EVIDENCE-BASED MEDICINE

Evidence-Based Interventional Pain Medicine
According to Clinical Diagnoses

25. Ischemic Pain in the Extremities and Raynaud's Phenomenon

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■ **Abstract:** Two important groups of disorders result from an insufficient blood supply to the extremities: critical vascular disease and the Raynaud's phenomenon. The latter can be subdivided into a primary and a secondary type. *Critical ischemic disease* is often caused by arteriosclerosis due to hypertension or diabetes. *Primary Raynaud's* is idiopathic and will be diagnosed as such if underlying systemic pathology has been excluded. *Secondary Raynaud's* is often a manifestation of a systemic disease. It is essential to try to establish a diagnosis as soon as possible in order to influence the evolution of the disease.

A sympathetic nerve block can be considered in patients with *critical ischemic vascular disease* after extensive conservative treatment, preferably in the context of a study (2B±). If this has insufficient effect, spinal cord stimulation can be considered in a selected patient group (2B±). In view of the degree of invasiveness and the costs involved, this treatment should preferably be applied in the context of a study and with the use of transcutaneous pO_2 measurements.

In case of *primary Raynaud's*, life style changes are the first step. Sympathectomy can be considered as a treatment of Raynaud's phenomenon (2C+), but only after multidisciplinary evaluation of the patient and in close consultation with the patient's rheumatologist, vascular surgeon or internist. ■

Key Words: evidence-based medicine, ischemic pain, Raynaud's phenomenon

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INTRODUCTION

This review on ischemic pain in the extremities and Raynaud's phenomenon is part of the series "Evidence-based Interventional Pain Medicine according to clinical diagnoses." Recommendations formulated in this chapter are based on "Grading strength of recommendations and quality of evidence in clinical guidelines" described by Guyatt et al.,[1] and adapted by van Kleef et al. in the editorial accompanying the first article of this series[2] (Table 1). The latest literature update was performed in September 2010.

Pain takes a central position in a varied group of disorders, due to insufficient blood supply to the extremities. It results in ischemia of the peripheral tissues, which causes pain and often functional limitation in the patient. Pain is a signal indicating a serious problem. Two important groups of disorders can be distinguished: critical vascular disease[3] and the Raynaud's phenomenon.[4–6] The latter can be subdivided into a primary and a secondary type.[4,5] The context and the cause of each of these three groups is different, which means that good diagnostics are essential to identify and influence the prognosis.

EPIDEMIOLOGY

Since there are two subgroups, the incidence and epidemiology of these groups is also different.

Critical ischemic vascular disease is most common in patients over 55 years old as a result of arterial vascular disease. The annual incidence is 0.25 to 0.45 patients per 1,000 population. The disease initially presents as vague pain in the extremities, but ends in necrosis and amputation of the extremity in the course of 5 years.

Raynaud's phenomenon occurs frequently in our society with an incidence of 3% to 21%.

There is a primary form, also termed Raynaud's disease, in which no underlying cause for the symptoms can be found. The secondary form, indicated with the general term Raynaud's syndrome, does have an underlying cause. It is usually associated with systemic pathology, in particular rheumatic pathology.

The main pathophysiology is impaired perfusion of the peripheral parts of the extremities. Initially, it manifests itself as white discoloration of the fingers or toes and later as blue discoloration leading to ulcers. The most important diseases to consider include systemic diseases such as generalized sclerosis and scleroderma. In 90% of the cases with these diseases, Raynaud's phenomenon is the first symptom. Thromboangiitis obliterans or Buerger's disease[7] can also be classified under secondary Raynaud's. The age at onset is usually under 45 years. It is an immune-mediated arteritis of which the pathology is not fully known, but smoking or smoke cessation can seriously affect the symptomatology. The incidence of the diseases varies considerably throughout the world. In the U.S. and Europe, the

Table 1. Summary of Evidence Scores and Implications for Recommendation

Score	Description	Implication
1A+	Effectiveness demonstrated in various RCTs of good quality. The benefits clearly outweigh risk and burdens	Positive recommendation
1B+	One RCT or more RCTs with methodological weaknesses, demonstrate effectiveness. The benefits clearly outweigh risk and burdens	
2B+	One or more RCTs with methodological weaknesses, demonstrate effectiveness. Benefits closely balanced with risk and burdens	
2B±	Multiple RCTs, with methodological weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens	Considered, preferably study-related
2C+	Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens	
0	There is no literature or there are case reports available, but these are insufficient to prove effectiveness and/or safety. These treatments should only be applied in relation to studies	Only study-related
2C–	Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	Negative recommendation
2B–	One or more RCTs with methodological weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	
2A–	RCT of a good quality which does not exhibit any clinical effect. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	

RCT, randomized controlled trial.

incidence is 0.5% to 15%, whereas the incidence mounts to 60% in some Asian countries. It is not clear how this large difference can be explained; it may be related to smoking and the type of tobacco used.

ETIOLOGY

As indicated above, the etiology of the diseases is different.

Critical ischemic disease is often caused by arteriosclerosis due to hypertension or diabetes. Prevention by means of proper health hygiene is important and can influence the incidence and severity as well as the prognosis.

Primary Raynaud's is idiopathic and will be diagnosed as such if underlying systemic pathology has been excluded.

Secondary Raynaud's is often a manifestation of a systemic disease. It is essential to try to establish a diagnosis as soon as possible in order to influence the evolution of the disease. A sclerotic disease can indeed have a large impact on the functioning of vital organs such as the lungs, liver, or kidneys. Because secondary Raynaud's also occurs in other disorders such as Buerger's disease or even as an expression of a paraneoplastic phenomenon, these should always be considered. In some cases, it can be an adverse effect of chemotherapeutics.[8]

Buerger's disease appears to be an immune-mediated pathology, occurring both in men and in women. The symptoms already present at an early age, but are predominantly determined by smoking behavior. The first step in the treatment is therefore to refrain from tobacco use.

Table 2 gives an overview of the differences between primary and secondary Raynaud's phenomenon, based on a recent publication by Pope.[9]

Table 2. Differences between Primary and Secondary Raynaud's Phenomenon

	Primary	Secondary
Incidence	3% to 5%	0.2%
In combination with other diseases	No	Yes
Associated with antibodies	No	Often
Dilated capillaries in nail bed	No	Often
Familial predisposition	Yes	Yes
Connective tissue disorders in family	Yes	Yes
Medicinal treatment necessary	Rarely	Often
Complications	No, rarely	Yes
Improves after some time	Yes, often	Sometimes

From Pope JE[9] Reprinted by permission of the publisher.

PATHOPHYSIOLOGY

The exact pathophysiological mechanism remains as yet largely unclear. However, it has been shown that the physiological vasoconstriction on noradrenaline is enhanced by cold and that there is an increased sensitivity to α_2-agonists and serotonin. The vasoconstrictive endothelin-1 would also be involved, and the Calcitonin Gene Related Peptide (CGRP) and Cyclooxygenase supposedly play a (modulating) role.[10]

The primary or idiopathic form (Raynaud's disease) often presents without an apparent cause and has a favorable course over time. In case of the secondary form (Raynaud's syndrome), there is often a disorder of the connective tissue, collagen or a rheumatic disease, often with autoimmune features (scleroderma, Sjögren's disease, rheumatoid arthritis, systemic lupus erythematosus, polymyositis) or a peripheral vascular disease (thromboangiitis obliterans or Buerger's disease). In rare cases, it occurs in combination with a malignancy or chemotherapy (cisplatinum, bleomycin, and vincristine).

I. DIAGNOSIS

I.A HISTORY

The clinical history will mainly include pain in the extremities. In case of critical ischemic disease due to arteriosclerosis, patients often indicate evolution of nonspecific pain in the extremities while walking that disappears at rest. The first symptom is usually intermittent claudication followed by an increasingly serious symptomatology over the years. Eventually, slow-healing ulcers will develop.

Critical ischemic disease predominantly occurs in the older population. This is in contrast to Buerger's disease in which the first symptoms are also atypical pain with eventual discoloration and ulceration. Patients with Raynaud's phenomenon mostly complain of pain in the distal parts of extremities, often accompanied by white discoloration of the extremities. At a later stage, the discoloration darkens and ulcers may eventually develop.

I.B PHYSICAL EXAMINATION

Ischemic pain is usually accompanied by a discoloration of the extremities. This is mostly a white

discoloration of the distal parts of extremities, but it may change to a dark blue, color. Also important is that there are no arterial pulsations in the affected area. The extremity will feel colder and may show skin lesions that heal very poorly in a later stage. The distal peripheral parts may show a tendency to necrosis.

General examination to evaluate the patient's health (weight loss, malignancy) is relevant. The blood pressure should be measured and examination focusing on disorders of the connective tissues or on peripheral vascular disease should be carried out. The hands and feet should be inspected (wounds, ulcers); presence of dilated capillaries in the nail bed is also important.

I.C ADDITIONAL TESTS

Additional laboratory testing (sedimentation, antibodies, renal function) focusing on autoimmune disorders can best be performed by an internist/rheumatologist.

In case of critical ischemic vascular disease, the imaging of the coronary arteries will be important, because it provides information about the prognosis and about whether surgical intervention could be useful. Imaging is less relevant in cases of Buerger's disease and Raynaud's phenomenon; clinical and laboratory examination will provide sufficient information to make the diagnosis.

Once the diagnosis has been established, the evolution can be followed by means of capillaroscopy, which determines both the number of capillaries and the rate of red blood cell circulation. The determination of the transcutaneous oxygen saturation is also a parameter indicating the severity of the disease; it can also be used to demonstrate improvement in the microcirculation resulting from particular treatments.

I.D DIFFERENTIAL DIAGNOSIS

In cases of secondary Raynaud's especially, it is important to demonstrate or exclude concomitant disorders. Severe vascular disease may lead to organ damage. Medicinal therapy is often indicated. The primary form may resemble acrocyanosis (blue discoloration of the nails) and primary livedo reticularis (red-blue discolored skin in a reticular pattern); both are caused by reduced perfusion of the skin and are enhanced by cold exposure and emotional stress.

II. TREATMENT OPTIONS

A. II.A CONSERVATIVE MANAGEMENT FOR ISCHEMIC VASCULAR DISEASE

Patients with pain due to a vascular disease initially receive conservative and pharmacological therapy that aims at treating the underlying cause. If the symptoms persist, it may be decided to perform vascular surgery. The patient group discussed in this chapter concerns inoperable, vascular patients with pain at rest and/or ulcers (Fontaine III en IV)[11] (Table 3).

A. II.B INTERVENTIONAL MANAGEMENT FOR ISCHEMIC VASCULAR DISEASE

The treatment of these patients is aimed at pain reduction and cure of the ulcers in order to prevent amputation. The literature mentions two methods:

1. Sympathectomy
2. Spinal cord stimulation

Sympathectomy

Sympathectomy primarily has a vasodilatatory effect on the collateral circulation resulting from a reduced sympathetic tone. Improved oxygenation of the tissues leads to less tissue damage, which results in decreased pain and increased healing of the ulcers. Pain reduction also occurs due to the interruption of sympathetic nociceptive interaction.

Three randomized studies were reported in the literature. Only Cross and Cotton[12] found significant pain reduction in the group treated with chemical lumbar sympathectomy compared to the control group (bupivacaine injection) (66.7% vs. 23.5%), but no changes in the ankle-brachial index. The two other randomized controlled trials (RCTs) did not show any objective advantages.[13,14]

Over the years, however, several cohort studies have been conducted examining the effect of sympathectomy,

Table 3. Classification of Perfusion Disorders in Peripheral Arterial Vascular Disease according to Fontaine

Stage I	No symptoms (sufficient peripheral circulation)
Stage II	Pain upon exertion, intermittent claudication
IIa	ability to walk > 100 m
IIb	ability to walk < 100 m
Stage III	Pain at rest in the extremity concerned and in the supine position due to a poor muscle perfusion. The pain often temporarily decreases if the leg is dependent
Stage IV	Trophic disorders such as necrosis/gangrene

either surgical or chemical. Sanni et al.[15] concluded in their review that although the RCTs did not support its use, many cohort studies have shown a positive effect of sympathectomy in patients with critical ischemic vascular disease. A retrospective study by Repealer van Driel et al.,[16] including 60 successive surgical lumbar sympathectomies, showed good results (no rest pain, healing of ulcers and no major amputations) in 48% of the patients after 6 months.

Keane[17] performed lumbar chemical sympathectomy using phenol 6% under X-ray guidance in 132 patients with critical ischemic vascular disease. Favorable results (no rest pain, warm extremity, and no amputation) were obtained in 52% of the patients after a follow-up of 16 months. Mashiah[18] studied 373 patients with critical ischemic vascular disease who were treated with lumbar chemical sympathectomy. Success (no pain, healing of ulcers after 6 to 12 months and no amputation) was achieved in 58.7% of the patients. The amputation ratio was 20% and the mortality was 9%. Although the effect of sympathectomy in critical ischemic vascular disease is not consistent, several studies have shown a trend toward better pain reduction and ulcer healing, which justifies its consideration.

Spinal Cord Stimulation

Spinal cord stimulation (SCS) has been used to treat a variety of chronic pain syndromes since 1967. The effect of SCS is probably based on several mechanism of action.[19] In 1996, Jivegard et al.[20] published a randomized study on the effect of SCS in 51 patients with critical ischemic vascular disease with a follow-up of 18 months. He concluded that SCS resulted in better pain reduction than treatment with analgesics, but there was no significant difference in amputation rates between both groups. A subgroup analysis in patients without arterial hypertension did show a significant difference in amputation percentages.

A Belgian national study by Suy et al.[21] showed no significant difference in amputation percentages, although there was a tendency favoring fewer amputations in the group receiving SCS. A randomized study by Klomp et al.[22] including 120 patients with critical ischemic vascular disease showed that SCS with pharmacological treatment was not significantly better with respect to amputation scores at 2-year follow-up than the group receiving pharmacological treatment alone. In 2001, the same research group published the results of a subgroup in whom the difference in transcutaneous pO_2 between a lying and a sitting position was > 15 mm Hg, and who showed a significant amputation reduction.[23] Several nonrandomized studies have demonstrated a significantly lower amputation percentage in SCS groups.[3,24–26]

A Cochrane Review of 2005 concluded that SCS in critical ischemic vascular disease: (1) leads to fewer amputations; (2) provides better pain relief; and (3) restores more patients to Fontaine stage II.[3] Patients receiving conservative treatment exhibited more adverse effects due to medication, including: (1) gastrointestinal hemorrhage; (2) nausea; and (3) dizziness. It should be noted that SCS also is associated with complications including implantation problems, as well as additional intervention due to lead migration and infection. SCS is more expensive: 36,500 Euros (SCS) vs. 28,600 Euros (conservative).

Spinal cord stimulation may reduce amputation rate and pain in selected patients with critical ischemic vascular disease that is refractory to conservative and minimally invasive pain treatment.

A. II.C COMPLICATIONS OF INTERVENTIONAL MANAGEMENT FOR ISCHEMIC VASCULAR DISEASE

Complications of sympathectomy and SCS are described in another article in this series, "Complex Regional Pain Syndrome (CRPS)."[27]

A. II.D EVIDENCE FOR INTERVENTIONAL MANAGEMENT FOR ISCHEMIC VASCULAR DISEASE

The summary of the evidence for the interventional management of extremity pain due to vascular disease is given in Table 4.

A. III RECOMMENDATIONS FOR ISCHEMIC VASCULAR DISEASE

A sympathetic nerve block can be considered in patients with critical ischemic vascular disease after extensive

Table 4. Summary of the Evidence for Interventional Management for Ischemic Vascular Disease

Technique	Evaluation
Sympathectomy	2B±
Spinal cord stimulation	2B±

conservative treatment, preferably in the context of a study. If this has insufficient effect, SCS can be considered in a selected patient group. In view of the degree of invasiveness and the costs involved, this treatment should preferably be applied in the context of a study, with transcutaneous pO_2 measurements recommended.

A. III.A CLINICAL PRACTICE ALGORITHM FOR ISCHEMIC VASCULAR DISEASE

Figure 1 represents the treatment algorithm for ischemic vascular disease.

A. III.B TECHNIQUE(S)

We refer to the paper in this series on "CRPS" for the techniques.[27]

B. II.A CONSERVATIVE MANAGEMENT FOR RAYNAUD'S PHENOMENON

The treatment of the primary form of Raynaud's phenomenon is usually conservative and not pharmacological. In case of primary Raynaud's, it is generally sufficient to inform the patient well and advise them to avoid provoking factors by wearing warm clothes, stopping smoking, taking sufficient exercise and avoiding vasoconstrictive medication. If pharmacological treatment is required, the vasodilators nifedipine (Ca^+-antagonist) and prazosin (α_1-blocker) have been studied most, but their effects have been disappointing.[4,5] The main problems encountered with these drugs are the adverse effects and the loss of efficacy long-term.

The treatment of secondary Raynaud's is initially aimed at the underlying disease. Figure 2 presents an algorithm for the conventional treatment of Raynaud's disease.

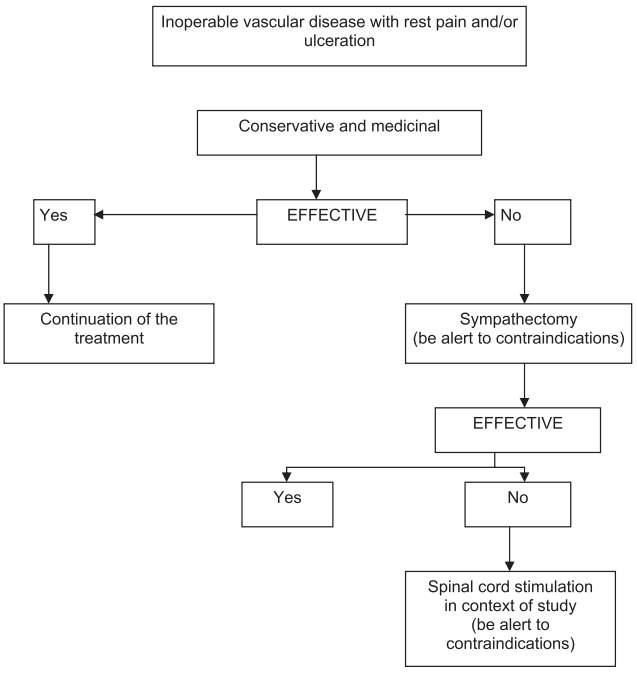

Figure 1. Algorithm for the treatment of critical ischemic vascular disease.

B. II.B INTERVENTIONAL MANAGEMENT FOR RAYNAUD'S PHENOMENON

Sympathectomy

Sympathectomy is not often performed in patients with Raynaud's. However, it can be considered in patients with dystrophic changes leading to ulceration. The literature does not include any RCTs. In their retrospective study (n = 28), Matsumoto et al.[28] found an initially favorable result in 92.9% after endoscopic thoracic sympathectomy (ETS); however, recurrent symptoms were subsequently noted in 82.1%. Despite recurrent symptoms, these patients did not exhibit ulcerations during the study period. Maga et al.[29] showed a long-lasting positive effect (follow-up 5 years) on microcirculation after ETS (Th2-Th4). Although symptoms returned in 28% of patients, no ulcerations were seen. A recent retrospective (n = 34) study by Thune et al.[30] demonstrated that most patients (83%) experience an immediate positive effect after thoracoscopic sympathectomy. In their study, this effect persisted in 33% of patients after a mean follow-up of 40 months.

B. II.C OTHER TREATMENTS

Botulinum Toxin A Injections

A study by Van Beek et al.[31] describes 11 patients with rest pain and finger ulcers who received perivascular injections with botulinum toxin A. There was an immediate favorable effect on the pain in 100% of the patients. In nine patients (82%), the ulcers healed spontaneously and this effect was still present in these patients after follow-up of as long as 30 months.

B. II.D COMPLICATIONS OF INTERVENTIONAL MANAGEMENT FOR RAYNAUD'S PHENOMENON

Complications of sympathectomy are described in the article "CRPS."[27]

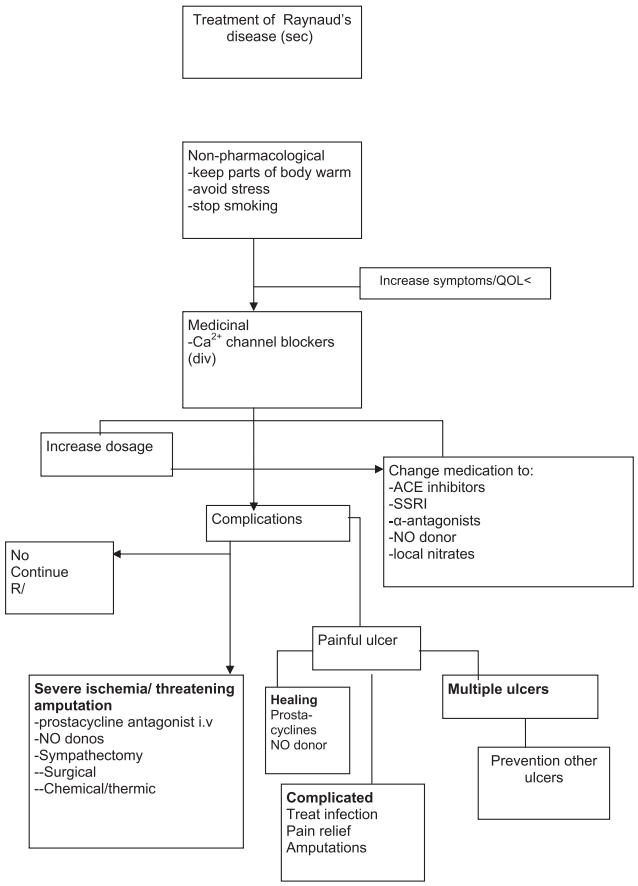

Figure 2. Algorithm for the conservative treatment of Raynaud's disease.

B. II.E EVIDENCE FOR INTERVENTIONAL MANAGEMENT FOR RAYNAUD'S PHENOMENON

The summary of the evidence for the interventional management of extremity pain due to vascular disease is given in Table 5.

B. III RECOMMENDATIONS RAYNAUD'S PHENOMENON

Sympathectomy can be considered in the treatment of Raynaud's phenomenon, but only after multidisciplinary evaluation of the patient and in close consultation with the patient's rheumatologist, vascular surgeon or internist.

B. III.A CLINICAL PRACTICAL ALGORITHM OF RAYNAUD'S PHENOMENON

The algorithm for the interventional management of Raynaud's phenomenon is illustrated in Figure 3.

Table 5. Summary of the Evidence for Interventional Management for Raynaud's Phenomenon

Technique	Evaluation
Sympathectomy	2C+

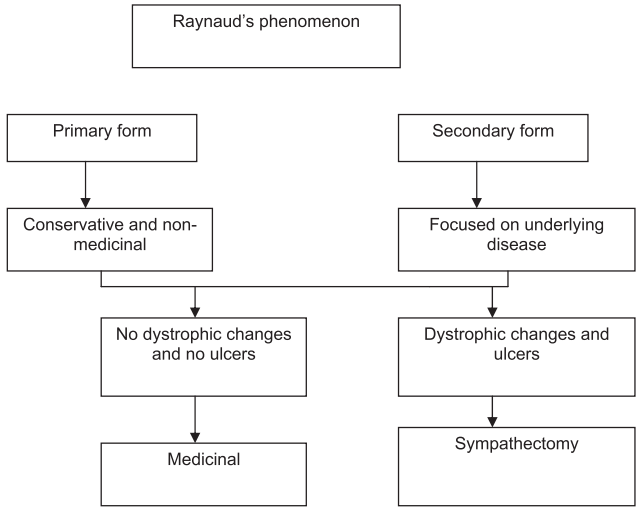

Figure 3. Algorithm for the treatment of Raynaud's phenomenon.

B. III.B TECHNIQUE

Both, the technique of SCS and of sympathetic nerve blocks are described in the article on CRPS.[27]

IV. SUMMARY

Patients with pain due to *critical ischemic vascular disease* should first receive conservative and medicinal treatment directed at the underlying cause.

A sympathetic nerve block can be considered in inoperable vascular patients with refractory rest pain and/or ulcers.

Considering the degree of invasiveness and the costs of the disease, SCS can be applied, preferably in the context of a study.

Treatment of the primary form of *Raynaud's* is generally conservative and nonmedicinal.

Treatment of secondary Raynaud's phenomenon is initially aimed at the underlying cause.

Sympathectomy can be considered in patients with refractory pain after extensive multidisciplinary evaluation and in consultation with the patient's rheumatologist, vascular surgeon or internist.

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