CHAPTER 9

Summary, general discussion and future perspectives
RAYNAUD’S PHENOMENON (RP) IS A PREVALENT CONDITION, ESPECIALLY IN YOUNG WOMEN.1

Although new knowledge about the pathophysiology of RP is emerging, it remains incompletely understood. However, in some patients it can be the first presenting symptom of a severe underlying connective tissue disease (CTD). It is a challenge to differentiate between the primary and secondary form of the phenomenon (PRP and SRP). Nailfold capillary microscopy (NCM) and serology are the most used diagnostic tests for this.2 However, these tests are not always conclusive or available. Of all CTDs, systemic sclerosis (SSc) is most consistently associated with RP, which is generally the first presenting symptom. Systemic sclerosis can develop into a serious disease characterised by microvasculopathy, inflammation and tissue fibrosis, with high disease burden and mortality. Early interventions to prevent disease progression are lacking; therefore, early diagnosis and new treatment options are of great importance. Furthermore, RP itself can produce serious complaints which reduce the quality of life. As vasculopathy is more pronounced in SRP, quality of life is often more reduced compared to PRP.3,4 In patients refractory to conventional therapy, including lifestyle interventions and vasodilatory drugs, treatment options for RP are limited. This thesis addresses microvascular and macrovascular aspects of PRP and SRP. In Chapter 1, a general introduction was provided and the aims of the thesis were outlined.

The association between the mean ischemic time, as a measure of the degree of vasospasm assessed by cooling and recovery photo-electric plethysmography, and nailfold capillary abnormalities was assessed in Chapter 2. In patients with advanced SSc, capillary abnormalities were previously reported to be associated with the severity of digital ischemia, the development of digital ulcers (DU) and negatively associated with blood perfusion.5,7 However, in RP patients with a wider spectrum of disease than SSc, the association between digital blood perfusion and capillary changes has never been described. Our results indicate that, with longer ischemic time, more nailfold capillary abnormalities were found, such as loss of capillaries. The results also revealed the presence of dilated and giant capillaries. A difference in duration of recovery time between patients with PRP and SRP was found. The most severe ischemia was seen in the index finger, which is in line with previous findings of observational studies showing the index and ring finger to be most affected by DU.8,9
Summary, general discussion and future perspectives

The clinical vignette of Chapter 3 presents the progression of the pattern of the nailfold capillaries of a limited cutaneous SSc patient over time. This is a unique illustration because, over a period of ten years, several capillaroscopic images were collected. Furthermore, the whole nailfold view was captured; therefore, the same capillaries could be tracked over time, which makes progression of an active pattern into a late pattern visible.

In Chapter 4, we investigated whether the recovery period of a RP attack and the involvement of the thumb can help to differentiate between PRP and SSc-related RP. As mentioned in Chapter 2, we found a remarkable difference between the recovery time in SRP (also including patients with diagnoses other than SSc) and PRP. Therefore, we hypothesised that the ischemic time during the recovery might help to separate patients who are at risk of SSc from those who are not. In previous studies by Chikura et al., it appeared that the thumb is more frequently involved in SSc patients. Our results demonstrated that patients with a quick restoration of perfusion in all fingers (within ten minutes) and without involvement of the thumb are at low risk of having underlying SSc, with high negative predictive values. However, positive predictive values were low; therefore, a clinical assessment by a specialised physician and more specific additional tests such as serology and NCM are required for selecting patients who are more prone to SSc.

Chapter 5 describes the presence of NCM abnormalities in patients with different body mass index (BMI) categories. In a previous study, the risk of RP increased with a decreasing BMI. In patients with anorexia nervosa, nailfold capillary abnormalities were found, even in those without an underlying CTD. We studied a cohort of RP patients without underlying CTD and found a lower capillary count and more dilated and giant capillaries in patients who were underweight (BMI<18.5 kg/m²). Furthermore, patients who were overweight (BMI>25 kg/m²) had a shorter recovery period, as assessed with cooling and recovery photo-electric plethysmography, compared to patients with a healthy weight or underweight patients. These results indicate that capillary changes are associated with BMI and can occur independently of a CTD.

Nailfold capillary microscopy is suggested as a biological marker of internal organ involvement in patients with SSc. For example, it is associated with the presence
and severity of internal organ involvement in SSc cohorts, and also seems to predict mortality. In other CTDs, such as mixed connective tissue disease (MCTD), systemic lupus erythematoses (SLE), primary Sjögren’s syndrome (pSS) and rheumatoid arthritis (RA), where RP can also be a symptom of the disease, the presence and value of nailfold capillary abnormalities has been less well studied. In Chapter 6, the aim was to describe the nailfold capillary changes in a consecutive cohort of RP patients. Secondly, in this diverse cohort, we examined whether an association between NCM abnormalities and an abnormal pulmonary function test was present. This can be the first sign of an underlying interstitial lung disease or pulmonary arterial hypertension in this diverse cohort. Capillary changes such as giants, capillary loss or microhaemorrhages were classified as pattern into normal, non-specific, or one of the SSc patterns (early, active or late). An SSc pattern was prevalent in all CTDs ranging from 13% in RA to 88% in SSc, and in patients without a definite diagnosis, almost half had an SSc pattern on NCM. An abnormal pulmonary function test (defined as functional vital capacity (FVC) < 70% and/or diffusing capacity of the lung for carbon monoxide (DLCO) < 70%) was seen more frequently in patients with an SSc pattern on NCM. Absence of an SSc pattern had a high negative predictive value (88%); positive predictive values were low.

In SSc, vasculopathy is thought to occur mainly on a microvascular level. However, narrowing or even occlusion can also be seen in the more proximal medium-sized arteries. Vascular changes in patients with SSc, such as endothelial dysfunction, intimal and medial thickening, and collagen formation, cause arterial wall thickening and thus, narrowing of the lumen. These changes can result in arterial stiffness. We hypothesised that at an early stage of the disease, these changes in the arterial wall can be detected by functional arterial stiffness measurements. If so, selection of patients in whom early intervention is required to prevent severe vasculopathy might be possible. In animal models, endothelin, a vasoconstrictor, increases arterial stiffness, whereas in patients with SSc, bosentan, a dual endothelin receptor antagonist, improves microvascular status. Therefore, bosentan potentially has an effect on arterial stiffness in SSc patients; however, this has never been investigated. In Chapter 7, we compared the arterial stiffness in SSc patients with age- and sex-matched healthy controls and investigated the effect of bosentan on arterial stiffness. In these limited cutaneous SSc patients, the aortic, upper arm, or forearm arterial stiffness was not increased compared to the healthy controls. Although no effect on aortic and upper arm arterial stiffness
due to bosentan was found, we did find that the forearm arterial stiffness in the patients receiving usual care with the addition of bosentan decreased compared to the patients receiving usual care only. This may suggest that bosentan has an effect on the medium-small sized muscular arteries, in addition to the known effect on the microvascular level. This is a step forward in the early treatment of vascular complications and provides guidance for future studies.

Although patients can benefit from bosentan or other vasodilatory agents, in some patients with RP these have insufficient effect or have severe side effects for standard vasodilatory treatment. Treatment options for these patients are limited. Chapter 8 presents the results of a unique study in which a single-port thoracoscopic sympatheticotomy (SPTS) was only performed left-sided in therapy-resistant RP patients. The right-side was the non-intervention side; therefore patients were their own controls. In the past, surgical intervention by sympathectomy was a major invasive procedure, in which, in the opinion of most physicians, the surgical risks did not outweigh the benefits. However, recent significant improvements in the procedure have changed the sympathectomy to a more selective sympathicotomy. Although still requiring a general anaesthetic, the novel SPTS procedure is minimally invasive. The aim of the study was to assess the feasibility and efficacy of the SPTS procedure for its application in RP patients. One month post-operatively, patient satisfaction of the effects in the left hand was 100%. Furthermore, with objective measurements of the perfusion of the hands, we found a unilateral improvement on the intervention (left) side. No serious adverse events occurred in a follow-up period of at least ten months. Three patients had minor adverse events. Two of these patients experienced an increase in sweating in other areas, and one patient had dry skin on the fingertips of the intervention hand, which resolved spontaneously. In conclusion, SPTS is feasible and in the short-term is effective in improving hand perfusion in patients with RP.

**GENERAL DISCUSSION AND FUTURE PERSPECTIVES**

When a patient presents with RP, it could be the first sign of a severe underlying disease. Still, it is important to be aware that RP is idiopathic in most patients. While early diagnosis of a possible underlying disease is of importance, performing
expensive additional tests for every RP patient will lead to false positives and excessive diagnostics. Therefore, simple signs and non-invasive tools are needed to differentiate patients into high and low risk of having an underlying disease. Furthermore, in patients with underlying autoimmune diseases, the extent to which the vessels are involved is unknown. Whether it is restricted to a microvascular level, or whether vessels on a macrovascular level are involved is yet to be discovered. Finally, patients with RP who do not respond to, or do not tolerate vasodilatory drugs have limited treatment options.

**Differentiating between primary and secondary Raynaud’s phenomenon during the consultation**

When a patient with RP visits a physician, it is important to determine the cause. During the consultation, the patient elaborates on the complaints, after which a physical examination is conducted. This can help to decide whether PRP or SRP is more likely. The differential diagnosis of SRP, as discussed in the introduction of this thesis and presented in Table 2, is broader than autoimmune diseases alone.29

In addition to specific symptoms and signs in the search for specific diagnoses, other patient characteristics and differences in the RP attacks can help to decide whether PRP or SRP is more likely. Secondary RP is more likely when RP occurs for the first time in a patient over 30 years of age, and on average, patients with SRP also experience more severe complaints.30 Patients with PRP are most often young women, and about 25% have a first degree relative with RP.31 When the symptoms of RP are asymmetrical, vascular causes and other factors exacerbating the symptoms on one side, such as carpal tunnel syndrome, should be assessed.29,32 Further to these observations, thumb involvement was previously suggested.31 In line with this, in Chapter 4 we found that when the thumb is unininvolved, underlying SSc is unlikely. Furthermore, when there is quick restoration of perfusion after cooling, SSc is also unlikely. For clinical practice, it can be useful to know that patients with a quick restoration of perfusion in the fingers and with no involvement of the thumb are at low risk of having underlying SSc. However, the main limitation of this study is that the involvement of the thumb and the restoration period were assessed by a cooling and recovery procedure. It is unknown if the complaints the patient experiences in daily life, such as observations of thumb involvement and duration of the attack, are related to this procedure. This requires further investigation,
but these findings do suggest a role for thumb involvement and restoration period after an attack help to rule out SSc.

**Structural capillary changes as a biomarker**

Structural assessment of microvascular changes in patients with RP is possible using NCM. This non-invasive method provides images of the capillaries in the nailfold, where the loops are parallel to the skin surface and therefore visible with the use of a microscope. Because these nailfold capillaries are easily accessible, there is growing interest in this method. The SSc patterns described by Cutolo et al. seem to not only help to diagnose the disease, but also provide information about the stage of the disease. In line with this, progression of microvascular changes during the stages of the disease is seen in the patient described in Chapter 3. Conversely, regression of the disease can also be seen, such as after autologous stem cell transplantation. Therefore, in addition to the more established role of NCM to differentiate between PRP and SRP, there are several studies that investigate the role of NCM as a biomarker (i.e. as an objective characteristic of the pathogenic process as a predictor of disease involvement).

In multiple studies, an association was found between presence or severity of organ involvement and abnormalities on NCM in SSc. In Chapter 6 we also found an association between NCM abnormalities and pulmonary function tests in a consecutive cohort of RP patients, also including patients with CTD other than SSc. A possible explanation for this association might be that microvascular changes are also a major pathological feature in internal organ involvement, which cannot be visualised in vivo. However, these studies are cross-sectional, and although they suggest a potential role of NCM as a biomarker, the prospective value is not assessable. In SSc patients, a prospective association was found for capillary changes with the development of DU and digital trophic lesions. Smith et al. also found increasing ratios with severity of NCM pattern (late>active>early) for developing severe peripheral vascular (i.e. DU) or severe lung disease (i.e. DLCO<50%, FVC<50% or estimated pulmonary arterial pressure of >65 mmHg). Further prospective studies are required to clarify the place of NCM as a biomarker for disease progression and/or severity. This should not be limited to SSc patients, but also include patients with RP in other CTD, as early detection of pulmonary involvement in these patients is also of importance to make early intervention possible.
In clinical trials, NCM is used to assess the microvascular changes. However, the limitation of this observation is that progression of structural changes over time is slow (Chapter 3). Therefore, for possible improvement of the studied interventions, a long follow-up period is required. This can also partially explain why no change was found in NCM in Chapter 7. With improving techniques, Herrick et al. are able to assess functional flow measurements with videocapillaroscopy. This is a promising measure for future clinical trials, as functional measures are more likely to already reflect change over a short period of time.

**Capillary abnormalities due to causes other than underlying autoimmune disease**

With NCM, structural changes of the capillaries can be non-invasively visualised. Different changes can be seen, representing microvasculopathy. Frequently, the first feature of microvasculopathy is enlargement of the capillaries. This is thought to occur in response to tissue hypoxia, and may represent the first sign of endothelial damage to the vessel wall. In general, enlargement is seen as abnormal when the apex has a width of >50µm, and then it is classified as a giant capillary. It is thought that microhaemorrhages originate when a giant capillary is leaking because of damage to the vessel wall. Subsequently, when the vessel wall is too damaged, the capillary will be lost, and avascular areas arise. Finally, neovascularisation may be seen, visually represented by highly tortuous and bushy capillary loops. This process is depicted in Figure 1.

![Figure 1](image-url)

**Figure 1.** Simplified representation of the possible capillary changes in systemic sclerosis.
However, in addition to giants, capillary loss, haemorrhages and neovascularisation, non-specific changes can also be found on NCM in different RP patients. These changes, such as mild dilatation between 20 and 50 µm, or abnormal morphology, are not pathognomonic for SSc, and their exact meaning remains unknown. In Bernero et al.’s study, 18% of the patients with non-specific changes progressed to an SSc pattern in a period of five years. However, it is also possible that non-specific changes might be caused by factors other than CTD. This is also supported by Bukhari et al., who found subtle structural vascular changes, mainly mild dilatation of the capillaries, in patients with PRP.

Based on the findings in Chapter 2, several factors for these changes can be hypothesised. For example, frequent ischemia and reperfusion (i.e. frequent RP attacks) causing oxidative stress during the attacks might lead to subtle endothelial damage resulting in capillary changes seen with NCM. Another explanation could be that it is a compensation mechanism for the lack of oxygen during the RP attacks and, to supply the tissue with more oxygen, dilatation of the capillaries occurs. Finally, in patients with cold hands (i.e. most patients with RP), the hands are warmed in a temperature-controlled room before NCM to ensure the capillaries are visible. It is possible that some of the dilatation seen is a reaction to this relatively warm environment. However, we cannot be certain of the direction of the causal relation between the microvascular changes and severity of RP attacks as Chapter 2 was a cross-sectional study.

In addition to our findings, mechanical damage (e.g. in hand-vibration syndrome) also seems to cause microvascular abnormalities, especially capillary loss. Furthermore, in Chapter 5 we found more capillary abnormalities in patients who were underweight, which is in line with Klein-Weigel et al.’s findings in patients with anorexia nervosa. It could be postulated that perivascular fat is protective of capillary damage because it consists of adipocytes producing adiponectin, which is vasodilatory. However, future studies should investigate the role of perivascular fat in RP in more detail. To conclude, more factors than autoimmune diseases should be taken into account when analysing the nailfold capillaries.
Macrovascular involvement in systemic sclerosis
In general, macrovascular refers to the vessels larger than the capillaries and arterioles. In the upper extremity, this means that the digital arteries are defined as macrovascular. The upper extremity’s arterial supply is delivered through five main arteries, starting with the subclavian artery, followed by the axillary artery, brachial artery (upper arm), and splitting into the radial and ulnar arteries in the forearm. The radial and ulnar arteries anastomose by forming two palmar arches, and together supply the digital arteries.

While microvascular involvement in SSc is widely acknowledged, macrovascular involvement is more controversial. Macrovascular involvement is currently receiving more attention, and different structural and functional methods are used to assess this in SSc. Structural vascular changes of the arteries are described in, for example, the ulnar artery. Allanore et al. found structural damage of the digital arteries with magnetic resonance angiography. More recently, Schioppo et al. used power Doppler ultrasound to assess the resistivity index of the radial and ulnar palmar digital arteries (being defined as macrovascular), and concluded that abnormalities found in macro- and microvascular vessels are independent of each other, as they were not present at the same time in each patient. Currently, no gold standard exists for the assessment of macrovascular disease in SSc, and the methods used have different limitations.

The vascular wall changes in SSc are believed to start with endothelial damage, possibly the initial start of the disease, represented by the occurrence of RP as the first symptom. This subsequently leads to endothelial apoptosis and the endothelial layer, therefore, is disrupted, leading to increased vascular permeability. Clinically, this leads to the puffy hands as seen in an early stage of the disease in SSc patients. Because the endothelial layer is disrupted, intimal fibrosis develops over time due to, for example, mononuclear cells and vascular smooth muscle cells migrating into the intimal layer, and differentiation of vascular smooth muscle cells into myofibroblasts. A representation of these processes is outlined in Abdulle et al.’s review. These processes lead to narrowing of the lumen, and also lead to thickening of the arterial wall, possibly increasing arterial stiffness.

Non-invasive pulse wave velocity (PWV) measurements assess the arterial stiffness; the higher the PWV, the stiffer the arteries. The PWV is a functional measure of the
macrovasculature. However, there are mixed results in SSc patients (an overview of the studies on arterial stiffness performed in SSc patients using PWV measurements is presented in Table 1 for aortic and in Table 2 for upper extremity arterial stiffness). In Chapter 7, we found no difference in arterial stiffness, in line with the most recent studies. However, the heterogeneity of the disease means that with the small number of patients, no definite conclusion can be drawn. It is possible that there are differences between the two subtypes of the disease and that, for example, in diffuse cutaneous patients, arterial stiffness may progress parallel with the severity of skin involvement. Cypiene et al. found that the aortic stiffness increased in patients with diffuse cutaneous disease; however, they did not assess the upper extremity arteries. In Chapter 7, we only included patients with limited cutaneous disease, and future studies are required to examine this in diffuse cutaneous SSc patients. Another limitation is that with PWV measurements the brachial-ulnar artery trajectory is not validated, which is of particular interest in SSc as this artery seems to be affected more frequently. Therefore, it would be of interest to test feasibility and validation of PWV measurements of the ulnar artery in a larger cohort. We recently added the brachial-ulnar trajectory and began to collect the PWV data for consecutive patients at the department’s vascular laboratory.

Although the SSc patients in Chapter 7 did not have increased arterial stiffness compared to healthy controls, the arterial stiffness of the forearm improved in the patients using bosentan compared to patients with usual care only. This suggests that the dual endothelin receptor antagonist also has an effect on the medium-small muscular arteries in addition to the improvement of the microvasculature. However, before proceeding to treatment, it is necessary to gain more insight into the development and progression of the macrovascular involvement. With a better understanding of the process, future patients who will benefit from improved management, or even prevention, of macrovascular involvement can be more carefully selected.

To gain more insight, an improvement in techniques is necessary. For example, local PWV measurements were not possible during the study described in Chapter 7 because of technical limitations with the small diameter of the arteries. However, with technical advances this will be possible in the near future. Local PWV measurements of radial, ulnar and digital arteries will make it possible to localize the vascular changes more precisely.
<table>
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<th>Reference (year of publication)</th>
<th>SSc, n</th>
<th>lcSSc, n</th>
<th>dcSSc, n</th>
<th>Female, %</th>
<th>SSc age (years), mean ±SD</th>
<th>DD (years), mean ±SD</th>
<th>SSc cfPWV (m/s), mean ±SD</th>
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\textsuperscript{a}Mean ±SD calculated with median (IQR) by method of Wan et al.\textsuperscript{68}

**Table 2.** Overview of studies in which upper limb pulse wave velocity was assessed in SSc patients

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<th>lcSSc, n</th>
<th>dcSSc, n</th>
<th>Female, %</th>
<th>SSc age (years), mean ±SD</th>
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<td>Cypiene* (2008)</td>
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<td>Dadoniene (2015)</td>
<td>47</td>
<td>35</td>
<td>12</td>
<td>87</td>
<td>52.6 ±11.2</td>
<td>12.7 ±9.5</td>
<td>9.0 ±1.6</td>
<td>47</td>
<td>52.6 ±7.7</td>
<td>8.6 ±1.2</td>
<td>Advanced glycation endproducts no difference</td>
<td></td>
</tr>
<tr>
<td>Bartoloni (2016)</td>
<td>34</td>
<td>22</td>
<td>12</td>
<td>100</td>
<td>61.0 ±15.0</td>
<td>17.0 ±12.0</td>
<td>8.3 ±1.0</td>
<td>34</td>
<td>59.0 ±13.0</td>
<td>8.3 ±1.0</td>
<td>no difference</td>
<td></td>
</tr>
<tr>
<td>Cypiene* (2017)</td>
<td>74</td>
<td>98</td>
<td></td>
<td></td>
<td>53.3 ±11.5</td>
<td>13.3 ±10.4</td>
<td>7.9</td>
<td>156</td>
<td>42.8 ±11.1</td>
<td>8.0</td>
<td>Mean blood pressure, age no difference</td>
<td></td>
</tr>
<tr>
<td><em>Upper arm (carotis-brachialis)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu (2011)</td>
<td>25</td>
<td>17</td>
<td>8</td>
<td>88</td>
<td>47.2 ±10.1</td>
<td>4.9 ±5.6</td>
<td>6.7 ±1.8</td>
<td>25</td>
<td>46.2 ±11.2</td>
<td>6.5 ±2.1</td>
<td>no difference</td>
<td></td>
</tr>
<tr>
<td><em>Forearm (brachialis-radialis)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Liu (2011)</td>
<td>25</td>
<td>17</td>
<td>8</td>
<td>88</td>
<td>47.2 ±10.1</td>
<td>4.9 ±5.6</td>
<td>12.1 ±7.1</td>
<td>25</td>
<td>46.2 ±11.2</td>
<td>8.3 ±3.5</td>
<td>higher in SSc compared to HC</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ±SD calculated with median (IQR) by method of Wan et al.64
brPWV: brachial-radial (forearm) pulse wave velocity, cbPWV: carotid-brachial (upper arm) pulse wave velocity, crPWV: carotid-radial (whole arm) pulse wave velocity, dcSSc: diffuse cutaneous systemic sclerosis, DD: disease duration, HC: healthy controls, lcSSc: limited cutaneous systemic sclerosis, SSc: systemic sclerosis
Summary, general discussion and future perspectives

Existing and new treatment options for Raynaud’s phenomenon

The first step in treatment of RP is lifestyle intervention. Preventing exposure to cold and discontinuing smoking are the two most important steps. In some patients, this is enough, but in patients with remaining complaints in daily life, vasodilatory drugs can be prescribed, most often starting with calcium channel blockers, but angiotensin receptor antagonists or selective serotonin reuptake inhibitors can also be prescribed. Of these vasodilatory drugs, only nifedipine has been proven to decrease the frequency of RP attacks, and is therefore the first choice of oral medication. In patients with DU or severe complaints refractory to oral vasodilatory drugs, continuous intravenous prostacyclin can be given. This treatment is expensive because of the need for supervised intravenous administration at the hospital, but in the short-term does seem to improve the RP attacks and healing of DU. In some cases, bosentan is prescribed to prevent the development of new DU. Bosentan seems to improve microvascularization, but does not improve RP complaints such as pain. In the study described in Chapter 7, we also found bosentan had no effect on the health-related quality of life (data not published).

In some patients, complaints are refractory to all of these vasodilatory drugs. They still experience severe complaints in daily life, which is, of course, also influenced by other factors such as stress and coping. Furthermore, all these drugs can have side effects such as dizziness, nausea, and malaise. In particular, in patients with low blood pressure, these vasodilatory drugs may be poorly tolerated. For patients not tolerating these vasodilatory drugs, treatment options are limited.

In patients with treatment-resistant RP, SPTS has been shown to be a novel treatment option, as described in Chapter 8. This therapeutic option (i.e. sympathectomy) has been renewed and is now minimally invasive. Our results indicated that hand perfusion improved subjectively and objectively after one month. After a follow-up period of one year, patients were offered the option of having right-sided SPTS, which all eight patients chose to do. The main limitation is that long-term effects need to be established, as in the long-term follow-up in previous studies of the conventional sympathectomy some patients developed complaints again; however, in most cases this was less severe compared to before surgery. To understand what the long-term effects of SPTS are, follow-up of the eight patients is on-going, and patients who undergo the procedure in the future will also be followed. Although the procedure is minimally invasive, it is still associated with several known surgical risks; therefore, this procedure should only be
conducted in frail patients after careful consideration. Data on patients undergoing the SPTS is structurally collected and will be analysed in the future. This will allow us to analyse patients with PRP and SRP separately.

In SSc patients, pulmonary and cardiac involvement are of high priority as they represent the greatest mortality risk. However, RP can reduce quality of life and DU can be very painful and limiting in daily life. Current therapies for DU (e.g. prostacyclin infusions and bosentan) are expensive. In SSc, the treatment options to prevent complications are scarce, as most treatments are designed to stabilize the disease. Ulcer healing or improvement was seen after conventional sympathectomy in 95% of the SRP patients because of improved perfusion in the hands. Therefore, for our future study it is of interest to discover if the SPTS procedure improves healing or even prevents DU and critical ischemia in SSc patients.

Although the long-term effects need to be established, and effects are limited to the hands, SPTS is a possible treatment option for patients with treatment-resistant RP. As described in Chapter 8, we took the first important step to show the effectiveness and feasibility of the procedure in the short term. With these results, we are now able to incorporate the procedure into current patient care for those with treatment-resistant RP.

**CONCLUSION**

Raynaud’s phenomenon is an important early symptom to address in improving vascular involvement in SSc. It can reflect underlying disease many years before other symptoms become clinically apparent. Therefore, it creates an important window of opportunity. This thesis sheds light on the pathophysiology of RP and differences between PRP and SRP, to improve further understanding of the mechanisms leading to this phenomenon. Furthermore, this thesis supports the on-going search for treatment options for RP and vascular involvement of SSc.
REFERENCES


Summary, general discussion and future perspectives


