed from studies of RP [1, 59]. We will focus on treatments that have shown some efficacy specifically for DU. Please refer to Chap. 15 for details on RP management.

Calcium channel blockers (*CCBs*): CCBs are moderately effective in the treatment of RP, reducing the severity of attacks by 35 % in secondary RP [60] and by 33 % in primary RP [61]. In addition, one study demonstrated a significant reduction in the number of DU compared to baseline after 16 weeks of nifedipine, as compared to intravenous infusions of iloprost, but without change in hand temperature or digital microcirculatory blood flow [62]. Another study compared nifedipine to placebo in the treatment of RP [63] and found no statistically significant difference in the prevention of new DU; however, the trial was underpowered since few new ulcers developed [64]. CCBs may potentially be useful as "background" therapy in patients with DU, and most randomized controlled trials (RCT) for DU permit CCB use at stable doses throughout the studies [52].

Alpha-adrenergic inhibitors: Two RCT showed that prazosin is more effective than placebo in the treatment of RP secondary to SSc [65] and one observational study found that terazosin reduced the number, intensity and duration of vasospastic attacks to the hands in patients with idiopathic and secondary RP [66]. However, although they may reduce RP, alpha-adrenergic blockers have not been directly studied for DU treatment [59].

Angiotensin converting enzyme (*ACE*)*-inhibitors and angiotensin receptor blockers* (*ARBs*): Similarly, ACE-inhibitors and ARBs have limited benefit in the treatment of RP secondary to SSc, but studies evaluating their effects on DU are lacking [1]. One multicenter, randomized, double blind, placebo controlled study included 210 patients with limited scleroderma or with RP and the presence of SSc-specific antinuclear antibodies. This study found that quinapril 80 mg/day, or the maximum tolerated dosage, did not affect the occurrence of new DU or the frequency or severity of RP episodes over a 3-year follow-up period [67].

Nitroglycerin ointment or patches: Nitrates are used in topical, sublingual, or oral formulations, as adjunctive therapy in the treatment of RP and DU in SSc [1], but there is no evidence supporting their role in DU healing [54]. One double blind, placebo-controlled, randomized trial showed that a short-acting topical nitroglycerin gel was more effective than placebo for the treatment of RP but did not prevent new DU [68].

Selective serotonin reuptake inhibitors (SSRI): A small study of 26 patients with primary and 27 patients with secondary RP suggested that

SSRI are more effective than nifedipine in reducing the frequency and severity of RP, particularly in female patients and those with primary RP [69]. However, no studies have evaluated the effect of SSRI on the treatment and prevention of DU [59].

Other Vasoactive Drugs

Endothelin-1 receptor antagonists

Endothelin receptor antagonists (ETRA) are a class of pulmonary arterial hypertension (PAH)-specific drugs that block the interaction of Endothelin-1 (ET-1) with its receptors (ET_A and ET_B) interfering with its vasoconstrictive effects [70]. ET_A receptors are located on vascular smooth muscle cells and primarily mediate vasoconstriction while ET_B receptors are located on endothelial cells mediating vasodilatation by release of nitric oxide and prostanoids, and also on smooth muscle cells mediating vasoconstriction [71]. ET-1 is also noted to promote cell growth and proliferation and thus can also mediate vascular and tissue fibrosis and remodeling.

Bosentan

The dual endothelin-1 receptor antagonist bosentan has been shown to prevent the development of new SSc-related DU in two randomized, double-blind controlled clinical trials [53, 72]. In the RAPIDS-1 trial, which included 122 patients with SSc, bosentan 62.5 mg twice daily for 4 weeks and thereafter 125 mg twice daily reduced the occurrence of new ulcers by 48 % after 16 weeks of treatment, particularly in patients with diffuse skin involvement, non-smokers, and patients with a high burden of DU. A slight trend toward slower healing was observed in patients treated with bosentan, but this did not reach statistical significance. RAPIDS-2, which enrolled 188 patients with SSc, confirmed the results of the previous RAPIDS-1 trial: 24 weeks of bosentan therapy was associated with a reduction in the number of new DU compared to placebo, but did not lead to more rapid ulcer healing. The most common side effect among patients treated with bosentan was elevation of liver enzymes, which was reported in 11.4–12.5 % of patients treated in clinical trials [64]; thus its use requires monthly liver function test monitoring. The FDA approved bosentan in the USA in November 2001 for the treatment of WHO functional class III/IV PAH, and in 2009 for the treatment of WHO functional class II PAH, while the EU approved it for PAH in May 2002. In June 2007, the EU extended the indication for bosentan as a therapy to reduce the number of new DU in patients with SSc and ongoing DU disease [70].

Ambrisentan

Although evaluated in only a small number of patients, this ET_A selective ETRA showed a reduction in the total number of DU in two open-label studies [73, 74]. In the first one, six patients with SSc with DU unresponsive to bosentan were treated with 5 mg daily of ambrisentan for 24 weeks. The recruited patients continued to receive intravenous therapy with prostanoids. Ambrisentan led to a reduction in baseline number of DU per patient with no appearance of new lesions [73]. In the second study, up to 10 mg daily as tolerated of ambrisentan significantly decreased DU burden and mean maximum diameter of lesions after 24 weeks of therapy in 20 patients with SSc. Ambrisentan did not prevent the incidence of new DU and no patients developed elevated transaminases, but 75 % experienced peripheral edema [74]. Ambrisentan does not require monthly liver function test monitoring, is given once daily, and two doses are available (5 and 10 mg). It is approved for the therapy of SSc-associated PAH in the USA, but has not been evaluated in RCT for the prevention and treatment of DU.

Macitentan

Macitentan is a dual endothelin-receptor antagonist, developed by modifying the structure of bosentan to increase efficacy and safety. Macitentan was FDA-approved for the treatment of WHO functional class II-IV PAH in October 2013 at a dose of 10 mg once daily. Liver enzyme abnormalities occurred in a similar percentage of patients receiving placebo and macitentan in the PAH trial, but higher percentages of patients in

the two macitentan groups had nasopharyngitis, headache, and anemia [75]. There are two ongoing multicenter randomized double-blind placebo controlled parallel group studies aimed to evaluate the effectiveness of macitentan in the prevention of new DU at 16 weeks. Although preliminary data analysis led to the early termination of these trials due to a lack of efficacy over placebo, results of final analyses are pending.

Phosphodiesterase inhibitors

By inhibiting the hydrolysis of cyclic guanosine monophosphate (cGMP), agents in this class increase cGMP levels, with consequent vasodilatory, antiproliferative, and pro-apoptotic effects that may reverse pulmonary artery remodeling. Studies have suggested these agents may have a role in the treatment and prevention of DU, but solid evidence is lacking. Common side effects of these medications include headaches, dizziness, dyspepsia, and nasal congestion.

Sildenafil

One open uncontrolled study of 16 patients with SSc treated with maximally tolerated doses of sildenafil (mean 114 mg daily for mean 5.2 months), and concomitant vasodilators and platelet inhibitors showed a significant decrease in the total number of DU. However, nine patients developed 12 new DU despite sildenafil therapy [76]. One double-blind placebo-controlled study, which did not measure DU outcomes, included 57 patients with limited cutaneous SSc and showed that 100 mg once daily for 3 days followed by 200 mg once daily for 25 days of modified-release sildenafil reduced RP frequency and was well tolerated [77].

Tadalafil

One study concluded that tadalafil as add-on therapy may contribute to DU prevention and healing. 24 patients with SSc or mixed connective tissue disease were treated with 20 mg of tadalafil every other day or placebo for 6 weeks and then crossed over, with concomitant vasodilators (CCBs, ACE-inhibitors, and ARBs) and platelet inhibitors. All 24-fingertip ulcers healed during tadalafil compared to 3 of 13 during placebo treatment. Tadalafil also significantly prevented the appearance of new DU (1 during tadalafil treatment versus 13 during placebo) [78]. However, another randomized, double-blind, placebo-controlled, crossover study of 39 women with RP secondary to SSc receiving 20 mg of tadalafil daily or placebo for a period of 4 weeks showed that tadalafil lacked efficacy as a treatment for RP. There were too few DU in this study population to analyze the role of tadalafil in DU healing or prevention [79].

Prostacyclins

Prostacyclins are potent pulmonary and systemic vasodilators that also inhibit platelet adhesion and aggregation, and smooth muscle cell proliferation in the blood vessels [59, 80]. Common side effects of these medications include hypotension, dizziness, headache, flushing, jaw pain, and gastrointestinal symptoms [81].

Oral Prostanoids

Overall, oral forms of prostanoids have not shown benefit in the treatment of DU. In one meta-analysis [64], none of the following studies showed a statistically significant difference in DU healing individually or in pooled analyses, and side effects were more common in subjects who received oral prostanoids compared to the placebo subjects.

Iloprost

Although no studies have evaluated the effects of oral iloprost on DU, one study showed that oral iloprost at a dose of 50 mcg twice daily did not significantly improve RP compared to placebo [82]. Higher doses of oral iloprost may be more effective for the treatment of RP and potentially DU, but with increased side effects that may limit tolerability [59].

Beraprost

In a study of 107 patients with SSc, the oral prostacyclin analog beraprost sodium at a dose of 60 μg three times daily, showed a trend towards fewer new DU compared to placebo [83]: 48 % of patients had new ulcers in the beraprost group

versus 59 % in the placebo group ($p = 0.325$), but this has not been confirmed in further studies.

Cisaprost

Cisaprost, another oral prostacyclin analog showed a trend for minimal improvement in efficacy when given orally at a dose of 2.5 or 5 μg three times daily for the treatment of RP secondary to SSc. This 4-month randomized, double-blind, placebo-controlled study involving 49 patients found that there were not statistically significant differences in the median change from baseline in the total number and duration of attacks, the number of painful attacks and the average severity of attacks between the three groups. However, cisaprost given at 5 μg three times daily produced a greater decrease in severity of RP at week 2 ($p = 0.02$). There were no significant changes in the number of active DU throughout the study between the three groups, but only five patients had DU at the time of enrollment [84].

Treprostinil

A study of 148 subjects with DU showed that the administration of the oral prostacyclin analog treprostinil as a sustained-release osmotic tablet up to 16 mg twice daily for 20 weeks did not result in a statistically significant reduction in net ulcer burden when compared to placebo [85].

Systemic prostanoids

Prostanoids delivered systemically, either by intravenous or subcutaneous administration, appear to be more effective for the treatment of DU than oral formulations likely related to better absorption. Intravenous prostanoids, in particular iloprost, are approved in the EU and recommended for the treatment of DU in patients with SSc [86].

Intravenous iloprost

Intravenous iloprost (0.5–2 ng/kg per minute for 3–5 consecutive days) significantly improved DU healing, particularly for ischemic digital tip ulcers, in comparison with placebo in two RCT including 35 and 131 SSc patients, respectively [87, 88]. A third small RCT including 17 patients treated over the course of 4 months with monthly 3-h intravenous infusion of 0.5–2.0 ng/kg/min of iloprost or placebo did not find statistically significant differences [89]. In addition, two RCT comparing intravenous iloprost to oral nifedipine for the treatment of RP showed a beneficial effect on DU healing in both groups, but the number of patients with DU was small [62, 90]. The first one included 23 patients with SSc-related RP and the mean number of digital lesions was reduced with iloprost from 3.5 to 0.6 and with nifedipine from 4.3 to 1.4 after 16 weeks. The second study included 46 patients with SSc-related RP, 17 patients had DU at entry into the study. Among these, all the patients treated with nifedipine (3/3) and 12 out of 14 of those treated with iloprost decreased the number of DU after 12 months. In contrast, one meta-analysis showed that intravenous iloprost was beneficial for the prevention of new DU, but did not affect DU healing [64]. Long-term low-dose iloprost (0.5 ng/kg per minute) has been shown to be equally effective and less harmful than high-dose (2 ng/kg per minute) when given for 21 days, with both regimes reducing DU in 70 % of treated patients [91]. There is currently no generally accepted dosage scheme for the administration of iloprost [92]. We recommend the use of 0.5–2 ng/kg per minute for 3–5 consecutive days, then reassessing response for additional infusions.

Intravenous epoprostenol

In one study that did not report effects on healing of existing ulcers, intravenous epoprostenol administered continuously for severe SSc-related pulmonary arterial hypertension tended to reduce the number of new DU when compare to conventional therapy [93]. Although not FDA approved for the treatment and prevention of DU, epoprostenol could potentially be used in a similar fashion to intravenous iloprost for the management of DU and digital ischemia.

Subcutaneous Treprostinil

Treprostinil is a prostacyclin analog that is currently approved for the treatment of PAH in subcutaneous, intravenous, and oral formulations. In one small study, subcutaneous treprostinil was

effective in both the healing and prevention of DU in patients with SSc [94]. However, only 5 of 12 patients were able to tolerate the medication due to severe injection site pain. Intravenous treprostinil has not been evaluated for the treatment of DU.

Anti-platelet Agents: Although a double blind controlled study of aspirin in combination with dipyridamole showed no benefit on RP or DU compared to placebo [95], 81 mg of aspirin daily is often prescribed for patients who do not have a contraindication, keeping in mind that patients with SSc often have gastrointestinal involvement and are at increased risk of side effects [96]. Cilostazol and its metabolites are inhibitors of phosphodiesterase III that increase cyclic adenosine monophosphate (cAMP) levels leading to reversible inhibition of platelet aggregation, vasodilation, and inhibition of vascular smooth muscle cell proliferation [97]. Pentoxifylline reduces blood viscosity and improves peripheral tissue oxygenation presumably through enhanced blood flow increasing leukocyte and erythrocyte deformability and decreasing neutrophil adhesion/activation [98]. A systematic review and network meta-analysis of 26 RCTs evaluated the efficacy and tolerability of cilostazol and pentoxifylline in patients with intermittent claudication due to peripheral arterial disease and found that cilostazol increased maximum and pain-free walking distance with minimal serious adverse events [99]. Although there is biologic rationale to use these agents for the treatment of DU, there is currently no strong evidence supporting their use for this indication. One small study of 11 females with primary RP treated with pentoxifylline 400 mg tid for 2 months showed photoplethysmographic improvement of peripheral blood flow and decrease in duration and frequency of attacks [100].

Statins: Extensive research suggests that the clinical benefits of statins are related to an improvement in vascular function and inhibition of smooth muscle proliferation [101], a reduction in blood thrombogenicity, anti-inflammatory properties, and immunomodulatory actions [102]. One single study involving 84 SSc patients showed that 12 weeks of atorvastatin therapy reduced RP and prevented new DU in comparison to placebo, without statistically significant differences in DU healing [102].

Botulinum toxin: The local administration of botulinum neurotoxin type A is thought to increase blood flow as a result of arteriolar vasodilation through sympathetic blockade [103]. One study of 26 patients found that the use of botulinum toxin type A (BTX-A) injection in patients with recalcitrant ischemia resolved pain in 75 % of patients; improved color in 57 % of patients, and improved transcutaneous oxygen saturation in 56 % of patients. A single treatment with BTX-A resulted in improvement 89 % of the time [104]. A recent review article [105] summarized the findings from four published studies [104, 106–108] of patients treated with botulinum neurotoxin A. All patients had overall improvement in pain as well as decrease in frequency and severity of vasospastic attacks and healing of DU. Current problems are the lack of a standardized injection site and dose, in addition to complications that include pain at the site of injection and transient intrinsic hand muscle weakness [104]. Further and longer-term evaluation is necessary to better define the role of botulinum toxin in DU treatment [96].

Topical Vitamin E: Vitamin E is believed to be the most important naturally occurring non-enzymatic, lipid-soluble antioxidative agent in human tissue, with also antiaggregant and mild vasodilating capabilities. It may both reduce the ischemic damage of reperfusion and stimulate the growth and stabilization of granulation tissue, as well as reepithelialization. In one single study, the application of topical vitamin E reduced time of healing of DU and was associated with a faster resolution of pain, with a significant reduction of costs [109].

More aggressive treatment may be necessary if conservative medical treatment is ineffective in treating digital ischemia. These include sympathectomy, surgery, and amputation.

Sympathectomy: [Also see Chap. 22]

Chemical sympathectomy: While more commonly performed for lower limb complications, upper limb chemical sympathectomy can provide relief and healing. Lidocaine or bupivacaine digital blocks have also been reported as effective in immediately decreasing pain [110, 111]. However, chemical sympathectomy can be complicated by neuritis and surgical sympathectomy may be favored [112, 113].

Surgical sympathectomy: Because of the relationship between blood flow and vessel radius, a small change in the vessel radius can impart a large effect on blood flow. Surgical sympathectomy is a procedure in which at least one sympathetic ganglion is removed. Eliminating sympathetic innervation creates a corresponding dilatation of blood vessels [114]. Sympathectomy may prevent the need for digital amputation if performed early enough [114]. Both cervical and digital sympathectomy can be useful in managing digital ischemia; however, cervical sympathectomy has been found to have limited results [115, 116]. Cervical sympathectomy involves blocking the sympathetic chain/ganglia in the lower cervical and upper thoracic region [117]. Patients with connective tissue disease, such as SSc, may only temporarily respond to sympathetic ablation, while digital sympathectomy to treat RP associated with occupational diseases typically results in longer lasting effects [28, 114]. It has been suggested that the success of cervical sympathectomy in digital ischemia is limited due to the fact that the brachial plexus does not receive its communicating rami exclusively from the cervicothoracic sympathetic trunk [57]. In a study of eight patients with SSc receiving cervical sympathectomy, four (50 %) patients experienced reduction of pain for 1–2 years, one patient had relief of symptoms for 10 years, while three (38 %) patients received no symptomatic relief [57].

Digital sympathectomy including the ulnar artery and the radial artery with its dorsal branch at the wrist level has been found to more successful than cervical sympathectomy in interrupting sympathetic supply to the digital arteries [118]. Distal sympathectomy has been favored over proximal upper limb sympathectomy in treating distal circulatory problems [115]. Distal digital sympathectomy entails stripping the adventitia from the superficial palmar arch, the radial digital artery to the index finger, the common digital artery, and the ulnar and radial digital arteries to the second, third, and fourth web spaces and the ulnar digital artery to the little finger at the level of the web spaces [2, 119].

The efficacy of digital sympathectomy is determined by assessing hand pain relief and DU healing, and more objectively by assessing postoperative pulse volume recordings in comparison to preoperative values [2]. At our center, digital sympathectomy was performed on 26 hands in 17 patients with SSc, resulting in improved pain in 92 % and healed DU in 88 % of patients (unpublished data). However, the results of surgical sympathectomy for the treatment of RP and DU are not always prolonged [118, 120]. Relapse has been attributed to incomplete denervation, regeneration of autonomic nerve fibers, and reorganization and activation of alternative pathways [118]. A study of sympathectomy outcomes in 22 patients with SSc reported fewer ulcers, faster ulcer healing, and decreased pain in 18 (82 %) of patients that persisted for a mean of 46 months [121].

Surgery: [See Also Chap. MMM]

Vascular reconstruction: Patients with persistent pain and multiple DU may be good candidates for vascular reconstruction. This option may be considered if chemical or surgical sympathectomy is unable to control symptoms [122]. Suboptimal fingertip perfusion and digital arterial occlusive disease may be signs for patients to undergo vascular reconstruction [123]. The best candidates for this procedure are those who show satisfactory distal runoff by visualization of the common digital arteries on angiography and if there is satisfactory backflow from the common digital arteries [2]. The reconstruction procedure creates a new palmar arch in which an interposition vein graft is anastomosed end to end to the distal radial or ulnar artery, and the common digital arteries are anastomosed end to side to the graft [2]. Vascular reconstruction has been able to significantly improve digital temperatures and microvascular perfusion, in addition to upper extremity function [124, 125].

Amputation: In cases where digital infection and necrosis is recurrent, conservative amputations can be useful in preserving fingertip length [28]. Moreover, fingertip amputation can sometimes be the only definitive solution for relieving the excruciating pain experienced by patients [57]. Wet gangrene or osteomyelitis of a phalanx can serve as indications for amputation. In the case of dry gangrene, auto-amputation is preferred in order to preserve the maximal amount of tissue [40, 126].

Supporting Therapy

Antibiotics for infections: An antibiotic should be prescribed if there is any suspicion of superinfection of DU, as indicated by spreading erythema around the lesion or evidence of purulent drainage [96]. We recommend oral antibiotics with good coverage for streptococci and methicillin sensitive staphylococci, such as cephalexin, dicloxacillin, or clindamycin. If there is purulent drainage, we recommend empirically covering for methicillin resistant staphylococcus with trimethoprim–sulfamethoxazole or clindamycin, after obtaining cultures. Antibiotics can then be changed based on the sensitivity results. Persistent infections can spread to underlying bone and cause osteomyelitis, requiring prolonged courses of intravenous antibiotics [1]. In such cases, we recommend consultation with Infectious Disease specialists for comanagement in determining the best antibiotic coverage and length of therapy.

Pain medications: DU are exquisitely painful. Acetaminophen and nonsteroidal anti-inflammatory agents can help, however narcotics may be necessary for adequate pain control. Tramadol is an effective oral analgesic that is not a controlled substance and can be used at doses of up to 100 mg every 6 h. Topical lidocaine can relieve pain, but its local effect on cutaneous blood flow is complex with evidence for both vasoconstriction and vasodilation [127]. In our opinion its overall benefit outweighs the risk. Referral to a Pain Clinic for management of narcotic medications is often helpful.

Critical Digital Ischemia

Definition

Critical digital ischemia is the sustained reduction in digital perfusion with resultant impaired tissue viability [128]. It is a digit-threatening event [55], may cause severe pain and well-demarcated persistent cyanosis or pallor with surrounding hyperemia [129]. Although it occurs much less frequently than DU [96], it is always a medical emergency since it may progress to digital loss [7]. One single-center, retrospective, longitudinal study of 103 patients with SSc (of whom 46 had history of DU) found that 68 % of patients had critical finger ischemia at least once over a 12-year period of follow-up [130]. However, in a cohort of 1,168 patients with SSc followed for an 18-month period, only 19 patients (1.6 %) developed critical ischemia [128].

Diagnosis

Clinical evaluation: It is crucial to assess for persistent cyanosis or pallor, increased pain, loss of epithelium, or gangrene, to examine peripheral pulses, and in patients with SSc, to look for capillary dilatation, hemorrhage, and dropout since progression of these nailfold capillaroscopic changes predicts the development of digital ischemia [131]. If pulses are weak or nonpalpable, an arterial Doppler should be performed. All patients should undergo laboratory analysis for the presence of antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta2-glycoprotein I antibodies) and consider evaluation for other prothrombotic states.

Imaging: [*See Chaps. 13 and 14*] Imaging is especially indicated to identify lesions amenable to angioplasty or surgery. Conventional angiography is still considered the gold standard to visualize compromised arteries [51] but is invasive, and involves high radiation and contrast load. Advances in magnetic resonance angiography (MRA) and computed tomography (CT)

angiography may replace the need of invasive diagnostic tools [132], but these are still investigational techniques [133, 134].

Treatment: Digital critical ischemia requires an aggressive approach to control symptoms and prevent digital loss.

Hospitalization: As this is considered a medical emergency, hospitalization and bed rest is useful to expedite interventions, provide warm environmental temperature and appropriate pain control, and decrease trauma and activity of the involved limb [51].

Analgesics: As pain due to critical digital ischemia is extremely intense, appropriate pain control is essential. Opioids are often needed. Local anesthetic blocks with lidocaine or bupivacaine without epinephrine and temporary chemical sympathetic block in patients that will undergo sympathectomy may also be helpful [55].

Optimizing Vasodilator Treatment

Short-acting CCBs: Oral calcium channel blockers should be titrated to the maximum tolerated dose [51], and maintained once the acute episode has passed [96].

Intravenous prostanoids: Intravenous iloprost or epoprostenol at doses of 0.5–2 ng/kg/min, administered daily during 6 h through a peripheral line for 1–3 days should be considered [55]. Intravenous iloprost has been shown to reduce both the frequency and severity of ischemic attacks and to improve DU healing; epoprostenol has been shown to prevent the development of new DU [87, 88, 93]. Further studies are necessary to define the optimal dose and length of treatment with intravenous prostanoids for critical digital ischemia.

Treating Procoagulant Tendency

In some patients with SSc arterial thromboses have been found in digital arteries from amputation specimens [135]. Although there are no studies supporting this approach, low-dose aspirin and short-term anticoagulation with unfractionated or low molecular weight heparin are recommended for patients with rapidly advancing ischemic tissue who do not have contraindications. Of note, gastric antral vascular ectasia (GAVE) can affect up to one fourth of SSc patients and therefore anticoagulation might not be appropriate for all patients [136]. Chronic anticoagulation is not recommended unless a hypercoagulable state is defined. However, the exact duration of anticoagulation for digital ischemia also has not been studied. One study has demonstrated the benefit of low-molecular-weight heparin for symptomatic improvement in primary and secondary RP [137]. Thrombolytic therapy (e.g., with tissue plasminogen activator) may be helpful in selected patients with a new thrombotic or embolic event [138–140] In one randomized, placebo-controlled study urokinase improved capillaroscopic findings and promoted DU healing in patients with SSc [141]. New antithrombin agents such as direct thrombin inhibitors (argatroban, inogatran, efegatran, hirudin, and bivalirudin) have not been studied and controlled clinical trials would be necessary to determine if there is a role for these agents in the treatment of critical digital ischemia.

Sympathectomy: Similar to chronic digital ischemia, sympathectomy is a reasonable option for patients suffering from acute critical digital ischemia.

Hand Vascular Surgery

Debridement of necrotic tissue: An embolectomy may be performed to remove lodged emboli that are blocking blood flow [2, 142, 143]. Microvascular hand surgery should be done as soon as possible after the onset of symptoms to optimize results [142, 143].

Amputation: Because of the accelerated progression of critical digital ischemia, the digits may be unable to be saved and amputation may be required [143].

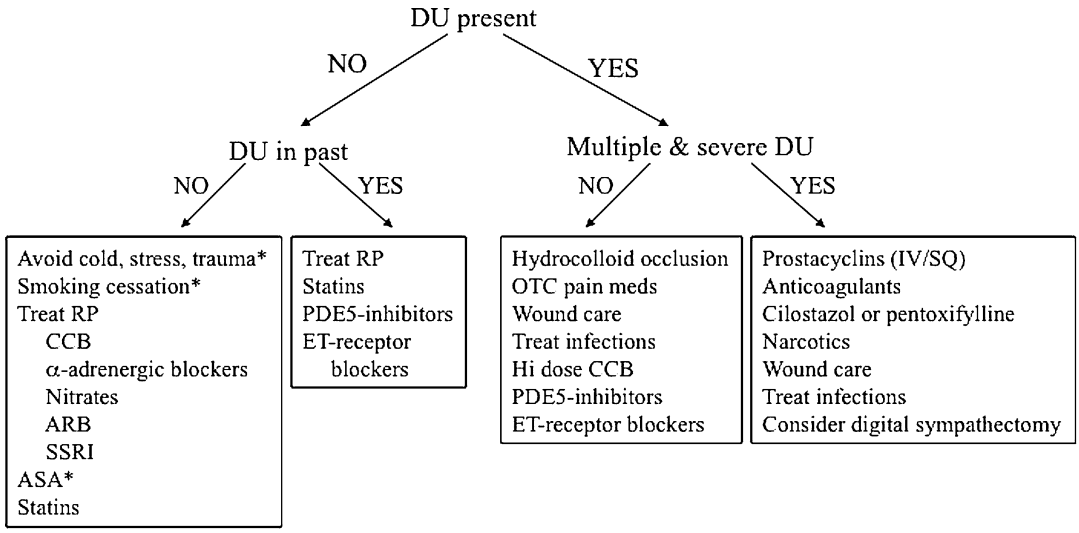

Fig. 21.8 Algorithm for the treatment and prevention of digital ulcers in systemic sclerosis. (Modified with permission forms from: Chung L. Therapeutic options for digital ulcers in patients with systemic sclerosis. JDDG. 2007 Jun; 5(6):460–5). * All patients should be educated to avoid cold, stress, trauma, and nicotine. Aspirin 81 mg daily should be considered for all patients who do not have a contraindication. ACE-inhibitors and ARBs should be used as adjunctive therapy. DU = digital ulcers; RP = Raynaud's phenomenon; CCB = calcium channel blockers; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; SSRI = selective serotonin reuptake inhibitor; ASA = aspirin; PDE5 = phosphodiesterase-5; ET = endothelin; OTC = over the counter; IV = intravenous; SQ = subcutaneous

Author Recommendations (Fig. 21.8)

DU are associated with substantial pain, disability, and complications. We recommend preventative measures such as smoking cessation, avoidance of cold, stress, and trauma in all patients.

If a patient does not have existing ulcers, we consider aspirin 81 mg daily (for all patients who do not have a contraindication) and aggressive treatment of RP primarily with CCB (nifedipine 10–30 mg tid-qid, amlodipine 2.5–10 mg qd). Adjunctive therapy for RP might include ARB (losartan 50 mg bid), or SSRI (usually Lexapro 10–20 mg daily). In patients with history of DU in addition we recommend considering the adjunctive use of statins, PDE5-inhibitors, or ET-receptor blockers for the prevention of DU.

In patients with 1–2 active ulcers, we use hydrocolloid occlusion if the locations are amenable to such treatment; pain medications; wound care; and medical therapy typically with PDE5-inhibitors and ET-receptor blockers. In case of infection we add antibiotics as described above. For patients with refractory, progressive ulcers or multiple severe DU, our approach may include the use of prostacyclins, anticoagulants, cilostazol or pentoxifylline, and narcotics. We refer a significant proportion of patients with problematic DU for digital sympathectomy or revascularization.

In patients with acute critical ischemia we recommend hospitalization, anticoagulation and high dose vasodilator therapy with intravenous prostacyclins. We typically initiate therapy at 0.5–2 ng/kg per minute for 3–5 consecutive days then consider additional days of infusion or higher dosing if necessary. We also refer for consideration of surgical sympathectomy or vascular reconstruction while the patients are in the hospital. Surgical debridement or amputation may be necessary in some cases.

Conclusion

Digital ischemia is associated with substantial pain, disability, and complications. Clinicians should have a proactive approach to management including non-pharmacologic therapies,

pharmacologic therapies and collaboration with surgeons, as debridement and sympathectomy may help to preserve a digit. Presumably, optimization of RP therapy should be helpful in the prevention and healing of DU by improving blood flow to the digits, although many of these medications have not been specifically evaluated for the treatment of DU. Oral forms of prostanoids have not shown benefit in the treatment of DU while prostanoids delivered systemically appear to be more effective. Other key recent advances include the promising use of endothelin-1 receptor antagonists. Early intervention will likely lead to better outcomes in patients suffering from digital ischemia. In severe cases, hand surgery is an appropriate and effective intervention that can provide rapid pain relief and improve vascular perfusion.

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Surgical Management

22

Lindsay Muir

Abbreviations

CHFS	Cochin hand function scale
HAMIS	Hand mobility in scleroderma
RP	Raynaud's phenomenon
SFI	Scleroderma functional index
SHAQ	Scleroderma health assessment questionnaire
SSc	Systemic sclerosis

Key Points

1. Surgery may be of benefit in the management of RP when medical management has failed.
2. Close cooperation between the patient's physician (who will often be a rheumatologist) and surgeon will ensure timely and prompt referral for surgery.
3. Urgent surgery may be required for acute ischemic pain or for painful digital ulcers which are secondarily infected.
4. The aims of surgery are to restore blood flow, relieve pain, protect against further dysfunction, reduce infection, and (in some patients) remove calcinotic deposits.
5. Available procedures include digital ulcer débridement, sympathectomy, balloon angioplasty, arterial reconstruction, and amputation.
6. Botulinum toxin injections may benefit patients with severe ischemia and/or digital ulcers, but longer term studies are required to better establish their role.

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Introduction

The mainstay of the management of Raynaud's phenomenon (RP) is medical. Surgery may be of some benefit however if medical management has failed.

This chapter examines the surgical treatment options available in RP. An overview of surgical techniques is offered, but for a more detailed explanation the reader is referred to the various texts cited in the references.

It is critical to understand that the management of patients with Raynaud's phenomenon must be pursued in close cooperation with the patient's physician, usually their primary care physician or rheumatologist. These physicians may wish urgent surgical consultation when a patient has acute ischemic pain or a secondary wound infection. It does not help to put such patients on to a long waiting list; we have an open surgical clinic policy that has never been abused, and the rheumatologist and others are free to contact the surgical specialist quickly or to book patients onto the next week's clinic for review. Close cooperation and understanding are thus essential.

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Primary Raynaud's Phenomenon

The management of primary Raynaud's phenomenon is primarily medical.

Coveliers et al. (2011) reviewed the literature on the effect of thoracic sympathectomy in primary Raynaud's [1]. They reported on average an initial positive postoperative effect in 92 %, with 58 % benefiting in the longer term. The complication rates varied widely, and the authors believe that some of the trials discussed underreported their rates of adverse effects. Compensatory sweating was reported in up to 86 %, with one series reporting that almost all patients had developed Horner's syndrome. The consensus in the hand surgery literature is that surgery does not have a role to offer although Higgins does advocate peripheral sympathectomy for the condition [2, 3].

Injection of botulinum toxin may be considered for primary RP. This topic is covered in more detail in the subsequent sections.

Secondary Raynaud's Phenomenon

In the patient with secondary Raynaud's, surgery may be indicated when medical treatment fails, or in conjunction with medical treatment. As the majority of patients with secondary Raynaud's whom we see suffer from systemic sclerosis (SSc) a significant part of the discussion will be devoted to this aspect, although the principles are generic.

Anatomy

The blood supply of the skin is complex. Subcutaneous arterioles arise from myocutaneous or fasciocutaneous perforators. They give off branches to form a deep dermal arterial plexus. This level gives branches to the hair follicles and sweat glands. It also supplies a subpapillary arterial plexus from which arise ascending arterial and descending venous vessels extending into each papilla [4, 5]. The capillary beds have both nutritional and thermoregulatory roles, and in normal circumstances 80–95 % of flow is through the thermoregulatory beds [6]. The glomus bodies assist in the control of blood flow. Glomus bodies are small arteriovenous anastomoses with a coiled arteriole and abundant nerve supply that control blood flow and temperature, particularly in the fingers and toes [7].

The blood supply of the hand is derived from the radial and from the ulnar arteries. The radial artery ends in the deep palmar arch, and the ulnar in the superficial palmar arch. As always, the anatomy is inconsistent. The "typical" arrangement of the arches communicating in the palm occurs in only 35 % of the population with 16 % having no communication [4, 6].

In systemic sclerosis the blood vessels are damaged and occlusion may occur at any level [8]. Janevski [9] looked specifically at the arteries of patients with biopsy-proven systemic sclerosis. In 24 arteriograms, the greatest number of occlusions was found in the proper digital arteries of the index to little fingers. The thumb vessels were often spared. The ulnar artery and superficial palmar arch were totally occluded in 10/24 arteriograms. In this series the radial artery and deep palmar arch were never affected.

Kim et al. analyzed the angiographic features in 351 hands in 178 patients with RP (nearly half of whom had an associated systemic disease) [8]. They described a six-part anatomical classification (Table 22.1). It is based on a division of the arteries of the hand into level 1 arteries (radial and ulnar), level 2 arteries (palmar arch and common digital), and level 3 (digital) arteries.

Kim and his group use the classification to influence their choice of surgical treatment.

It is notable that the ulnar artery is disproportionately affected in patients with secondary RP; 53.5 % of the patients reported by Kim et al. had disease primarily at the level of the radial or ulnar arteries, and in these, 88.5 % of occlusions and 95.7 % of stenoses affected primarily the ulnar artery. 27.1 % of patients had disease primarily in the palmar arch and common digital vessels. These findings are consistent with those of Janevski [9], who (as discussed above) found occlusion of the ulnar artery and superficial palmar arch on 10 of 24 arteriograms performed in 12 patients with systemic sclerosis and of Park et al. [10] who found

Table 22.1 Anatomical classification

Type I	Complete occlusion of radial or ulnar artery; decreased flow and narrowing in level 2 and 3 arteries
Type II	As I, but with stenosis of radial or ulnar artery
Type IIIa	The main disorder is in the common digital or digital arteries
Type IIIb	A rare subset characterized by selective occlusion of the digital arteries to the index finger, secondary to vibrating machinery use
Type IV	All levels of vessel are stenotic
Type V	Global ischemia, paucity of vessels, scant flow on angiography

occlusion or stenosis of the ulnar artery in 63 % of 19 patients studied with arteriography. Higgins and McClinton describe that by the time patients with collagen vascular disease have ulcers or digit-threatening ischemia, two-thirds have ulnar artery thrombosis at the wrist [3].

Evaluation and Anesthesia

In most instances the patient will be referred to the surgeon by a rheumatologist. The probability is that an extensive work-up will already have been undertaken. If not a careful history and examination will naturally be required. Often the presenting complaint will be of pain and or ulceration. Laboratory investigations will include full blood count and biochemistry. If unilateral disease is present a single source of ischemia, such as hypothenar hammer syndrome, thoracic outlet syndrome, or thromboembolic disease, should be suspected. The vascular supply of the hand may most accurately be assessed by arteriography [6]. Other, less invasive, methods include Doppler evaluation (to assess the presence of pulsatile blood flow in the radial and ulnar arteries), laser Doppler fluxmetry, laser Doppler perfusion imaging, digital:brachial index measurement (the ratio of the pressure in the finger compared to the pressure in the brachial artery), digital plethysmography, measurement of cutaneous surface temperature, isolated cold stress testing, nailfold capillaroscopy, color duplex imaging, and magnetic resonance angiography (see Chap. 14). In practical terms in the hand surgical clinic Doppler ultrasound is convenient and readily performed with a handheld machine. We use angiography if we are contemplating reconstruction, but otherwise start with simple surgical measures and do not routinely arrange angiography for every patient.

Various hand function assessment tools are available to assist in evaluating the results of treatment. These include the Hand Mobility in Scleroderma (HAMIS) test [11], the Scleroderma Health Assessment Questionnaire (SHAQ) [12], the Scleroderma Functional Index (SFI) [13], and the Cochin Hand Function Scale (CHFS) [14]. None of the standard hand assessment tools such as DASH have been validated in Raynaud's.

Plain radiology may demonstrate acrolysis. It may be very difficult to differentiate between this and osteomyelitis. MRI scanning may be more sensitive in assessing whether there is infection in the terminal phalanx or in other parts of the hand or foot.

Patients with systemic sclerosis or other causes of RP may have significant cardiorespiratory dysfunction and may thus present an increased anesthetic risk. If major surgery is to be undertaken preoperative anesthetic consultation is advisable. Surgery may however readily be performed under regional anesthesia. We have not experienced any problems with performing surgery under metacarpal block anesthesia and in a willing patient this form of anesthesia is ideal for surgery on a single digit. Whilst the use of epinephrine in metacarpal block anesthesia is generally accepted in healthy patients, we do not use it in patients with systemic sclerosis or other forms of RP because of the risk of provoking vasospasm and tissue ischemia.

Ulcer Débridement

Digital ulcers (Figs. 22.1 and 22.2) in patients with RP are often very painful. The simple expedient of debriding the ulcer may be surprisingly effective at relieving pain, especially if, as often happens, there is a bead of pus under an overlying scab.

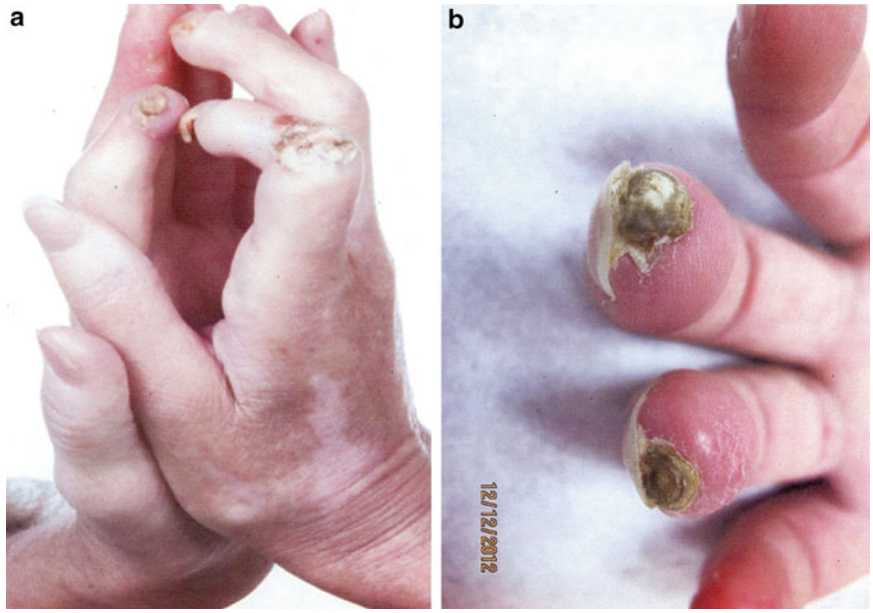

Fig. 22.1 (**a**) and (**b**) Multiple skin ulcers

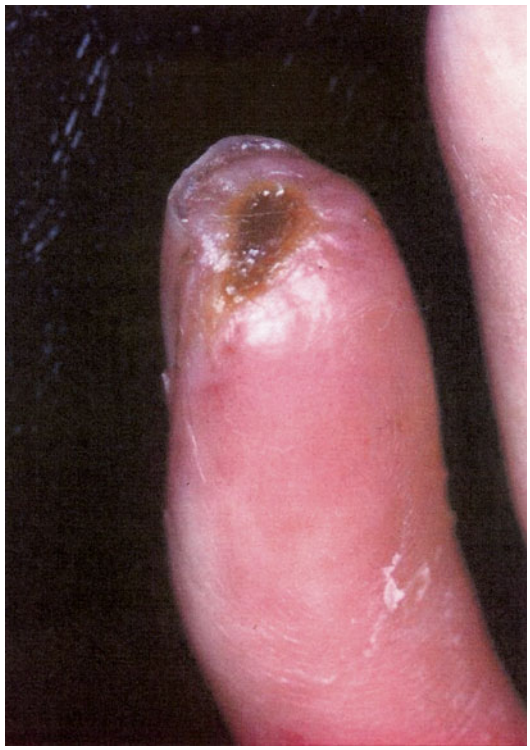

Fig. 22.2 Painful fingertip ulcer; note the surrounding mild erythema

Technique

Surgery may be performed with the use of local, regional, or general anesthesia. No tourniquet is required. The ulcer is debrided, and the base gently curetted with a No. 15 blade. The surgeon should not expect to see normal bleeding; the finger tip will almost inevitably be relatively avascular. The normal surgical dictum of resecting until healthy tissue is encountered should be resisted, as this will often not be found until a large part of the finger has been amputated. Whilst this may be good for one finger, the patient may be back with other ulcers and poorly thought through amputations may result in the loss of multiple fingers. The patient should be warned that the ulcer will take some time to heal. Mepitel™ (Mölnlycke Health Care) is an excellent choice of dressing as it causes less pain on removal than do some others. Dry scabs may be left exposed if there is no sign of infection.

Sympathectomy

Cervical Sympathectomy

Cervical sympathectomy results in improvement in perfusion in the short term. However, return of sympathetic tone may occur within 6–12 weeks and indeed may be increased. Claes et al. [15] noted return of symptoms after 6 months in all nine operated patients with Raynaud's phenomenon in his study. Thus, cervical sympathectomy is no longer considered appropriate treatment for the condition.

Periarterial (Digital, Radial, and Ulnar) Sympathectomy

The sympathetic supply to the hand arises not only from the sympathetic chain but also from alternative pathways. Digital sympathectomy was first described by Flatt, who postulated that interrupting the sympathetic nervous supply more distally would be more likely to address all constituents of the supply and thus produce more long-lasting effects than simple division of the cervicothoracic sympathetic trunk [16]. Morgan and Wilgis [17] demonstrated in a rabbit ear model that sympathetic fibers in the adventitia have limited capacity for regeneration even after 1 year.

Balogh et al. [18] emphasized the importance of identifying the nerve of Henlé if possible. The nerve of Henlé sends a consistent branch carrying sympathetic fibers to the ulnar artery [19].

Flatt's original series of periarterial sympathectomy was of eight patients. The underlying pathology was varied, and Flatt himself describes the difficulty in assessing objectively the results of treatment. Hartzell et al. [20] studied 28 patients with an average follow-up of 96 months (minimum 23 months). Their patients had a mixture of autoimmune and arteriosclerotic disease. Their technique was tailored to each patient's pattern of disease and involved surgery at any of the levels described previously. Eleven of the 20 patients with autoimmune disease saw complete healing of ulcers, with 15 experiencing some improvement. However, seven eventually underwent amputation (these are included in the unhealed ulcer group).

Kim et al. [8] undertook a combination of digital sympathectomy of the common digital vessels alone and radical sympathectomy including the proper digital vessels for their patients with type IV and V disease. 66.7 % of patients with type IV and 53.3 % of patients with type V disease saw an improvement in symptoms but 22.9 and 33.3 % had no change and 10.4 and 13.3 % experienced a deterioration.

Koman et al. [5] studied the microvascular physiology in seven hands with refractory pain and ulceration undergoing digital sympathectomy. Following surgery all seven hands had diminished pain. The ulcers healed in six hands and improved in the remaining one. The results were assessed further by isolated cold stress testing, digital pulp temperature evaluation, and laser Doppler flowmetry. After sympathectomy, fingertip temperature did not increase (contrary to some other writers' experiences), suggesting that total blood flow was unaffected. The investigators did, however, note that microvascular perfusion and vasomotion increased. Vasomotion describes the natural rhythmic oscillations in vascular tone caused by local changes in smooth muscle constriction and dilatation. The significance of vasomotion is not certain, but one hypothesis suggests that it may increase tissue oxygenation when blood flow is compromised [21]. On this basis, they hypothesized that the mechanism for the clinical effectiveness of sympathectomy is a preferential increase in flow in nutritional rather than thermoregulatory vessels.

Kotsis and Chung [22] performed a systematic review of the literature on peripheral sympathectomy. 16 papers met their inclusion criteria. Most, but not all, of the patients studied had SSc. Ulcer healing time took from 2 weeks to 7 months. 15 % eventually required amputation despite the sympathectomy, 16 % had recurrence/incomplete healing, and 37 % had a postoperative complication. The authors therefore counsel that long-term prospective studies are still required in this field, and that patients should be warned of the uncertain success rate.

Technique

Peripheral sympathectomy may be performed at the level of the ulnar and radial arteries, the common digital arteries, and the proper digital arteries. The surgery is performed with the use of general or regional anesthesia and an exsanguinating tourniquet. The use of loupe magnification or of an operating microscope is advisable. For digital sympathectomy the common digital artery is approached through a Bruner incision. A 2-cm stretch of the artery is stripped of adventitia. We do not normally drain the wound; the transverse limb may safely be left open. For radial and ulnar artery sympathectomy, the arteries are approached via a straight 3-cm incision. The adventitia is stripped over a 2-cm stretch of artery.

O'Brien et al. [23] describe an extensive sympathectomy of the ulnar artery, superficial palmar arch, and proper digital arteries.

A radical exposure is also described by Koman et al. [38], in which the superficial palmar arch and the three volar common digital vessels are exposed. In addition Koman et al. strip a section of the deep branch of the radial artery and the origin of the deep palmar arch through a fourth incision in the anatomic snuffbox.

Figure 22.3a shows a painful ischemic ring finger in a 53-year-old patient with systemic sclerosis. Sympathectomy was planned (Fig. 22.3b–d).

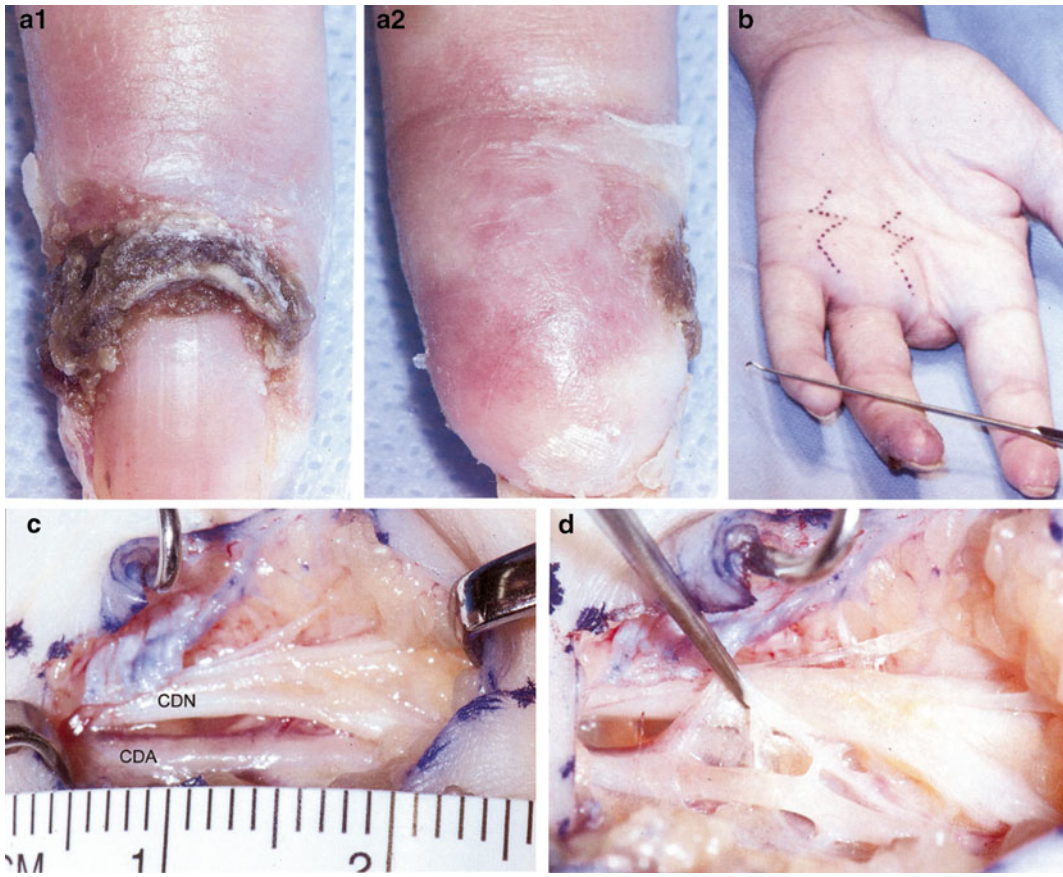

Fig. 22.3 (**a**—Part 1 and 2) Ischemic fingertip; (**b**) incisions for sympathectomy. We plan these to overlie the common digital artery; (**c**) intraoperative photograph. The wrist is on the *left*, the fingers on the *right*. The common digital artery has been exposed. With skin retraction we shall be able to strip the whole 2 cm of artery. The artery (CDA) with the venae comitantes is at the *bottom* of the picture, the bifurcating common digital nerve (CDN) at the *top*. Remember that at this level the nerve is volar to the artery. Also it is worth noting that the bifurcation of the artery is well distal to the bifurcation of the nerve; (**d**) the adventitia is being stripped off the artery

Balloon Angioplasty

Kim et al. [8] performed balloon angioplasty in patients with type II disease in whom either the ulnar or radial artery was stenotic. They used a balloon catheter with a 2.0-mm diameter and 14-mm length. This was inserted into the ulnar artery and advanced as far as the common digital arteries. If balloon angioplasty was not successful, they proceeded to excision of the stenosed segment and interposition vein or arterial graft. They reported overall improvement in 79 % of this group with 16 % no better and 4 % worse. One notable complication was an ulnar artery rupture.

Arterial Reconstruction

Tomaino [24] described arterial reconstruction of the long finger radial digital artery. Kim et al. [8] described tailored surgical intervention. In the case of a thrombosed radial or ulnar artery, the involved segment was excised and replaced with an interposition vein or arterial graft, with their preferred donor artery being the deep inferior epigastric artery. If the arteries were only stenotic, a balloon angioplasty was preferred. In the case of an involved superficial palmar arch and spared common digital vessels, Kim et al. [8] advocate reconstruction of the arch with a deep inferior epigastric artery graft anastomosed to the common digital arteries. They base this procedure on the observation that the deep inferior epigastric artery has numerous branches and can thus be used to construct a new palmar arch, connecting the branches end to end to the common digital arteries. This approach is supported by the work of Higgins and McClinton [3]. These investigators believe that such patients can experience substantial and long-term improvement in the vascular status of their hands with arterial bypass procedures. They discuss alternative donor arteries, including the thoracodorsal artery and the descending branch of the lateral circumflex femoral artery. Trocchia and Hammett [25] also argue that arterial grafts should be studied in more detail in the hand, given the experience of higher patency rates in coronary artery surgery. Kryger et al. [26] describe a reversed lesser saphenous vein graft anastomosed end to side to the radial artery and tunneled to the common digital artery. In a series of six patients they found that no patient had any further ischemia leading to tissue loss after a follow-up of 4–40 months.

Technique

The surgery is performed with the patient under general or regional anesthesia. Careful preoperative planning with angiography is recommended. Standard techniques of venous or arterial grafting are recommended, with careful attention to resection of all diseased arteries until normal vessel is found and meticulous microsurgical technique. The exact pattern of the reconstruction depends on the extent of the disease. The graft may be a local interposition graft of a short segment of ulnar artery or may involve reconstruction of the whole of the palmar arch from the radial artery as described by Kim et al. [8].

The role of postoperative anticoagulation is not yet clearly established. Various regimens have been used in microsurgery [27]. Aspirin and low-molecular-weight heparin are the commonest agents, but the ideal duration of treatment has not been established, and the use of these agents does run the risk of bleeding. Tomaino [24] recommends oral aspirin for 6 weeks postoperatively. Hansen et al. [28] suggest Dextran 40 or aspirin, but the efficacy of Dextran has been questioned [27].

Revascularization of the Hand by Retrograde Venous Flow

Kind [29] reported a short series of revascularization of chronically ischemic hands by means of anastomosis of a vein to an artery, thereby arterializing the venous system. The surgical technique is described in detail by Matarrese and Hammert [30]. The cephalic vein is identified and the side branches ligated. Matarrese and Hammert

describe anastomosing the vein to the brachial artery, but it may more simply be anastomosed to the radial artery if this latter is patent. The valves of the cephalic vein need to be divided with a valvulotome. The vein is then transected and joined end to side to the parent artery. The authors emphasize that this is a last chance solution and that the long-term results are not clear.

Excision of Calcific Deposits

Calcific deposits are often painful and distressing for the patient (Fig. 22.4a, b) They are well visualized on plain radiography. In extreme cases the whole finger becomes stiff. The skin may ulcerate over a large deposit. Occasionally the deposits may liquefy and extrude in paste form with some relief of symptoms.

It is important to realize that the deposits are similar to gouty tophi; they replace and infiltrate the normal tissues, and, despite the tempting radiologic appearance, they may not be expressed after blunt dissection such as one would for a lipoma. The corollary of this warning is that the digital neurovascular bundle may run through such a calcific mass and is vulnerable to injury. Further, the risk of recurrence of such deposits is significant. Caution should thus be exercised in offering to remove them. In particular, excision of large deposits in the pulp will remove the normal padding and may leave a rather atrophic and unprotected fingertip (Fig. 22.4c). Our indications for excision of calcium are largely patient driven. Most commonly patients seek help because of the stiffness or ulceration or the inconvenience of a large solid mass in the pulp of the thumb or index making gripping difficult. In this circumstance we recommend careful discussion with the patient to understand his or her hopes for surgery and gentle debulking of the pulp rather than aggressive excision of all palpable calcium.

Technique

Surgery may be performed with use of local, regional, or general anesthesia. Incisions are planned on the basis of standard hand surgical techniques. After exposure of the calcific mass, blunt dissection with a curette or the end of a MacDonald dissector is helpful in scraping away the disease. Some authorities advocate the use of a power burr [31]. This latter technique may also be used percutaneously, debriding the calcium deposit via a short incision. We recommend a rather cautious approach.

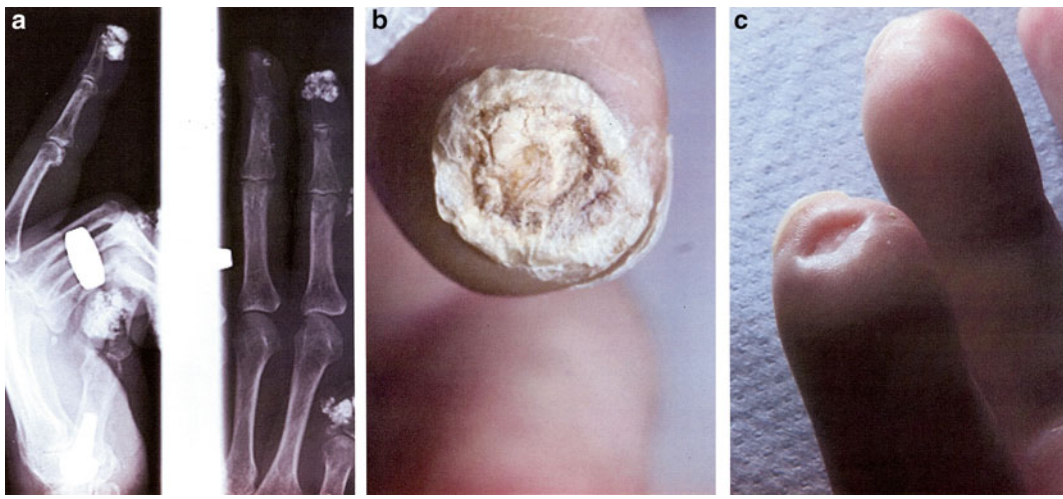

Fig. 22.4 (**a**) Calcific deposits in the index fingertip; (**b**) calcific deposits in ring finger tip; (**c**) after excision the patient is left with a pulp defect

Amputation

In cases refractory to treatment, amputation may be inevitable (Figs. 22.5 and 22.6). This may be considered as a more radical form of débridement. Before simply considering amputation as an end in itself consideration should be given to how best to protect the rest of the hand, with reference to the above procedures.

Sometimes the fingertip mummifies and autoamputates with relatively little pain. In a patient with a pain free, noninfected mummified tip it is reasonable to allow this, although often they need some surgical help when the necrotic portion is almost detached. The patient may be distressed by the appearance, and surgery may then be considered, although allowing the finger to epithelialize under the biological dressing that is the necrotic end will leave a reasonable scar.

In the case of an ischemic, necrotic, and painful fingertip that has not improved with the preceding treatments, amputation is likely to help the pain. Amputation may be performed at any level. We tend toward conservative resection, as some patients lose multiple fingertips. General hand surgical procedures should be used, but as the fingers are often abnormal in their movement, and as cosmesis may not be a major priority, we do not stick slavishly to generally recommended levels of amputation. We amputate at the level that is going to leave maximum length.

Botulinum Toxin Injections (Chap. 20)

Botulinum A toxin is produced by the bacterium *Clostridium botulinum*. It blocks neurotransmitter response across the neuromuscular endplate by inhibiting the release of acetylcholine vesicles at the motor endplate terminals [32]. The exact mechanism of action is however as yet unclear and is probably multifactorial. Two mechanisms are postulated: one is modulation of abnormal adrenergic innervation, leading to a decrease in blood shunting and increased nutritional flow. Effectively this produces a sympathetic blockade [33]. The second is reduction of pain through antinociceptive pathways; the toxin can theoretically reduce

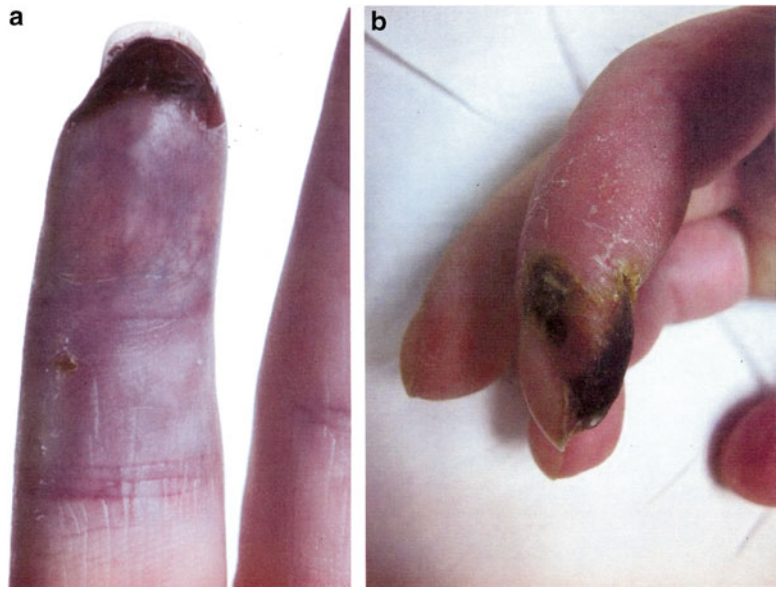

Fig. 22.5 (**a** and **b**) Necrotic fingertip. In this case further treatment is advisable, as there is ischemia proximal to the necrotic tip

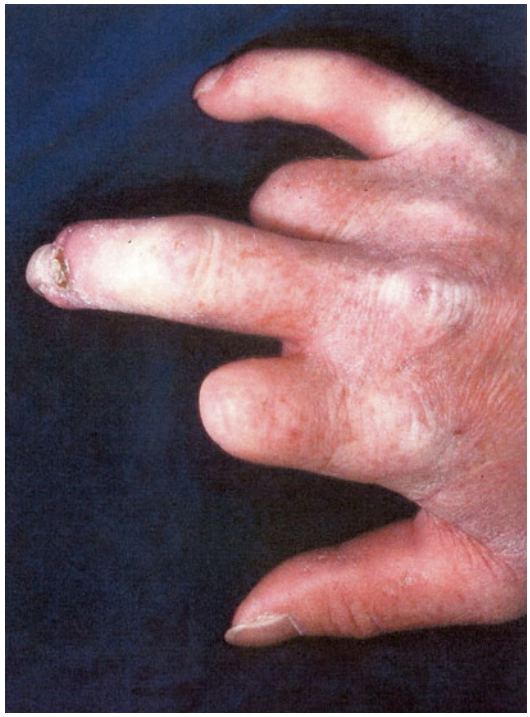

Fig. 22.6 Hand of scleroderma patient following digital amputation

glutamate, substance P, and calcitonin gene-related peptide levels [34]. Injection of botulinum toxin has been reported to be of help in systemic sclerosis and in severe primary RP. The toxin is injected adjacent to the neurovascular bundles at the level of bifurcation of the common digital arteries [35], at the level of the superficial palmar arch, or on either side of the base of the finger [36]. Dhaliwal et al. [37] injected 100 international units of botulinum toxin in patients with RP associated with systemic sclerosis: At 6 months, 80 % of patients reported overall improvement in their symptoms as assessed by DASH (Disabilities of the Arm, Shoulder, and Hand) score, cold intolerance, power, and pinch grip.

Neumeister [35] studied 35 patients whom he had injected with botulinum toxin (A). The patient group was mixed and the primary Raynaud patient results are not presented separately. He used 10 i.u per neurovascular bundle. The patient age range was 18–72 years. 28 patients had a reduction in pain at rest. The five nonresponders had secondary Raynaud's. Iorio et al. [32] found five studies detailing the use of botulinum toxin. They concluded that the initial results were promising but that the studies had significant limitations and recommend a larger more careful study. Further and longer term evaluation is required to better establish the role of botulinum toxin in the patient with severe RP.

Author's Preferred Treatment

Primary RP

- Nonoperative treatment, including general patient advice and education.
- Consider botulinum toxin injections.

Secondary RP

Assessment

- Clinical—pain, infection, treatment to date.
- Examination—ulcer, ischemia; necrosis.
- Tests—X-ray ± MR; handheld Doppler; angiography if doubt and arterial reconstruction considered, but not if plan is for simple sympathectomy.

Ulcers and osteomyelitis

- Debride and inject botulinum toxin.
- If no better in 6 weeks—sympathectomy.

Ischemia (finger blue but not critical)

- Sympathectomy.
- If no better—arterial assessment and consider reconstruction as last resort arterialization of venous system.

Dead fingertip

- Resect as little as possible, preserving length; if pain-free dry gangrene and patient not concerned by cosmesis, reasonable to allow this to auto-amputate; sometimes they need a bit of help when the finger is almost off.

Calcinosis causing pain or loss of movement

- Conservative debridement of calcium by blunt dissection.

Summary

- The mainstay of treatment in Raynaud's phenomenon is medical.
- Surgery may help if medical treatment fails.
- Close cooperation between rheumatologist and surgeon will ensure that the patient is offered prompt referral and treatment where surgery may help.

The aims of surgery are to:

- Restore pulsatile blood flow to nutritional beds
- Relieve pain
- Protect against further dysfunction
- Reduce infection
- Remove calcification.

The available procedures include:

- Ulcer débridement
- Sympathectomy
- Balloon angioplasty
- Arterial reconstruction
- Revascularization by reverse venous arterialization
- Excision of calcinotic deposits (for patients in whom subcutaneous calcium deposits are a contributor to digital ulceration or a source of pain or inconvenience)
- Amputation
- Botulinum toxin injection
- In patients with RP in conjunction with SSc, joint procedures, specifically PIP fusion and MCP arthroplasty, may also be helpful.

The indications for surgery are thus:

- Refractory ulcers
- Rest pain
- Calcinosis that is causing functional problems or ulceration
- Stiff joints secondary to SSc

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Practical Approaches to Treatment: Case Studies

23

Fredrick M. Wigley

Abbreviations

CCB	Calcium channel blocker
RP	Raynaud's phenomenon
SSc	Scleroderma

Key Points

1. In a patient with scleroderma (SSc) and Raynaud's alone without digital ischemic events, the goal is not to eliminate every Raynaud's event but to reduce the risk of ischemic ulcers or tissue loss and to improve quality of life.
2. In patients with recurrent digital ulcers who have not responded to enhanced vasodilator therapy, we move to intravenous prostacyclin. In the USA we use epoprostenol and in Europe iloprost is available.
3. If acute digital ischemia and no correctable lesion are discovered and prostacyclin therapy is not available or prostacyclin is not quickly reversing signs of ischemia, then a digital sympathectomy is recommended.
4. When a patient presents with a toe ulcer, macrovascular disease should be suspected; if the peripheral pulses are absent or not easily felt then further assessment is always required and a combined medical and surgical approach is often required.
5. In a case of vasculitis early intervention treating the underlying disease to prevent further vascular damage is most important. At the same time, associated vasospasm can be a major component of vasculitis that should not be ignored.

This chapter presents cases with Raynaud's phenomenon (RP) to provide a practical approach to the treatment of RP. The approach is defined by the authors and is based on experience. The specific evidence to support the treatment approach is covered in Chaps. 19–22. A comprehensive approach to managing primary RP is covered in Chap. 6.

Case 1: Newly Diagnosed Scleroderma (SSc) with Raynaud's Phenomenon

Discussion points—Newly diagnosed patient with SSc and RP

Amlodipine is selected because it is a dihydropyridine-type calcium channel blocker and this second-generation CCB has less negative inotropic effects on cardiac

(continued)

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(continued)

myocardium than the first-generation agents like nifedipine; thus it is also preferred if there is heart failure.

The use of aspirin is not yet supported by evidence-based studies and one may decide not to use aspirin at all or in cases who have a risk of GI distress or bleeding. An alternative antiplatelet agent could also be considered.

There is no solid evidence to support antioxidant therapy, but this may be secondary to the challenges of proving benefit or not. These challenges include having a potent agent and solid long-term clinical outcomes in an RCT with a placebo arm.

Although symptoms may improve during summer months, we continue therapy given the risk of digital lesions in this patient with SSC and anti-centromere antibodies. In addition, there are many cold triggers that are present year round. It is often the change in temperature rather than the absolute temperature which triggers an attack.

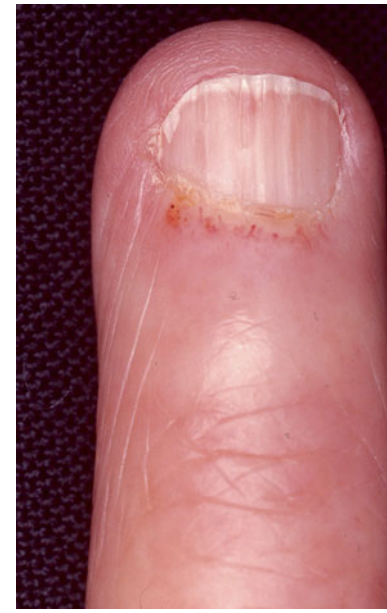

Fig. 23.1 Bedside examination of nailfold demonstrates enlarged capillary loops and areas of dropout of capillaries typical of scleroderma

The patient is a 35-year-old female with newly diagnosed limited SSc. Her first symptom was cold-induced color changes of her fingers and toes starting at age 25. The events involve all her fingers and the attacks are occurring daily with modest exposure to shifts in the ambient temperature. Despite her efforts to keep warm, she is quite distressed by cold hands, recurrent finger numbness, and discomfort but she has never experienced a digital ulcer or skin lesion. She has mild gastrointestinal reflux disease managed with a proton pump inhibitor. Her lung function and cardiac evaluation is normal. Her examination shows a blood pressure of 110/70 with a pulse of 79. The notable findings are sclerodactyly, facial and mucosal telangiectasis, and abnormal nailfold capillaries (see Fig. 23.1) with mildly enlarged capillary loops. Her examination is otherwise normal. Laboratory investigations for comorbid conditions including evidence of diabetes, hyperlipidemia, or hypercoagulable state were negative. She is a never smoker. She did have a positive ANA with high-titer anti-centromere antibodies.

In managing this patient it is recognized that she is at risk for vascular lesions including digital ischemic ulcers. She may also be at risk overtime of larger vessel disease in that patients with limited SSc may have an increased risk to develop ulnar artery occlusion. There is also a risk of digital artery disease with digital loss among patients who are anti-centromere positive. However, she has never had any lesions. Her treatment starts with the foundation of non-drug therapy including education to reduce fear and enhance self-care, clear instruction on cold avoidance, avoidance of any potential aggravating drugs (see Chap. 19), and ready access for communication of problems. I prefer to start a calcium channel blocker (CCB) alone in this case and would start with amlodipine at 5 mg. The patient is asked to have access to blood pressure monitoring at home. I would start additional antiplatelet therapy (CCBs do block platelets) with aspirin at

81 mg po daily. An antioxidant is not discouraged but I make no specific recommendation except a healthy diet. The patient is asked to report the degree of benefit or any problems in a 2-week period following starting amlodipine and if doing well with no complications the amlodipine is continued at the low daily dosing. If no benefit and no significant side effects, then the amlodipine is increased to 10 mg daily. Most patients will do well at 5–10 mg and do not benefit from higher dosing. I only move to higher doses (15–20 mg) or combination vasodilator therapy if ischemic lesions occur. The goal is not to eliminate every Raynaud's event but to reduce the risk of ischemic ulcers or tissue loss and to improve quality of life. Once these goals are accomplished then it is appropriate to continue the same therapy year round and to make sure that the patient calls immediately with any worsening symptoms, signs of digital lesions, or new adverse side effects of the medication.

Case 2: Patient with Scleroderma Digital Ischemic Ulcer

Discussion points—Patient with SSc digital ischemic ulcers

Moving the dose of a sustained-release CCB to the maximum tolerated dose is usually the best option for several reasons: the class of dihydropyridine CCBs are the best studied and are potent peripheral vasodilators; the extended release are safer; there is no definitive data that combination therapy is better or safer.

The phosphodiesterase five inhibitors are popular because it makes biological sense that they would work by increasing nitric oxide in the vasculature. However, the studies show variable benefit and they may not be as potent as the CCB, although studies are required to compare CCBs and phosphodiesterase inhibitors.

Angiotensin-converting enzyme inhibitors are most important in a high renin state as seen in a scleroderma renal crisis; but they do not appear to have an impact in treating RP.

The enthusiasm for botulinum injection at the base of finger for severe RP is growing. However, it is largely based on uncontrolled case series. The biological effect of botulinum is complex and more studies are needed to define its use.

While the use of the endothelin-1 receptor antagonist (ERA) bosentan is approved, one needs to be selective on its use. It has the potential of liver toxicity and reduced new ulcer formation but did not eliminate the risk. In addition, the study of the second-generation ERA macitentan was stopped yet to be reported reasons.

It is often challenging to know if an ulcer is secondarily infected or not. We recommend to treat with systemic antibiotics if there is any indication of infection. We recommend erroring on the use of a statin because it makes biological sense, although it is recognized that more studies are needed to define their role.

A 50-year-old woman with SSc and interstitial lung disease presents with recurrent intense Raynaud's complicated by digital ulcers despite the use of intense cold avoidance and the use of nifedipine XL at a 30 mg dosage. The examination discloses no evidence of larger vessel disease and a negative Allen's test excluding significant ulnar artery disease. She has no comorbid risk factors and is a never smoker. The ulcers are distal painful typical of ischemic digital ulcers (Fig. 23.2) and have been reoccurring on the index and middle fingers bilaterally.

This patient is at risk for the complications of digital ulcers including pain with poor quality of life, loss of hand function, soft tissue infection, and possible loss of involved digits. The underlying disease process is the vascular disease related to SSc. The options for the acute situation for this patient include using combination oral vasodilators, moving to intravenous prostaglandin therapy,

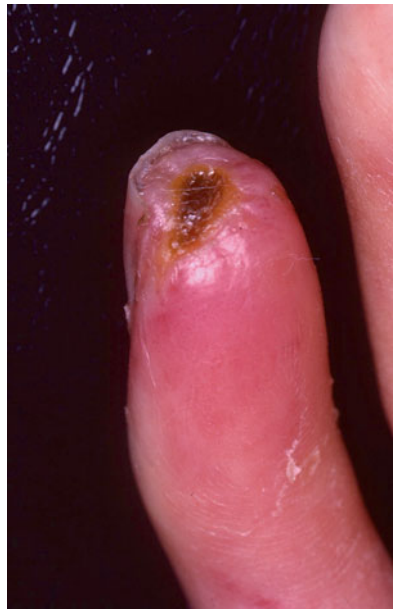

Fig. 23.2 Examination of the finger demonstrates a distal ischemic ulcer secondary to peripheral vascular disease of scleroderma

combination oral therapy, topical nitrates, local botox injections, or considering surgical options. Given the idea of a practical long-term treatment, I would recommend first moving the nifedipine XL (or amlodipine) to maximum tolerated dose (usually nifedipine XL 90 mg); if on maximum tolerated dose there is no benefit then I would add a PDE5 inhibitor (if available); I use sildenafil at 20 mg po tid; I usually titrate up slowly to the maximum dosing. Some experts use topical nitrates instead of a PDE5 inhibitor. I have not found the addition of an ACE inhibitor to be helpful but have used an ARB (losartan 50 mg) or SSRI (fluoxetine 20 mg) with some benefit (recognizing this strategy is not evidence based) when the PDE5 inhibitor is not available. If the patient does not tolerate (low blood pressure or edema) the enhanced vasodilator therapy or there is no benefit, then a trial of digital botulinum toxin (botox) injections can be tried. The usual tolerable dose of the CCB is continued. While success of botox injections in this setting is reported, it is not yet supported by insurance in the USA and I have been disappointed with long-term outcomes in similar cases.

In patients with recurrent digital ulcers who have not responded to enhanced vasodilator therapy, we move to intravenous prostacyclin. In the USA we use epoprostenol and in Europe iloprost is available. This is given via a peripheral vein at a low-dose infusion of 2 ng/kg/min over 5–6 h daily for 3–5 days, either in an outpatient infusion center or in hospital, depending on local arrangements. I usually stop the CCB or other vasodilators during days of the infusion treatment. This approach of acute administration of intravenous prostacyclin both provides immediate benefit by reducing acute vasospasm and, coupled with restarting and continued use of a daily oral vasodilator, may prevent new ischemic ulcers.

We do not move to surgical options unless the patient has signs of larger vessel disease or deep-tissue ischemia not responding to medical management. Local care of the ulcer is critical for improved outcome (see Chap. 21). We carefully debride ulcers with excess necrotic tissue or if there are signs of secondary sequestered infection. A hydrocolloid dressing with topical antibiotics (mupirocin) or silver-impregnated dressing is used. Any sign of deeper tissue infection is treated with systemic antibiotics that cover for resistant staphylococcal aureus (trimethoprim/sulfamethoxazole). I have a low threshold to use systemic antibiotics due to the complications that can occur in the avascular tissue of SSc. Thus any suggestion of infection and I start systemic antibiotics. Once the ulcer appears clear with good granulation tissue then I move to light dressing with Vaseline or as it becomes small and contracts I move to no dressing; allowing the small ulcer to crust over, dry, and heal with time. Ulcers are painful and adequate analgesia is required. Pain isolated to the bed of the ulcer is expected. However, pain beyond the ulcer, extending into the proximal finger, suggests continued ischemia and the threat of a deep injury or spreading infection.

I manage pain first with topical care. Often covering the ulcer with Vaseline will reduce pain if the ulcer itself is the sole source of pain. The use of a nonsteroidal anti-inflammatory drug (ibuprofen) alone or with acetaminophen is our first approach. Opiates at low dose (oxycodone 5 mg every 6 h) may be needed. Topical lidocaine or

lidocaine/prilocaine use on the finger outside of the ulcer bed is helpful to some patients. Keeping the ulcer protected from trauma and the involved finger(s) warm is very important. We will have the patient stay home away from a work situation that may cause finger trauma (typing) or undue cold exposure, at least until the acute phase is over. One can tell if the acute phase is over when the patient has well-controlled pain, no signs of current ulcer worsening, and no new ulcers emerging.

Once the acute situation is improved with topical care of the ulcers (see Chap. 21), then in patients with SSc one can consider the use of either a statin or an endothelin-1 inhibitor (bosentan). In the USA, I have used atorvastatin at 40 mg daily with success, recognizing that the scientific evidence for benefit is still under study. In Europe, bosentan is approved and can be used to prevent new digital ulcers.

Case 3: Patient with Scleroderma and Acute Digital Ischemia

Discussion points—Patient with SSc and Acute Digital Ischemia

The impact of smoking on RP is complex but there is little debate that it complicates the management of cases with digital ischemia. This is due both to the increased risk of larger vessel disease and the vasoconstriction associated with smoke inhalation.

The use of anticoagulation during an acute digital ischemic event is not proven by clinical trials. However, it is likely that microthrombi are occurring and a decrease in fibrinolysis is likely present. If there is evidence of a hypercoagulable state or emboli then anticoagulation is indicated. In the absence of a well-defined clotting event, one must weigh the risk against potential benefit for each case.

If prostacyclin is to reverse the acute event, it must be used quickly before occlusion or structural problems negate its benefit. Some would move directly to digital sympathectomy.

We recommend digital sympathectomy rather than a cervical or proximal procedure due to reduced risk of complications from the procedure. It is also thought that the local procedure releases an entrapped vessel and improves blood flow. Long-term studies are few and reoccurrence can occur despite sympathectomy.

Cervical sympathectomy is also not thought to be as effective as digital or local sympathectomy.

A 50-year-old male patient with SSc presents with RP and a painful cyanotic right index finger (Fig. 23.3). The patient is a smoker and has had recurrent digital ulcers despite the use of a combination of a CCB and sildenafil 20 mg three times daily. He is also on atorvastatin and low-dose aspirin (81 mg). His exam demonstrates an ischemic finger; it is cold from the base to the fingertip with soft tissue swelling and early signs of tissue necrosis of the tip. He is in a great deal of pain, holding his hand down in an effort to improve blood flow to the finger. His examination demonstrates good pulses in both upper and lower extremity but a positive Allen's test suggesting ulnar artery occlusion.

This patient presents with a medical emergency with the likelihood of acute loss of his digit due to critical ischemia secondary to underlying macrovascular disease. The history of smoking suggests that there may also be arteriosclerosis of proximal vessels. One goal for long-term therapy will be smoking cessation. For the acute event, we ask our vascular (or hand) surgery colleague to get involved early in the case to be ready for surgical options. Evaluation for correctable lesion is recommended which is done first with Doppler ultrasound and then angiography (see Chap. 14), if the initial evaluation suggests a high suspicion of larger vessel occlusion or thrombus.

In this case, his current oral vasodilator therapy alone failed to prevent the ischemic crisis. I have used local digital injection of lidocaine or bupivacaine instilled at the base of the finger for

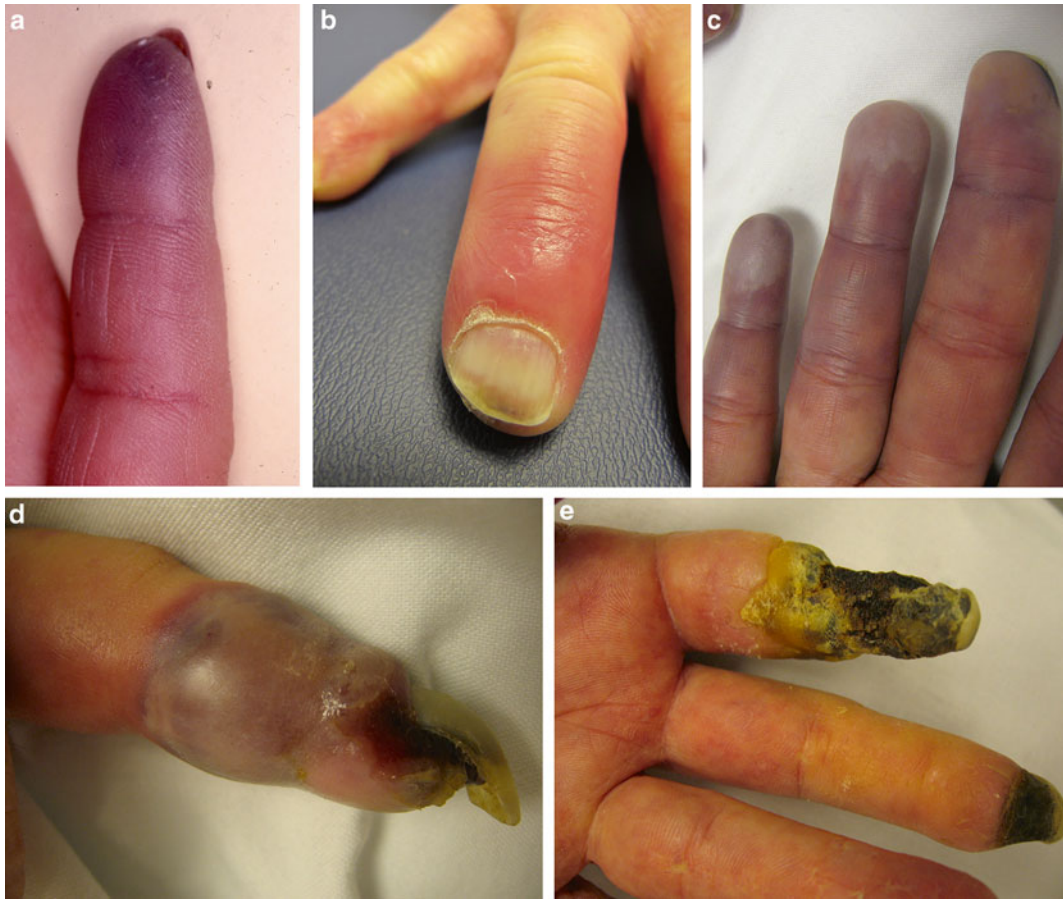

Fig. 23.3 (**a**) The photo shows a cyanotic skin of a finger in a patient with scleroderma. This is secondary to larger vessel disease and acute digital ischemia. (**b**) This photo demonstrates a hyperemic response secondary to acute ischemia. (**c**) This photo demonstrates fixed ischemia with vascular occlusion and superimposed severe vasospasm. (**d**) The photo demonstrates severe advanced ischemia with emerging gangrene. Note the hyperemic border of progressive ischemic tissue. (**e**) This photo demonstrates the late stage of macrovascular disease and digital loss with dry gangrene in a patient with scleroderma

immediate pain control and often will see immediate improvement in digital blood flow. If not contraindicated, we will acutely anticoagulate the patient for 48–72 h using intravenous heparin. I recommend intravenous prostacyclin (either epoprostenol or iloprost). I do not delay and start intravenous prostacyclin while in diagnostic studies to define any correctable vascular lesion (emboli, thrombus, or a large vessel lesion that can be bypassed). The rapid institution of the prostacyclin can stop the progression of the lesion if occlusion or structural disease is not advanced. It must be followed by allowing a long-term management plan with oral agents and smoking cessation. Some are recommending acute administration of botox injected locally into the base of the involved finger with or without prostaglandin infusion. Our experience in this setting is that botox has been helpful usually seeing benefit in 48 h; but again this recommendation is not evidence based.

If the imaging studies suggest a thrombus or correctable large vessel lesion then surgery may be indicated. Thrombolytic therapy for an acute thrombus can be done, but there is no good evidence to give specific guidance. I do not chronically anticoagulate once the acute situation is resolved, unless a hypercoagulable state is

defined. In this case, comorbid conditions need to addressed and I would start a statin to potentially prevent further ischemic events, again recognizing that this is not yet a proven strategy.

If there is no correctable lesion discovered, prostacyclin therapy is not available, or prostacyclin is not quickly reversing signs of ischemia, then we recommend moving to digital sympathectomy. This can be done with or without botox injection. In my experience, rapid intervention with digital sympathectomy can prevent digital loss and quickly reverse a critical ischemic event.

If the patient recovers then continued oral vasodilator therapy is indicated, but without smoking cessation he is at high risk for reoccurrence.

In this case we did not discover by angiogram a correctable lesion and despite intravenous prostacylcin and the finger progressed to distal gangrene (Fig. 23.3). Once the finger demarcated, a digital sympathectomy was not done. Ultimately, he required a distal finger amputation and on a CCB plus sildenafil, low-dose aspirin and smoking cessation have done well with no new events.

Case 4: A Patient with Raynaud's Phenomenon with Lower Limb Ischemia

Discussion points—Patient with RP with lower limb ischemia

Some now suggest that given the risk factors present in this case early use of a statin should be done. One can also argue that antiplatelet therapy with a statin could prevent progression of vascular disease.

While Doppler study can define the presence of macrovascular disease, a CT angiogram or MRA study can provide evidence of both vessel wall and lumen disease. However, most will require digital subtraction angiography before or at the time of actual surgical intervention.

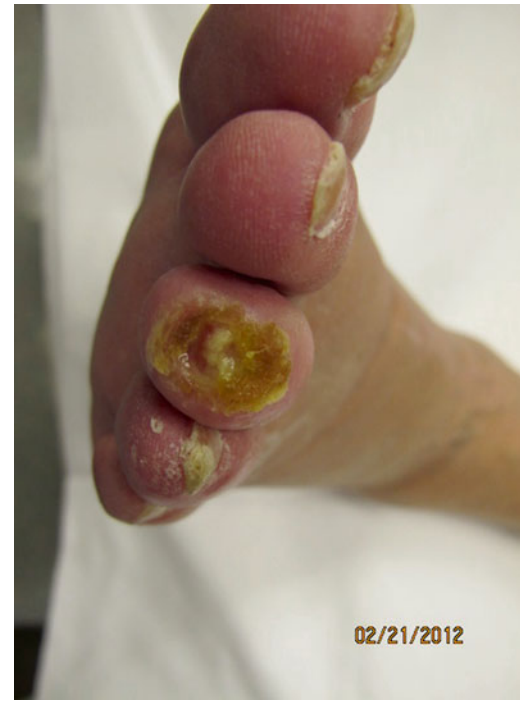

Fig. 23.4 An ischemic ulcer on the distal third toe associated with larger proximal vessel disease of the lower limb

The patient is a 65-year-old male with RP since age 20. He is a nonsmoker and has never been on specific therapy for his RP. He has a family history of coronary artery disease, hyperlipidemia, and diabetes but he has only been treated by his primary care doctor for hypertension with a combination of amlodipine and lisinopril. His RP improved in his fingers over the years but in recent months he notes worsening cold sensitivity in his feet and now has a painful non-healing ulcer on his left great toe. He also reports that he has cramps in the lower legs when walking. He has no signs of a rheumatic disease on examination. His examination is notable for the absence of dorsal pedal and posterior tibial pulses. His fingers and toes were symmetrically cool to touch and an ischemic ulcer was noted on his third toe (Fig. 23.4); the toe was slightly swollen and dusky in color. No bruits were heard over abdomen or other larger vessels.

This case illustrates the need to fully evaluate patients with RP for concomitant larger vessel disease if the signs and symptoms involve the

lower extremities. In this case the physical examination will usually reveal the underlying problem. If the pedal pulses are absent undoubtedly there is large vessel disease. I would confirm this by obtaining ankle/brachial pressure indices. If the index is less than 0.9 then peripheral arterial disease of larger vessels is confirmed in the presence of tissue necrosis then a vascular consultation and angiographic study is warranted. A CT angiogram provides a sensitive and accurate assessment, is faster than MRA studies, and is less invasive than digital subtraction arteriogram. Both the CT angiogram and MRA can demonstrate both vessel lumen and vessel wall changes. In this era of endovascular therapy, the advantage to digital subtraction angiography is that treatment of the lesion can be performed at the same time as the diagnostic study. Referral to a vascular surgeon at the onset of the evaluation is warranted because if a correctable lesion is found, rapid intervention is required. While vasodilator and antiplatelet therapy should be continued, it is unlikely to prevent new or allow healing of existing lesions if larger vessel disease is not corrected.

In this case a popliteal lesion was found and dilation of stenosis resulted in rapid healing. He continued to do well on amlodipine, ASA 81 mg daily, and atrovastatin 40 mg daily.

Case 5: A Young Woman with RP and Vasculitis

Discussion points—Patient with RP and vasculitis

Digital necrosis is a medical emergency: failure to act quickly may result in the need for amputation.

Suspect vasculitis in the context of a short history of digital ischemia progressing to necrosis, and other suggestive features (in this case these included a vasculitic rash).

When digital ischemia is a result of vasculitis, there are many different "pathways" to consider in treatment, including treatment of the underlying cause and treatment of vasospasm.

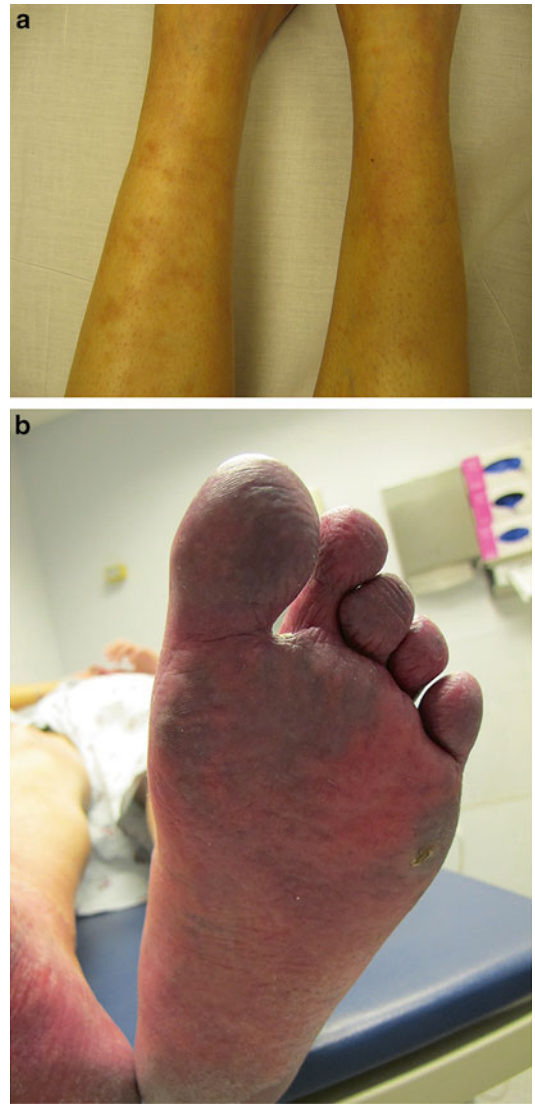

Fig. 23.5 (**a**) This photo shows cyanotic mottling of the foot secondary to vasospasm associated with vasculitis. (**b**) The photo shows a cutaneous eruption secondary to small-vessel vasculitis

A 28-year-old nonsmoking woman presents with a necrotic lesion on the distal middle finger and painful feet (Fig. 23.5). She has had RP that started 1 month ago that she managed with cold avoidance. She denies any change in her skin texture, but had noted polyarthralgias and muscle pain. The finger is noted to be cold and cyanotic with a digital ulcer noted. On further examination she has palpable purpura on her legs and scattered petechia. Her laboratory data was remarkable for

ANA positive with a titer of 1:80 in a speckled pattern, mild anemia, normal C3 but a depressed C4, a positive rheumatoid factor, and high ESR and CRP. The urinalysis was normal. Serum transaminases was elevated suggesting active hepatitis. A cryoglobulin was positive and serology demonstrated a reactive HCV antibody test and a positive molecular test for the presence of HCV RNA. There was no cardiopulmonary disease. The viral genotype 1 was defined. A liver biopsy was done to assess the severity of chronic hepatitis C.

The cornerstone of therapy for hepatitis-C-associated cryoglobulinemic vasculitis is antiviral therapy. Treatment of the primary infection should be considered whenever possible. One standard regimen is sofosbuvir, peginterferon, and ribavirin in treatment for naïve genotype 1-infected patients. The advent of interferon-sparing regimens should make antiviral therapy feasible in an even greater proportion of patients in the near future. This is particularly important to consider given that interferons can aggravate Raynaud's phenomenon.

Because of the activity of her disease, which places tissue at risk of permanent damage, it would be reasonable to simultaneously institute immunosuppression for treatment of the vasculitis. Glucocorticoids alone may be adequate, but it would be reasonable to consider a steroid-sparing agent, such as rituximab, which use has been supported in recent clinical trials.

It is important to note that the management of vasculitis is different from the management of RP with vasospasm alone. In fact, often the ischemic finger secondary to vasculitis or other causes of structural disease is inappropriately considered RP. Vasculitis may lead to a decrease in blood flow and tissue ischemia that is irreversible, unlike true RP. In theory when dealing with fixed circulatory abnormalities a vasodilator may inadvertently induce a shunt or steal phenomenon, moving blood into healthy vessels that can dilate away from the obstructed inflamed vessels, potentially worsening the ischemic event. Therefore, vasodilator therapy will be disappointing and not achieve the desired effect. Vasodilator therapy should be considered when there is clinical evidence of reversible vasospasm but it should be used with caution. This same situation can occur whenever there is underlying occlusion or structural vascular disease including patients with macrovascular and vessel occlusion secondary to SSc. Early intervention to prevent further vascular damage from active vasculitis is most important. At the same time, associated vasospasm can be a major component of vasculitis that should not be ignored (see below).

Asymmetric vasospastic attack of the digits of the hand or feet associated with prolonged signs of tissue ischemia or tissue necrosis (ulceration) is characteristic of vasculitis, particularly when there is a great deal of pain. One can often distinguish vasospasm from irreversible disease by physical examination. A fixed lesion will not show any recovery to blood flow after light compression of the distal finger. The presence of hyperemia of the tissue is a sign of a vasodilation response to tissue ischemia. Often serial observations will see the ischemia wax and wane with time, depending on the position of the involved limb and with various ambient temperatures. These findings suggest some element of reversible vasospasm and the potential benefit of vasodilator therapy.

When treating this patient I would start amlodipine (or another dihydropyridine CCB) at a dose of 5 mg and carefully evaluate clinically the benefit to her underlying RP and the digital ischemia. If vasospasm is persistent and the CCB is tolerated then the dose can be titrated up every 48 h to a maximum of 20 mg amlodipine (if needed). If there is no response to the higher dose CCB then I prefer to add sildenafil 20 mg three times daily, again watching the clinical response for signs of improved digital blood flow. Other options include topical nitroglycerin (1/4–1/2 inch of 2 % cream) on skin. We would not use sildenafil and the nitrate together. If the patient has progression of lesions with signs of severe vasospasm, then intravenous PGI2 (either epoprostenol or iloprost) can be given intravenously at 0.05–2 ng/kg/min; using the same protocol is used for SSc (see above). If available some use intravenous prostacyclin early before combination vasodilators. Generally, if the vasculitis is controlled the tissue ischemia and vasospasm will resolve. Further vasodilator therapy will be determined by the degree of residual vasospasm.

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