Raynaud’s phenomenon: a mirror of autoimmune disease
van Roon, Anniek Maaike

DOI:
10.33612/diss.98238042

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 1

General introduction
Chapter 1

RAYNAUD’S PHENOMENON

Raynaud’s phenomenon (RP) is a discolouration of the fingers, toes, and, in some cases, the nose and ears, provoked by cold temperatures or emotional stress (see Figure 1). It is named after Maurice Raynaud (1834–1881), who was the first to describe this phenomenon.¹ A typical attack starts with a white phase (ischemia), after which the extremities become blue (cyanosis) and during rewarming they will turn red (reperfusion).² It is the body’s exaggerated response to maintain its temperature when exposed to cold. This exaggerated response occurs in specialised skin areas where unique features exist to contribute to thermoregulation while nutritional flow remains protected.³ Not only do the RP attacks cause colour changes, but patients can experience numbness, tingling sensations, and pain. The prevalence of RP varies widely as diagnosis is dependent on the criteria used as well as the geographical location and climate. In a Dutch study where the diagnosis was made by the patients’ general practitioner when there was a bi- or triphasic discoloration, the prevalence was 2.9% in women and 0.5% in men.⁴ However, a recent study by the Lifelines cohort found a prevalence of 5.7% in women and 2.1% in men in the general population of the northern parts of the Netherlands.⁵ Raynaud’s phenomenon can be primary (PRP), which is idiopathic, or secondary (SRP) to an underlying disease, such as connective tissue diseases (CTD). The most important CTD is systemic sclerosis (SSc), as RP is the first presenting symptom in over 95% of SSc patients. Systemic sclerosis is a severe autoimmune disease, characterised by fibrosis and microvascular abnormalities, in which a broad range of symptoms can exist; therefore, SSc remains difficult for physicians to diagnose.

Pathophysiology

The pathogenesis of RP consists of a variety of mechanisms causing a disturbance in the balance between vasodilatation and vasoconstriction, in favour of the latter.² Vascular changes are most important, but neural and intravascular abnormalities also play a role, and they all interact.⁶ Although they remain incompletely clarified, genetic and hormonal factors have also been identified.⁷⁻¹⁰ There are several differences between PRP and RP secondary to SSc. These differences are of interest as they can help to gain an understanding of why PRP patients do not develop tissue damage while patients with SSc do.
Vascular abnormalities can be classified as functional or structural. The endothelium, the inner surface of the vessel, is a layer of cells that produces vasoconstrictors and vasodilators. The most important functional abnormality is endothelial dysfunction, which is thought to play a major role in the pathogenesis of RP secondary to SSc. When endothelial cells are injured, as occurs in patients with SSc, there is a disturbance in the balance of vasoactive substances. This results in impaired vasodilatation, reduced production of vasodilators and increased vasoconstriction. One of the vasoconstrictors produced by the endothelium is endothelin-1, which also has effects on vascular remodelling and is profibrotic. Endothelin-1 is demonstrated to be increased in the blood of SSc patients, and also to be overexpressed and have increased binding density in SSc patients’ skin. Vasodilators that may be reduced include nitric oxide and prostacyclin, although it is also suggested that SSc patients are resistant to prostacyclin and have overexpression of nitric oxide. Therefore, the exact role in the pathophysiology of these two vasodilators in RP remains unclear. In PRP, endothelial...
abnormalities are less likely to play such a major role in the pathogenesis, although there is some evidence for impaired endothelial-dependent vasodilation in these patients.\textsuperscript{18,19}

Furthermore, in PRP it is commonly accepted that no structural vascular damage exists, although subtle changes of microvasculature may occur.\textsuperscript{20} In SSc, structural damage of the microvasculature is one of the key features, as abnormalities seen with nailfold capillary microscopy (NCM) is one of the classification criteria.\textsuperscript{21} In addition, damage is seen in larger arteries such as the digital arteries as well as the ulnar artery.\textsuperscript{22,23} This structural damage is possibly a result of the functional endothelial dysfunction. With the endothelium being damaged, this may eventually lead to structural abnormalities.

Both systemic and local exposure to cold increases sympathetic adrenergic outflow to the skin, causing vasoconstriction in which the alpha-2 response seems to be the most important.\textsuperscript{24} One of the neural abnormalities in RP is that there is an increased expression of the alpha-2 adrenergic receptor, which would amplify the reaction to a normal stimulus.\textsuperscript{3} Furthermore, it is possible that the alpha-2 adrenergic receptors are already activated in RP at a higher temperature than in healthy controls.\textsuperscript{6} Intravascular abnormalities consist of diseases leading to increased viscosity or impaired digital perfusion.\textsuperscript{2}

Chapter 2 and 3 provide more insight into the pathophysiology of RP. In Chapter 2, the relation between the severity of the RP attack, assessed by cooling and recovery PPG (explained in more detail in the paragraph ‘additional vascular tests’), and the abnormalities of the microvasculature are examined. This will provide some insight into the mechanisms leading to structural microvascular changes. Chapter 3 is a clinical vignette which shows the transformation of an SSc patient’s microvascular structural changes over time.

**Primary Raynaud’s phenomenon**

In most patients, RP is primary and is a harmless condition as patients do not develop any tissue injury. Nevertheless, the attacks can be a burden in patients’ daily life because of pain and numbness. In 1992, LeRoy and Medsger proposed criteria for the diagnosis of PRP which are still used today (see Table 1).\textsuperscript{25} If a patient meets these criteria and there are normal findings in the subsequent two years, a secondary cause is unlikely.\textsuperscript{26}
**General introduction**

**Table 1. Criteria for the diagnosis of primary Raynaud’s phenomenon***

- Vasospastic attacks precipitated by cold or emotional stress
- Symmetric attacks involving both hands
- Absence of tissue necrosis or gangrene
- No history or physical findings suggestive of a secondary cause
- Normal nailfold capillaries
- Normal erythrocyte sedimentation rate
- Negative serologic findings, particularly negative test for antinuclear antibodies

*adapted from LeRoy and Medsger* 25

**Secondary Raynaud’s phenomenon**

Because SRP is a symptom of an underlying pathology, it is important to distinguish it from PRP. A secondary cause is more likely when the age of onset is over 30 years, the attacks are severe or asymmetric, there are skin lesions, other CTD symptoms are present, the patient has specific autoantibodies and/or there are abnormal nailfold capillaries.26 Table 2 lists the main causes of and associations with SRP. The CTD, especially SSc, are most important as RP can be the first presenting symptom of the disease. Sometimes RP can precede the disease by many years, and therefore is a window of opportunity for early diagnosis and treatment. The best prognostic tests are NCM and SSc-specific autoantibodies. When both these tests are abnormal on a patient with RP’s first visit, this is associated with a sensitivity of 89% and specificity of 85% for the development of SSc.27 However, for some patients the nailfold capillaries reveal non-specific changes, or the autoantibodies are not SSc specific. For these patients, it is uncertain how likely it is that an underlying disease will develop.

Chapters 4 and 5 contribute to the knowledge of RP for daily medical practice. Chapter 4 examines the differences between PRP and SSc-related RP in the recovery period and involvement of the thumb, while in Chapter 5, the association between microvascular changes, as assessed with NCM, and bodyweight is investigated. This will help the physician to differentiate between PRP and SRP during the diagnostic phase of RP. Chapter 6 addresses the role of microvascular abnormalities, as seen on NCM, as a predictor of underlying organ involvement in SRP, specifically the association with pulmonary function tests in RP patients with different underlying diseases.
Chapter 1

Systemic sclerosis

Systemic sclerosis is a severe autoimmune disease characterised by tissue fibrosis, microvasculopathy and the presence of autoantibodies. The incidence is low, affecting 7–20 people per million of the general population per year.\(^{28,29}\) It is more common in women (3:1) and the average age of onset is 50 years.\(^{30}\) As stated previously, RP is the first presenting symptom in most patients and can precede SSc by several years. Patients with SSc-related RP can develop digital ulceration or even critical ischemia. These vascular complications are a major source of pain, disability and distress.\(^{31}\) A hallmark of SSc is skin fibrosis, usually starting at the fingers, hands and face. Sometimes

Table 2. Main causes of and associations with secondary Raynaud’s phenomenon*

<table>
<thead>
<tr>
<th>Connective tissue disease</th>
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<tbody>
<tr>
<td>- Systemic sclerosis (SSc) and SSc-spectrum disorders (undifferentiated connective tissue disease, mixed connective tissue disease, other overlap syndromes)</td>
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<tr>
<td>- Inflammatory muscle disease</td>
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<tr>
<td>- Systemic lupus erythematosus</td>
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<td>- Sjögren’s syndrome</td>
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<td>- Vasculitis</td>
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| Hand-arm-vibration syndrome |

| Extrinsic vascular compression |

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<th>Other causes of large vessel disease</th>
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<tr>
<td>- Atherosclerosis</td>
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<td>- Thromboangiitis obliterator (Buerger’s disease)</td>
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<th>Intravascular disease and other diseases associated with increased viscosity</th>
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<tr>
<td>- Paraproteinaemia</td>
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<td>- Cryoglobulinaemia</td>
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<th>Drugs, chemicals or other occupational exposures</th>
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<td>- Beta-blockers</td>
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<td>- Clonidine</td>
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<td>- Ergotamine</td>
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<td>- Vinyl chloride</td>
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<td>- Cytostatics</td>
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<th>Other causes and associations</th>
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<tr>
<td>- Hypothyroidism</td>
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<td>- Carpal tunnel syndrome</td>
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<td>- Frostbite</td>
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*adapted from Herrick\(^2\)

Systemic sclerosis

Systemic sclerosis is a severe autoimmune disease characterised by tissue fibrosis, microvasculopathy and the presence of autoantibodies. The incidence is low, affecting 7–20 people per million of the general population per year.\(^{28,29}\) It is more common in women (3:1) and the average age of onset is 50 years.\(^{30}\) As stated previously, RP is the first presenting symptom in most patients and can precede SSc by several years. Patients with SSc-related RP can develop digital ulceration or even critical ischemia. These vascular complications are a major source of pain, disability and distress.\(^{31}\) A hallmark of SSc is skin fibrosis, usually starting at the fingers, hands and face. Sometimes
development of oedematous swelling in the hands, so-called puffy hands, precedes the skin fibrosis. Together with RP, puffy hands are a "red flag" for SSc.\textsuperscript{32} The severity of the skin involvement is assessed using the modified Rodnan skin score (mRSS) for both clinical purposes and research purposes.\textsuperscript{33} Systemic sclerosis has a high mortality rate, higher than other rheumatic diseases, and a high disease burden. Disease-related death is mainly related to pulmonary fibrosis, pulmonary arterial hypertension and cardiac causes.\textsuperscript{34}

SSc can be divided into two subtypes which are distinguished by the extension of the skin fibrosis, but also have a clinically different course. However, this division can be seen as arbitrary, as overlapping occurs and SSc may be more of a spectrum than two subtypes. Patients with limited cutaneous SSc (lcSSc) have skin fibrosis of the hands and feet, distal of the elbows and knees. The progression of the disease is usually slow. After the first symptoms of RP, it can take 10–15 years before the first non-RP symptom occurs. The internal disease progression consists mainly of oesophageal and lung involvement (interstitial lung disease and pulmonary arterial hypertension).\textsuperscript{35} The diffuse cutaneous subtype of SSc (dcSSc) is present when skin fibrosis is proximal to the elbows and knees, at any time during the disease. The skin fibrosis rapidly worsens, causing joint contractures. Internal organ involvement, such as interstitial lung disease and heart or kidney involvement, is commonly present in the early stage of the disease. After the early phase of the disease (defined as the first three years), the skin fibrosis stabilises or even improves. Internal organ involvement, however, may worsen over time, but new internal complications are rare after the early phase.\textsuperscript{35}

In most SSc patients, antinuclear antibodies (ANA) are detected, most commonly anticentromere antibodies and anti-topoisomerase; however, an increasing number of ANA specificities are characterised for the disease. Each ANA pattern is associated with a different disease subtype; for example, anticentromere is seen more in lcSSc, while anti-topoisomerase is associated with dcSSc, and patients with anti-RNA polymerase III are more likely to develop renal crises.\textsuperscript{36} Therefore, next to differentiating between lcSSc and dcSSc, the ANA patterns can also help to characterize patients.

In 2013, new classification criteria were published, and are now widely used. The new criteria allow more patients to be correctly classified as SSc.\textsuperscript{21} However, even when
classified according to the same criteria and divided into the two subtypes of the disease, the clinical course of the disease is heterogenic. While this makes the disease interesting, it also makes it hard to study. Due to the high heterogeneity and small patient population, most studies entail small cohorts and/or patient groups with a high level of variety.

Additional vascular tests
In a clinical setting such as our centre, when it is uncertain if the patient’s complaints are indeed RP, a cooling and recovery photo-electric plethysmography (PPG) is performed. If RP is diagnosed, NCM is one of the most important additional tests to differentiate between PRP and SRP. In a research setting, the cooling and recovery PPG is used to assess the perfusion during an RP attack, and NCM is used to assess the microvasculature. Other tests used in a research setting, but not used for clinical purposes, are laser speckle contrast analysis (LASCA) and pulse wave velocity (PWV). These two tests assess the vascular status of a patient. Figure 2 is a schematic representation of the areas in which the different techniques assess the vasculature. All these tests are non-invasive and, in our centre, are performed at the vascular laboratory.

Cooling and recovery photo-electric plethysmography
The cooling and recovery procedure with fingertip PPG is a unique technique which is used in our centre.\textsuperscript{37,38} One of the patient’s hands is submerged into water up to the radio carpal joint (Figure 3). The water temperature starts at 33°C and is cooled down in steps of 3°C every four minutes until it reaches 6°C, or until the pain is intolerable for the patient. At the end of every step during the cooling, 15 seconds of perfusion is recorded with (waterproof) fingertip PPG (Figure 3). Photo-electric plethysmography is an optical technique that uses infrared light for the transcutaneous registration of beat-to-beat blood volume changes in the microvascular bed of the skin.\textsuperscript{39} It provides information on the peripheral circulation at the site where the PPG sensor is placed, in this case the fingertips. After cooling, the hand is taken out of the water and dried softly. Perfusion is then measured for the last 15 seconds of every minute for 10 minutes. In the 15 seconds of recordings, PPG pulses are analysed from R-peak (detected in the ECG) up to 600ms. Mean and SD of the amplitude of the pulses are determined.

An RP attack is provoked by cooling. In a clinical setting, RP is diagnosed when two or more fingers lose perfusion during two or more subsequent steps, or when during
Figure 2. Schematic representation of the areas in which the different techniques assess the vasculature.

Figure 3. The cooling and recovery fingertip photo-electric plethysmography set-up, with the hand in water up to the radio carpal joint and the photo-electric plethysmography sensors attached to the fingers with tape.
10 minutes of recovery there is no restoration of perfusion. In a research setting, this technique can also be used to calculate the time of ischemia during this procedure, which represents the severity of the provoked RP attack. The time when perfusion is lost until the time of restoration of perfusion is seen as the ischemic time.

**Nailfold capillary microscopy**

The structural damage of the nailfold capillaries, as seen on NCM, can help to differentiate between PRP and SRP. When there are specific SSc abnormalities at first examination after referral, combined with the presence of SSc specific autoantibodies, it has a positive predictive value of 79% and a negative predictive value of 93% for the development of SSc. Independent of RP, abnormal capillaries are also one of the criteria of the ACR/EULAR criteria for SSc. Therefore, this is a commonly used method in clinical settings.

To assess the capillaries, immersion oil is placed on the nailfold to increase transparency. It is important to let the patients adjust to a room temperature of 23–24°C. It is standard procedure to assess all fingers except for the thumbs. However, previously in our centre only the middle and ring fingers of both hands were assessed. The custom of examining these four fingers was based on the experience that the index finger possibly gives false positive results because of traumata and the little finger was often technically hard to assess with the NCM set-up that was used. Currently, a more advanced NCM set-up is installed and all eight fingers are examined.

There are several parameters to observe with NCM. First, the density (e.g. the number of capillaries per mm). In different centres, including ours, the number of capillaries is counted over 3 mm; other centres count over 1 mm, or 1 mm in four different places in one nailfold, or between the most left and most right capillary of one wide field image. Seven or more capillaries per mm is classified as normal. Furthermore, the shape of the capillaries is assessed. Typically, the capillaries are hairpin-shaped. Sometimes there are tortuous or crossing capillaries, which are non-specific abnormalities and can be considered in the normal spectrum. When capillaries are enlarged, the apex (the middle, most distal part of the capillary) can be measured. A capillary with a diameter of 20–50 µm is considered dilated, and when the diameter is >50 µm, a giant capillary. Giant capillaries are typical for SSc. Neovascularisations are capillaries which evolve into...
different branches, somewhat bushy, and are always abnormal. Finally, haemorrhages can be present, which can be a sign of SSc, but without other abnormal findings this can be a non-specific finding.

Maricq and LeRoy were among the first to describe the changes found on NCM into an SSc pattern. In 2000, Cutolo et al. divided the SSc pattern into three different SSc patterns: early, active and late (Figure 4). When there are giants present but a normal density, it is classified as an early pattern. When there are giants, loss of capillaries and haemorrhages, then it is an active pattern. A late pattern is defined as severe loss of capillaries, no presence of giants and few to no haemorrhages and the presence of neovascularisation. These patterns seem to be strongly correlated to RP duration and SSc disease duration; therefore, they might represent the evolution of the disease. However, there are other abnormalities that can be found, but are not specific for SSc, for example, tortuous or dilated (not giant) capillaries. When these changes are present, the pattern is often referred to as a non-specific pattern.

Figure 4. Examples of the different nailfold capillaroscopic patterns.
Next to the patterns, different scores have been proposed to predict the development of future organ involvement. First, the microangiopathy evolution score (MES) was proposed as a tool to observe microvascular changes. A semi-quantitative rating scale (Table 3) was used to score loss of capillaries, disorganisation and capillary ramifications. Per parameter, the mean of eight fingers was used, and the sum of the three parameters was used to calculate the MES (thus ranging from 0–9). During the follow-up of SSc patients, the MES significantly increased, thus confirming the evolution of the microvascular changes. Other studies indicate a correlation between MES and the perfusion of the hand, as well as the presence of skin teleangectasia. Then the prognostic index for digital trophic lesions (PIDL) was proposed. This score also used the semi-quantitative rating scale, as presented in Table 3, to score capillary loss. The mean score of eight images (one image of 1 mm for every finger except the thumbs) was calculated. This score was associated with the presence of digital trophic lesions, and Smith et al. suggest it be used as a simple clinical prognostic index for the present and future digital trophic lesions. However, validation studies for both the MES and PIDL scoring system are lacking. Finally, the capillaroscopic skin ulcer risk index (CSURI) uses the number of capillaries (N), the number of giants (M) and the diameter of the largest giant (Dmax). The CSURI is calculated in the finger with the lowest N or, secondarily, the highest M, by Dmax · M/N². Patients with a CSURI higher than 2.96 are at risk of developing digital ulcers in the next three months, with a positive predictive value of 61%, and a negative predictive value of 98%.

**Laser speckle contrast analysis**

Laser speckle contrast analysis is a method that assesses peripheral blood perfusion of tissue. The set-up uses laser light. The theory behind this method is that a static object will give a stationary speckle pattern of backscattered light, but the more movement there is, the more the speckle pattern will change (blur), giving an indication of the degree of movement of the object. If, for example, a fixated hand is illuminated with laser light, the only moving objects in the tissue will be the red blood cells; thus movement indicates perfusion. Figure 5 is an example of a normal image acquired with LASCA. Most commonly, the PeriCam PSI System (PeriMed, Jarfalla, Sweden) is used. It provides the blood perfusion of an area in arbitrary units called perfusion units (PU).
While LASCA has only been applied in RP and SSc for a short period of time, several studies indicate that it has good potential as an outcome measure in clinical trials. Furthermore, it has good convergent validity with other measures of blood perfusion and microvasculopathy, such as thermography and the MES. It is suggested that, when combined with cold provocation, LASCA helps to differentiate between PRP and SRP.

**Figure 5.** Example of a laser speckle contrast analysis image.

**Pulse wave velocity**
Arterial stiffness can be assessed by PWV in metres/second. Due to the pulsatile character of the blood flow through the arteries, the pulse wave spreads through them with a velocity that depends on their stiffness. The stiffer the arteries are, the higher the velocity of the pulse wave. The PWV can be measured by dividing the difference in distance by the time between the locations of the measurements. Applanation tonometry (Sphygmocor, AtCor Medical, West Ryde, Australia) is the most used method for these measurements, but arteriography and ultrasound are also used. Carotid-femoral PWV
(cfPWV) is commonly accepted as the gold standard measurement for arterial stiffness, and it has been demonstrated to predict cardiovascular disease.\textsuperscript{54}

In contrast to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), there seems to be no increased atherosclerotic plaque formation and generalised atherosclerosis in SSc.\textsuperscript{55,56} In SSc, the vascular changes consist mainly of endothelial damage, intimal and medial thickening, and collagen formation. All these result in narrowing of the blood vessel lumen and in a possible increase of arterial stiffness. Previously, it was suggested that the cfPWV in SSc was higher than in healthy controls, although the literature on this point is mixed.\textsuperscript{57-66} Only one study compared the cfPWV of SSc patients with both healthy controls and PRP patients; it did not find any difference between the three groups.\textsuperscript{57} Age and disease duration seem to be related to a higher cfPWV.\textsuperscript{58,61,65} One study found no difference in dcSSc and lcSSc, and one study found a higher PWV in dcSSc patients.\textsuperscript{60,62} However, the challenge in studying this patient population is the diversity of the expression of the disease, which may explain why the results are also diverse, and no definite conclusion can be drawn. Furthermore, the number of patients involved these studies is low (ranging from 15 to 75), meaning the diversity between patients has more significant consequences.

The PWV can also be determined at the trajectory of the upper limb but is performed less frequently. This is particularly interesting in RP patients, as not only is structural damage seen in the capillaries, but also in the arteries of the forearm.\textsuperscript{22,23} There are five studies that compare the carotid-radial PWV (crPWV) of SSc patients with healthy controls. Two studies revealed a higher crPWV in SSc patients, but three more recent studies found no significant difference between the groups.\textsuperscript{60,64,66-68} One study found a relation of crPWV with age and blood pressure.\textsuperscript{68} Advanced glycation end products (AGEs), measured by skin autofluorescences (SAF) which are thought to increase arterial stiffness, were also found to be related to crPWV.\textsuperscript{64} Liu et al. is the only group studying the site of the carotid-brachial (cbPWV) and brachial-radial (brPWV). They found no difference in cbPWV when they compared SSc patients to healthy controls, but there was a difference in crPWV and brPWV.\textsuperscript{60} This might suggest that the forearm is more involved than the upper arm.
TREATMENT

Patient education and lifestyle interventions that try to minimize provoking factors are most important in the treatment of RP. This entails preventing exposure of not only the hands or feet to cold, but the whole body. Aggravating factors such as smoking, repetitive finger trauma and stress should be stopped or minimised. If this is not satisfactory, patients can be treated with vasodilatory drugs.

The first step is a calcium channel blocker, such as nifedipine, which decreases peripheral vascular resistance and therefore increases peripheral perfusion. A systematic review by Rirash et al. demonstrates that calcium channel blockers may be useful in reducing the frequency, duration and severity of RP attacks. Higher doses may be more effective and the calcium channel blockers seem more effective in PRP than in SRP, however, evidence is of low to moderate quality. When calcium channel blockers are not tolerated, selective serotonin reuptake inhibitors or low dose angiotensin receptor blockers can be prescribed. Serotonin is a selective vasoconstrictor, and a pilot study found fluoxetine, a selective serotonin reuptake inhibitor, to be well tolerated and effective, but larger placebo-controlled trials are lacking. Angiotensin II is a strong vasoconstrictor; however, evidence to prescribe angiotensin receptor blockers for relief of RP is conflicting. A phosphodiesterase-5 inhibitor can also be tried, but in the Netherlands, with RP as indication, patients are not reimbursed. It improves the availability of nitric oxide, which is vasodilatory.

In patients with SRP secondary to SSc, intravenous iloprost, a prostacyclin analogue, is effective for reducing the frequency and severity of the RP attacks and also for preventing and healing digital ulcers (DU). When the DU are recurrent, the dual endothelin receptor antagonist bosentan is also demonstrated to be effective for reducing the number of new DU. There is also some evidence suggesting long-term bosentan enhances the microvasculature, as seen with NCM.

When patients cannot tolerate vasodilatory drugs, remaining options are limited. While sympathectomy as a treatment for RP has been tried in the past, the thoracic procedure was invasive, and improvement of complaints was only short-term in some of the patients, and it became obsolete. With the development of endoscopic techniques, the
The aim of Chapter 7 is two-fold. First, it describes the arterial stiffness in patients with SSc compared to sex- and age-matched healthy controls. Second, it examines the potential effect of bosentan on the macrovasculature, as assessed with PWV. In Chapter 8, the feasibility of an improved and minimally invasive thoracic sympathectomy procedure, the single-port thoracoscopic sympathectomy, as treatment for treatment-resistant RP is evaluated.

**AIMS AND OUTLINE OF THE THESIS**

Patients with RP can develop a CTD, with RP being the first presenting symptom of the CTD in most patients. This indicates that, after the occurrence of RP, there is a window of opportunity for early diagnosis and intervention. Therefore, it is important to understand how the microvasculature and macrovasculature develop over time in these patients, focusing on the difference between PRP and SRP. In this thesis, several aspects of the microvascular and macrovascular changes, including pathophysiology, diagnostics and treatment, are studied. Figure 6 presents an overview of the chapters.
Figure 6. Chapter overview.
REFERENCES


Chapter 1


