English translation of the dissertation

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DISSERTATION

On the influence of Deep Oscillation and biofeedback on subjective disease perception and tissue findings in systemic scleroderma

for the award of the academic degree Doctor medicinae (Dr. med.)

submitted to the Faculty of Medicine of Charité - Universitätsmedizin Berlin

by

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Paul Klee, "Forgetful Angel", pencil drawing, 1939. 29.5 x 21 cm. In this drawing by Paul Klee, who himself suffered from systemic scleroderma, changes of the hands associated with the disease can be seen. Paul Klee Foundation, Kunstmuseum Bern.

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ABBREVIATIONS

Fig. - Figure
ACR - American College of Rheumatology
AWE - Acral rewarming time
BVP - Blood volume pulse
ECP - Extracorporeal photopheresis
HAQ - Health Assessment Questionnaire
max - Maximum
min - Minimum
MLD - Manual lymph drainage
MRHS - Modified Rodnan Skin Score
n - Number of cases
p - Probability of error / significance value
PAH - Pulmonary arterial hypertension
PUVA - Psoralen plus UV-A, photoactivated chemotherapy
SC - Skin conductance

sd - Standard deviation

sec - Second(s)

SSc - Systemic scleroderma / systemic sclerosis

Tab. - Table

TEMP - Temperature

TENS - Transcutaneous electrical nerve stimulation

TO - Deep Oscillation

VAS - Visual analogue scale

1 INTRODUCTION

Systemic scleroderma, also known as progressive systemic sclerosis or scleroderma, affects approximately two in 100,000 people in Central Europe [1]. The disease is considered one of the most difficult rheumatic diseases to treat because it represents a heterogeneous group of disorders with many clinical manifestations and different courses [2].

As a chronic inflammatory systemic autoimmune disease of vascular connective tissue and internal organs, it belongs to the collagenoses. It initially leads to fibrosis and, as the disease progresses, to sclerosis of the tissue.

Skin thickening is a major clinical symptom of the disease and an important differential diagnostic criterion for classifying systemic scleroderma in relation to other collagenoses [3]. Local skin thickening, involvement of tendons and tendon sheaths, and synovial involvement lead to pain and impaired joint function, resulting in a considerable reduction in quality of life. In addition to the aesthetic problem, microstomia impairs food intake and dental care.

In up to 90% of affected patients the disease begins with Raynaud's phenomenon [4]. Vascular spasms triggered by cold or emotional stimuli first cause reduced tissue perfusion and may later lead to ulceration and necrosis, in extreme cases to the loss of fingers.

Because knowledge of the aetiology and pathogenesis remains insufficient, therapy is often polypragmatic. Physical treatment methods have been used for a long time, but until now have mainly been examined in small observational studies. A review article from 1997 [2] mentions ultrasound, CO2 laser, biofeedback, therapeutic exercise and acupuncture among the therapeutic methods. At the Department of Physical Medicine and Rehabilitation of the Faculty of Medicine of Charité - Universitätsmedizin Berlin, studies on sauna therapy and mild infrared-A therapy were conducted [5,6].

In recent years diagnostic methods and parameters for monitoring disease course in clinical studies have improved considerably. However, methods suitable for everyday clinical practice for early diagnosis, status indices for disease activity and disease-related damage, and reliable prognostic criteria are still lacking [7]. At the time of this dissertation there was also no guideline for systemic scleroderma.

2 DISCUSSION OF THE PROBLEM

2.1 Epidemiology, pathogenesis and classification

Systemic scleroderma, abbreviated below as SSc, is a rare chronic inflammatory systemic disease of vascular connective tissue based on excessive production of collagen. In addition to local or extensive sclerosis and thickening of the skin, the disease also affects internal organs to varying degrees [8].

The name derives from the Greek words "skleros" (hard) and "derma" (skin). The disease may have been described for the first time by Curzio as early as 1753 [9].

Prevalence is reported as 3 to 24 cases per 100,000 inhabitants [1]. Women are affected in particular, with the disease occurring three to eight times more often in women than in men. Peak onset is between the ages of 30 and 50 years. Systemic scleroderma is found worldwide. The Black population appears to have an increased risk of disease, a younger age at manifestation and a more severe course [10]. The 10-year survival rate has improved significantly from about 50% in the 1970s and is currently between 70% and 90% [1]. Mortality depends on the degree of organ involvement, especially involvement of the heart, lungs and kidneys [1,10]. Pulmonary fibrosis and pulmonary arterial hypertension (PAH) are now the main causes of death associated with the disease [1].

Three main features characterize systemic scleroderma: damage to blood vessels (microangiopathy), markedly increased collagen formation, and an excessive inflammatory immune response (autoimmunity). The aetiology of the disease remains largely unknown, although many findings on pathogenetic pathways have become available in recent years. Direct and indirect genetic predispositions [11-14], epigenetic mechanisms [15], environmental influences [16-18], and infections with cytomegalovirus [19] and parvovirus B19 [20] are discussed as disease-modifying factors.

The interaction of the factors contributing to disease development is highly complex. A scientifically supported hypothesis postulates an interaction between the immune and vascular systems. Endothelial damage in small vessels can lead to increased permeability with oedema formation and infiltration by T lymphocytes and macrophages, as well as platelet aggregation and thrombus formation. This creates an imbalance in the regulation of vascular tone, with increased occurrence of vasoconstrictor substances such as endothelin [21] and serotonin, and vasodilator substances such as nitric oxides [4]. The result is a cycle of fibroblast proliferation, collagen deposition and further immune activation. Stimulation and proliferation of fibroblasts are based on elevated serum levels of various pro-inflammatory cytokines. These include interleukin-4 and interleukin-6 [22], transforming growth factor beta (TGF-beta), which is also produced by fibroblasts themselves, connective tissue growth factor [23], platelet-derived growth factor [24] and tumour necrosis factor alpha [25]. Fibroblasts promote overproduction of type 1 and type 3 collagen, fibronectin and proteoglycans. These fibrotic processes are initiated and amplified by endothelins [26]. The participation of antibodies against fibroblasts [27] and antibodies against the collagen-degrading matrix metalloproteinases 1 and 3 [28] is also discussed.

The result is chronic vasculopathy, which causes complications such as Raynaud's phenomenon, ulcerations, pulmonary arterial hypertension and acute renal crises [29], as well as ongoing inflammatory stimulation. This leads to excessive migration of fibroblasts, which deposit large amounts of collagen in the extracellular matrix of skin and organs and are responsible for clinically relevant fibrosis and therefore for skin sclerosis [30].

A characteristic feature of systemic scleroderma is extreme variability in the clinical picture and in disease progression [31]. Starting therapy therefore requires the most precise possible classification of the disease manifestation.

At present the classification proposed in 1980 by a subcommittee of the American College of Rheumatology (ACR) is used [32]. The sole major criterion is symmetrical scleroderma-like skin changes proximal to the metacarpophalangeal or metatarsophalangeal joints. Minor criteria are sclerodactyly, pitting scars or loss of substance of the skin pads of the distal phalanges, and bibasal pulmonary fibrosis. The criteria are fulfilled if the major criterion or at least two of the three minor criteria are present. Initially, specificity was given as 98% and sensitivity as 97% [32]. In clinical practice, however, sensitivity proved to be considerably lower; early forms and milder courses were not captured in about 30% of cases [33,34]. Early detection is essential, because many therapeutic concepts aim to reduce disease progression and therefore to prevent further organ damage. Diagnostic methods have improved significantly in recent years. Inclusion of the detection of specific antibodies and typical changes in capillaroscopy could substantially improve the classification criteria [35]. A joint working group of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) was working on a classification system that takes account of the new findings and current proposals [36].

2.2 Clinical picture

In order to reflect the many clinical manifestations of the disease, the descriptive division into limited systemic and diffuse systemic forms of scleroderma has become generally accepted [37]. The extent of skin involvement - either only distal to the elbow (limited systemic form) or also proximal to the elbow (diffuse systemic form) - is a major criterion for allocation because it is associated with organ involvement (Table 1).

In most patients with limited systemic scleroderma, Raynaud's phenomenon is the first manifestation. Skin sclerosis of the fingers and toes is another early symptom. Mild pulmonary fibrosis often occurs during the course of the disease; otherwise there is no or only mild sclerosis of the internal organs with slow progression. Early diagnostic methods include, in particular, detection of anti-centromere antibodies (50-60%) and anti-Th/To antibodies [38], as well as nailfold capillaroscopy, which visualizes typical findings of limited systemic scleroderma such as telangiectasias and megacapillaries [7]. Patients who show these disease features without cutaneous involvement are sometimes assigned to so-called scleroderma sine scleroderma, although it is not clear whether this form is a separate entity or should be classified as part of the limited form [39].

In patients with diffuse systemic scleroderma, scleroderma-like skin changes are found not only on the extremities but also on the trunk. Raynaud's phenomenon often begins less than one year before the skin changes. Diffuse systemic scleroderma has a less favourable prognosis because organ involvement occurs early and frequently. A palpable tendon friction rub is a common examination finding and is strongly associated with this form of systemic scleroderma and with an unfavourable prognosis [40]. Antibodies against DNA topoisomerase 1 (Scl-70) are detectable in 20-40% of cases [38], and avascular zones are seen in capillaroscopy [41].

Radiologically, periarticular osteoporosis and acro-osteolysis are found, sometimes also erosions [42]. Antibodies against RNA polymerase I, II and III (5-22%), fibrillarin (U3-RNP; approximately 3%), Th (7-2 RNA protein complex; 4-13%) or anti-collagen antibodies are detected less often [38]. Certain subgroups show features of rheumatoid arthritis. Up to 25% of these patients have elevated serum concentrations of rheumatoid factor [43].

The CREST syndrome, formerly considered a special form and named after calcinosis cutis, Raynaud's syndrome, oesophageal dysfunction, sclerodactyly and telangiectasias [8], is no longer used internationally as a separate category, because it is assigned to limited systemic scleroderma and does not differ clinically, serologically or prognostically from that form [39].

Systemic scleroderma must be differentiated from circumscribed scleroderma (morphea). This is characterized by localized scleroderma-like, sometimes hyperpigmented lesions limited to the skin and by a benign course [42].

Table 1: Classification criteria for limited and diffuse systemic scleroderma.

Limited systemic scleroderma: skin changes distal to the elbows and/or knees, with possible facial involvement; Raynaud's phenomenon is usually the first symptom and skin changes follow after months to years; organ involvement occurs later, with PAH and other organ manifestations usually milder; anti-centromere antibodies are frequent; prognosis is rather favourable except in PAH.

Diffuse systemic scleroderma: skin changes proximal to the elbows and/or knees; Raynaud's phenomenon often occurs at the same time as the skin changes; organ involvement is early and common, especially lung (PAH), heart, kidney and gastrointestinal tract; anti-Scl-70 antibodies are common; prognosis is variable and often more rapidly progressive.

Inflammation and fibrosis

The skin changes typical of scleroderma begin mainly on the hands and first appear as an oedematous phase in which patients complain of tight, swollen, sausage-like fingers. This phase gradually passes into the indurative phase. It is characterized by massive thickening and hardening of the dermis, while the epidermis is thinned. Both skin layers are firmly attached to the underlying tissues, restricting the free mobility of the skin at the surface. Consequences include reduced skin wrinkling, hair loss and reduced sweating. Hypopigmentation and hyperpigmentation may occur. Permanently dilated small blood vessels (telangiectasias) at the proximal nailfold and on the face may accompany the disease. The face appears mask-like and facial expression is restricted (amimia). A reduced mouth opening with perioral wrinkling ("purse-string mouth") and a shortened frenulum of the tongue are common; in addition to the aesthetic problem, these findings may cause difficulties with food intake and dental care. This is followed by an atrophic phase [44]. The skin is tight and tense, pale and waxy-shiny; the finger segments appear tapered ("Madonna fingers") (Fig. 1). Patients suffer from progressive restriction of finger flexion caused by the tension and the associated development of cutaneous and arthrogenic contractures, which can give the hand a claw-like appearance (Fig. 2) [45].

Fig. 1: "Madonna fingers". Fig. 2: "Claw hand".

In the advanced stage of the disease, arthralgias, joint effusions and swelling of large and small joints may occur. These are possibly partly caused by skin thickening and are associated with strong tissue tension [44]. Symptoms are intensified, leading to pain, impaired joint function and reduced quality of life. In the trunk-dominant form, sclerosis of the skin in the thoracic region may severely impair respiratory excursions [46].

Because improvement of the skin condition is associated with a more favourable survival rate [47,48], assessment of cutaneous involvement is essential. The Modified Rodnan Skin Score (MRHS) is currently considered the most suitable and reproducible method in clinical studies [48-51]. The MRHS evaluates skin characteristics in 17 body areas by clinical palpation using a four-point ordinal scale ranging from normal to severely sclerosed skin [50,52]. After addition of all values, the score ranges from 0 (no skin thickening) to 51 (grade 3 changes in all 17 regions). The areas examined are the fingers, hands, forearms and upper arms, feet, lower legs and thighs, face, chest and abdomen [49]. Although the MRHS is a simple and well validated method for assessing treatment success in SSc-related skin involvement, there are indications that it may not be sensitive enough to capture slight but clinically relevant changes within the same score [53,54]. Since the subjective MRHS is also subject to variation due to different perceptions by different examiners, assessment should be performed by the same well trained examiner [49]. In 2008 Kuwahara presented a new objective method (Vesmeter) for quantifying skin involvement, measuring hardness, elasticity and viscosity of the skin [54].

Reduced mobility of the hands and the facial area ("purse-string mouth"), which considerably affects patients, is assessed by measurements of tooth-row distance, hand strength, hand spreading and the distance between fingers and palm during fist closure [55,56].

After the skin, the gastrointestinal tract is the organ system most often affected by SSc (75-90%) [57]. This is manifested primarily by impaired oesophageal motility with reflux symptoms and swallowing disorders, malabsorption and intestinal atony [58]. The main features of clinically evident cardiac involvement include myocardial fibrosis, pericarditis, myocarditis, left heart failure and rhythm disturbances [44]. Dry eyes and dry mouth, with associated deterioration of dental status and taste, are also frequent complaints in systemic scleroderma [44]. Clinically manifest nervous system involvement occurs in up to 40% of those affected [59]. Disturbances of sexuality are also not uncommon. Men complain of erectile dysfunction [60], while women report dyspareunia, which may occur because of dryness and narrowing of the vaginal introitus [61].

The organ manifestation most dangerous for survival in patients with limited systemic scleroderma is pulmonary arterial hypertension (PAH). A first indication of respiratory system involvement, a frequent SSc-related cause of death [44], may be reduced carbon monoxide diffusion capacity [62]. Possible causes include pulmonary vascular damage, alveolitis and pulmonary fibrosis, or a combination of these three mechanisms. Resulting pulmonary hypertension may occur early, is present in up to 30% of cases and indicates a poor prognosis [44].

Vasculopathy

According to current knowledge, systemic scleroderma is based mainly on three interacting pathogenetic mechanisms: disturbance of collagen metabolism with massive collagen deposition and therefore skin thickening, an excessive immune response, and dysregulation of vascular tone. This vasculopathy is a serious and very early clinical feature and leads to complications such as Raynaud's phenomenon, pulmonary arterial hypertension, malnutrition or cardiac microangiopathy [63]. One of the most serious complications of vascular manifestations is renal crisis, which develops in about 3-18% of cases. Patients with diffuse systemic scleroderma and rapidly progressive skin fibrosis in the first years of disease are particularly at risk [64].

Raynaud's phenomenon is a relatively common symptom complex in the general population, with a prevalence of 3-5% [65]. In up to 90% of patients affected by SSc it occurs as the first symptom of the disease in the sense of peripheral vasculopathy [4]. Maurice Raynaud first described it as local asphyxia of the extremities [66]. It is characterized by vascular spasms of the fingers, usually triggered by cold or emotional stress. Vasoconstriction physiologically prevents heat loss from the fingers; in Raynaud's phenomenon, however, an excessive vasospastic reaction occurs. Clinically, a sudden sharply demarcated ischaemic blanching of individual fingers, more rarely toes, is followed by cyanotic blue discolouration and then reactive hyperaemia with redness (Fig. 3). This is also referred to as the "tricolour phenomenon" and is often accompanied by paraesthesias [65].

The frequency and severity of Raynaud attacks are much milder in warmer outdoor temperatures in summer than in winter [67]. The occurrence of vascular spasms during emotional stress has an anatomical basis: acral innervation is exclusively via noradrenergic sympathetic fibres that are connected to brain centres of emotional activity. Autonomic tension increases sympathetic tone and triggers vasoconstriction [68].

Fig. 3: "Raynaud's phenomenon". Fig. 4: "Acral ulcerations".

Raynaud's phenomenon occurs particularly frequently on the index, middle and ring fingers, while the thumb is often spared [69]. Later in the course, ulcerations may develop on the fingertips ("rat-bite necroses") (Fig. 4). Compared with involvement of the lungs, heart and kidneys, these are less important for life expectancy, but they can considerably impair hand function in everyday life and quality of life because of severe pain and stigmatization. Ulcerations at the fingertips are caused by circulatory disturbances. Over the interphalangeal joints and in the elbow region they arise because of excessively tense or thinned skin and through injuries [44]. Necroses may occur and may require amputation because of gangrene and wound, soft-tissue and bone infections. Risk factors for ulcerations include diffuse systemic scleroderma, male sex, lower age at first diagnosis of Raynaud's phenomenon and the presence of anti-topoisomerase I antibodies [70].

Pathogenetically, primary and secondary Raynaud's phenomenon are distinguished. Primary Raynaud's phenomenon occurs independently of underlying diseases or triggering factors and, at about 90%, is much more widespread than the secondary form [71]. The diseases most frequently associated with secondary Raynaud's phenomenon are collagenoses and vascular diseases. Repeated mechanical trauma and the use of specific disease-triggering medications are the main causes [71]. Collagenoses seem to account for a relatively small proportion [72].

Diagnosis is made clinically and by history, as well as by using a cold provocation test in which resting blood flow and the dynamics of perfusion change after a defined cold stimulus are measured. Acral rewarming time is a measure of cutaneous thermal conductivity and changes in blood flow [73]. To assess the later development of systemic scleroderma, detection of antinuclear antibodies (ANA) by immunofluorescence is useful as a screening test and succeeds in about 90% of cases. If positive, antibodies specific for SSc can then be determined: anti-centromere antibodies, anti-Scl-70 antibodies and anti-RNA polymerase III antibodies. Together with evidence of typical microangiopathy in capillaroscopy, this allows a simple and useful risk assessment [74].

To supplement objective measurement methods, quantification of the subjective perception of disease is also included. Recording the frequency and duration of attacks in a Raynaud diary and determining their severity by means of a visual analogue scale (VAS) allow reliable statements about disease burden and activity [52,75].

In relation to the musculoskeletal system, visual analogue scales are also used to assess the intensity of arthralgias in connection with calculation of the Disease Activity Score based on 28 joints (DAS 28) [52-53]. Evaluation of quality of life using specific, comparable questionnaires (HAQ, systemic-scleroderma HAQ and SF-36) has proved useful for making significant statements about disease course and the burden in everyday life [52,7].

2.3 Treatment options for systemic scleroderma

A major problem in the therapeutic management of systemic scleroderma is the individually highly variable and difficult-to-predict course of the disease [31], together with the fact that knowledge of aetiology and pathogenesis remains insufficient.

The aim of the therapeutic concept is to influence the different pathogenetic pillars [46]. The focus is on basic drug therapy to combat the inflammatory response, inhibit cutaneous and organ-related sclerosis, and improve microcirculation [42,46].

Anti-inflammatory therapy

Non-steroidal anti-inflammatory drugs such as indomethacin or naproxen may be considered as anti-inflammatory medication [44]. Immunosuppressants such as azathioprine and cyclophosphamide are also partly successful [76]. Photochemotherapeutic methods such as PUVA bath therapy and extracorporeal photochemotherapy or photopheresis (ECP) can be tried [77-79]. Overall, studies on these therapy options are not very convincing.

Antifibrotic therapy

For reduction of fibrosis, D-penicillamine was long considered an effective drug [80]. However, in a randomized controlled study conducted in 1999, no significant effect of this substance on skin fibrosis could be demonstrated [81]. The previously mentioned immunosuppressants cyclophosphamide and methotrexate are also said to have antifibrotic effects, but only relatively small effects with borderline clinical significance have been observed [82-84]. Partial success has been achieved with bosentan [85] and iloprost [86].

Therapy of vasculopathy

Raynaud's phenomenon, as an early symptom and characteristic feature of systemic scleroderma, is associated with direct trigger factors for fibrotic remodelling processes, ulcerations and their progression to gangrene with the risk of finger loss [4,63]. Reducing the frequency and severity of Raynaud attacks is therefore an important aim of therapeutic concepts. Various medications are currently used, although they often produce only limited effects and may cause unpleasant side effects [29].

The main drugs used are calcium antagonists such as nifedipine and amlodipine, the angiotensin II antagonist losartan and, when hypertension is also present, the alpha-1 receptor blocker prazosin. However, only moderate effects on the severity and frequency of Raynaud's phenomenon could be demonstrated for all three drug groups [87-90]. Treatment with the serotonin reuptake inhibitor fluoxetine also reduces the severity of Raynaud attacks, but their frequency remains unchanged [91].

For severe Raynaud symptoms and ischaemic acral ulcerations, iloprost is recommended in various studies [92-95]. Its pharmacological properties largely correspond to those of natural prostacyclin (PGI2). Compared with the other substances mentioned, the evidence for iloprost is the best [92]. Cyclic intravenous administration over three to five days, and in individual cases up to 21 days, has proved useful [94,95]. In addition, because of its vasodilatory, anti-inflammatory and platelet aggregation-inhibiting effects, it also improves acral circulatory disturbances and probably also lung function and intestinal absorption [93]. In therapy-resistant symptoms, phosphodiesterase V inhibitors such as sildenafil [96] may be tried for ulcer healing [97], and endothelin receptor antagonists such as bosentan may be tried for prevention of new ulcerations [85].

Among topical therapies, glyceryl trinitrate improved blood flow and reduced the frequency and intensity of Raynaud attacks [29]. New treatment approaches under investigation include botulinum toxin A injections [98] and periarterial sympathectomy [99].

Many drug and surgical therapies are associated with sometimes serious side effects [29] and should therefore be used only when supportive measures such as consistent protection of the whole body against cold [65] or skin care with fatty ointments [94] are insufficient.

The influence of nicotine on the severity and consequences of Raynaud's phenomenon is assessed negatively in the literature [94,100]. Studies that investigated risk factors separately for men and women could demonstrate this effect only for males. In women, however, an association between increased alcohol consumption and the occurrence of Raynaud's phenomenon was shown [101,102].

One of the most severe complications associated with vasculopathy is renal crisis. Mortality resulting from this complication has been markedly reduced in recent years, particularly through therapeutic use of ACE inhibitors [103]. The 10-year survival rate is now between 70% and 90% [1].

2.3.1 Physiotherapy in systemic scleroderma

For effective treatment of peripheral vascular complications and for early counteraction of contractures of the skin and joints, adaptive physiotherapy is central to existing treatment concepts for systemic scleroderma, especially because despite major progress in pharmacotherapy no satisfactory drug treatment exists.

The individual methods aim at local influence on pathological tissue changes, for example in skin, connective tissue and muscles, prevention of movement restrictions and modulation of autonomic processes. They are also directed at pain relief and improvement of general well-being [104]. The skin and joint findings and the disturbed acral blood-flow regulation present in SSc are accessible to physical methods.

The following treatment options are described.

Thermotherapy

Desired effects of heat applications include pain relief, modulation of muscle tone, increased extensibility of the skin, increased blood circulation and improved defence function. An undesirable effect may be an increase in oedema.

The use of heat supply in patients with SSc has been investigated several times. Infrared-A radiation in particular proved to be an effective method [5,105,106]. In a study conducted at Charité in 2005 and including 58 patients, serial application of mild whole-body hyperthermia by infrared-A irradiation (wavelength 780-1400 nm) reduced acral rewarming time and therefore improved Raynaud symptoms. Skin findings, lung function and general well-being could also be favourably influenced [105].

Local heat applications are also useful. Sandqvist achieved improvement in hand mobility, stiffness and skin elasticity by applying a paraffin pack in combination with a hand exercise programme [107].

Although cold is generally not recommended for the therapy of systemic scleroderma because of vasomotor instability in Raynaud's phenomenon [2], and protection against cold exposure is rather the goal [105], Fricke showed that intensive whole-body cold therapy can have a positive effect in selected patients with SSc. This effect is probably due to a reduction in swelling and a feeling of tension in the acral areas. Raynaud attacks were not observed [108].

Ultrasound therapy

Ultrasound is applied locally and in the sense of neural-therapeutic buildup [104]. A favourable effect of ultrasound in systemic scleroderma was reported as early as 1956. Two patients described by Tuchman showed a clear reduction in pain, skin firmness and stiffness of the hands [109]. Similar effects were also observed by Uhlemann in 1990 in 24 patients [110].

Exercise therapy

Active and passive movement exercises can prevent dermatogenic and arthrogenic contractures and have a favourable effect on skin vascularization [2]. In 2003 Pizzo had ten patients with SSc perform an eighteen-week mouth exercise programme that included both stretching exercises and grimacing. He achieved an improvement in mouth opening, which considerably facilitated eating, speaking and oral hygiene [111].

Similar effects were observed in 2003 in a group of 45 patients. Here the effects of a hand exercise programme were investigated (stretching for 10 seconds, 3 to 10 times per day). Joint mobility improved significantly after one month of stretching exercises and was still present one year after the start of exercises [112].

Massage therapy

Good clinical experience also exists with the use of different massage techniques. Vibrations loosen tissue. Circular, oscillating techniques are suitable for harmonizing phases of breathing. Mild shaking is indicated for the treatment of atelectasis.

Because a local reflex action dilates the capillaries [113], massage applications can also increase skin temperature [2]. Since the skin vessels are functionally severely disturbed by the disease, patients with SSc show drastically reduced skin oxygenation [114]. Connective tissue massage, with its skin-hyperaemic effect, can achieve improvement here.

Manual lymph drainage is also considered beneficial [115], since in the early stage it reduces oedema of the extremities [116] and can positively influence joint pain, most likely because of its sympatholytic effect [116].

Controlled studies on the effects of the different massage techniques are not currently available. Only one study comments on the influence of underwater massage and was able to demonstrate an improvement in local blood flow [117].

Electrotherapy

A review article states that both electrical acupuncture and transcutaneous electrical nerve stimulation (TENS) improve vascularization of the skin [2].

TENS increases skin temperature as an effect of reflex vasodilatation [118]. In a case report of a patient with SSc, painful ulcerations and Raynaud symptoms, Kaada achieved significant improvement in clinical symptoms relating to pain, calcinosis cutis and dysphagia using acupuncture-like low-frequency TENS [119]. Relief of swallowing difficulties by TENS was also demonstrated in 2007 in a group of 17 patients [120].

There is also good clinical experience with Deep Oscillation (DEEP OSCILLATION®), which has been used for seven years at the Department of Physical Medicine and Rehabilitation of Charité in patients with systemic scleroderma and lymphoedema. Initial studies show a significant reduction in symptoms in patients with secondary breast lymphoedema [121,122], especially in relation to skin findings in fibrotic changes. However, no studies on the effect of electrical vibration massage in collagenoses could be found in the standard search systems during the literature search. Since the tissue constellation of skin manifestations in SSc is very similar to that in lymphoedema [44], a reduction in symptoms is very likely.

The therapy concept and the device used for it were developed in Amberg in the 1980s by the physiotherapists H. Seidl and W. Walder. The basis is a pulsed electrostatic field generated by DEEP OSCILLATION® between the therapist's hands and the patient's tissue. At the selected frequency (5-200 Hz), Deep Oscillation occurs in the patient's connective tissue.

The system is now used in many ways, for example to improve wound healing [123], to reduce gynoid lipodystrophy [124], after radiation therapy, or as an adjunctive therapy to conventional decongestive treatment [125]. Success has been seen especially in the treatment of lymphoedema as a supplement to manual lymph drainage [121,126].

Exactly how Deep Oscillation works has not yet been fully clarified. It is assumed that the therapeutic benefit is attributable to a combination of different effects: stimulation of lymphatic drainage, reduction of muscle tone, pain reduction through mechanical stimulation of pain receptors, and mechanical influence on collagen metabolism.

Biomechanical stimulation works with stimulation parameters similar to DEEP OSCILLATION®. In an uncontrolled study of eight SSc patients, significant improvements in skin flexibility and healing of digital ulcerations were achieved [127].

These observations suggest that vibrating massage techniques may also have a positive effect on acral microcirculation. The efficacy of the method in Raynaud's phenomenon had not yet been investigated.

Biofeedback and autonomically modulating approaches

Biofeedback methods are used therapeutically in many different diseases to make patients aware of physiological processes for therapeutic purposes and to improve self-perception [128]. Biofeedback mediated by skin conductance measurement, skin temperature and pulse curve is already used clinically in primary Raynaud's phenomenon [129-131]. There are also studies suggesting therapeutic benefit of biofeedback in treatment of secondary Raynaud's phenomenon associated with different collagenoses [132] and in advanced systemic scleroderma [133]. A retrospective study using data from 23 patients, 11 with primary and 12 with secondary Raynaud's phenomenon, showed increased baseline digital temperatures after biofeedback training in all patients examined (exact time point not specified). Improvements in subjective symptoms (57%) and reduction in ulcerations (44%) were still detectable in long-term follow-up. Five of seven patients could still increase their digital temperatures within five minutes eighteen months after the last therapy session [132].

Other relaxation techniques that modulate the autonomic system, such as hypnosis and autogenic training, are also recommended as supportive treatment methods for Raynaud's phenomenon in SSc [134].

Overall, physical therapy methods have been used for a long time but have so far often been investigated only in observational and uncontrolled studies.

3 OBJECTIVE

Because the evidence regarding physiotherapeutic and physical measures in SSc patients is unsatisfactory, this dissertation investigates the possible influence of Deep Oscillation and biofeedback therapy on tissue findings and subjective disease perception in comparison with a control group.

Based on previous experience, improvement of subjective disease burden and functional parameters through Deep Oscillation is expected [121-123,125,126,135].

Based on the literature analysis on biofeedback therapy, we expect an improvement in skin blood flow and, secondarily, improvement of functional parameters and subjective disease perception [129,131-133].

The study is intended to answer the following questions.

4. 1. Are there differences between the groups examined regarding subjective symptoms in systemic scleroderma (primary endpoint) or skin findings (secondary endpoint)?
5. 2. Are there differences at the individual examination times in the sense of a short-term or long-term effect regarding symptoms (primary endpoint) or skin findings (secondary endpoint)?
6. 3. Are there factors that influence the therapy results in the individual groups?

4 SUBJECTS AND METHODS

4.1 Patient population

4.1.1 Recruitment

Patients were recruited from October 2004 to February 2008 through the special consultation service of the Department of Rheumatology of Prof. Dr. Riemekasten, through self-help groups and through the website of the Department of Physical Medicine and Rehabilitation of Charité - Universitätsmedizin Berlin, in close cooperation with Prof. Dr. Riemekasten.

Adult SSc patients who had given written consent to participate in the study, according to the principle of voluntariness and independence from therapeutic measures, were included if their disease phase was stable and if no iloprost infusion, medication change or Deep Oscillation treatment had occurred in the preceding three months.

The following inclusion and exclusion criteria applied.

Inclusion criteria:

- systemic scleroderma, with diagnosis according to ACR criteria confirmed exclusively by PD Dr. Riemekasten;
- age 18 to 80 years, both sexes;
- stable disease phase (activity score below 3 according to Valentini, severity grade 1 or 2);
- at least three months after iloprost or medication change;
- patient reachable;
- patient information completed;
- written consent;
- no participation in other studies during the three months before and during participation.

Exclusion criteria:

- acute inflammation;
- infectious skin diseases;
- active tuberculosis;
- untreated thrombosis or vascular disease;
- untreated malignant disease;
- heart disease;
- pacemaker and other electronic implants;
- pregnancy;
- increased sensitivity to electrical fields;
- unwillingness to allow storage and transfer of personal disease data within the protocol.

Despite optimal access methods, the initially planned total number of 60 patients could not be reached. Seventy-six potential participants were recruited, but after review of inclusion and exclusion criteria 42 could not be admitted to the study. The reasons, summarized in Table 2, were a Valentini score greater than 3 (n=12), excessive time required for the patient (n=11), concomitant diseases (n=10), recent iloprost infusion (n=4), too long a travel distance (n=2), planned travel abroad during the study period (n=1), no definite diagnosis (n=1), and participation in another study (n=1).

Finally, 34 subjects were included. The group consisted of 30 women and 4 men. The mean age was 55 years (minimum 28, maximum 71).

Table 2: Reasons for exclusion from the study.

12 subjects: Valentini score greater than 3.

11 subjects: excessive time required.

10 subjects: concomitant diseases.

4 subjects: iloprost infusion.

2 subjects: travel distance too long.

1 subject: travel abroad.

1 subject: no definite diagnosis.

1 subject: participation in another study.

Subjects were allocated to the three study groups in blocks of six using a randomization table prepared by the Biomedical Institute of Charité. Preliminary examination with randomization and clinical examinations were performed by different study staff members.

At study start, subjects were distributed as follows: 11 belonged to the control group, 12 received Deep Oscillation (DEEP OSCILLATION®), and 11 received the biofeedback programme.

The duration of examinations and patient interviews was approximately two hours at all three examination appointments: T1 = start of therapy, T2 = end of therapy, T3 = follow-up.

Each study participant could discontinue participation at any time.

At study completion, data from all three appointments were available for 27 participants. Seven subjects terminated the study prematurely: five after start of therapy (T1) and two after therapy end (T2). Causes of discontinuation were accident or illness in two participants, iloprost infusion during the study in two participants, non-attendance with inability to reach the participant in two cases, and discontinuation by one participant because of allocation to the control group.

Table 3: Reasons for premature discontinuation.

2 subjects: accident or illness.

2 subjects: iloprost infusion during the study.

2 subjects: did not attend.

1 subject: allocation to the control group.

4.1.2 Description of the study population

The constellation of relevant baseline clinical parameters of the patient collective, taking randomization into account, is summarized in Table 4. At study start the patient cohort was as follows.

Table 4: Relevant baseline clinical parameters.

Overall n=34; control n=11; Deep Oscillation n=12; biofeedback n=11.

Age in years, median [min-max]: overall 57 [28-71]; control 58 [51-66]; Deep Oscillation 55 [32-71]; biofeedback 53 [28-70].

Female sex: overall 30 (88%); control 10 (91%); Deep Oscillation 10 (83%); biofeedback 10 (91%).

Disease duration in years: overall 4.5 [0-26]; control 1.5 [0-8]; Deep Oscillation 9 [1-26]; biofeedback 6 [4-20].

Valentini score, median [min-max]: overall 1.3 [0-3.0]; control 1.0 [1.5-3.0]; Deep Oscillation 1.5 [0-3.0]; biofeedback 1.5 [0.5-3.0].

MRHS, median [min-max]: overall 4.0 [0-45]; control 2.0 [0-7]; Deep Oscillation 7.5 [2-45]; biofeedback 4.0 [0-22].

Ulcerations: overall 4 (12%); control 1 (9%); Deep Oscillation 2 (17%); biofeedback 1 (9%).

Previous physiotherapy: overall 20 (59%); control 5 (46%); Deep Oscillation 8 (67%); biofeedback 7 (64%).

4.2 Examination and treatment procedure

4.2.1 Assessment of therapeutic success of the interventions

Because few studies on physical therapy in systemic scleroderma had been conducted, there was neither a gold standard for treatment design nor for assessment of therapeutic success. Different methods are recommended for assessing therapeutic effects [41,48,52,75,136]. Methods relating to the skin and to subjective disease burden were included in this study. All examinations were performed at all three examination times.

No risks are known for the diagnostic procedures used.

4.2.1.1 SSc-specific visual analogue scales (VAS)

Standardized questionnaires have proved useful in rheumatic diseases for assessing general health status and disease burden in daily life [136]. Among other instruments, they contain five visual analogue scales with which subjective disease-related symptoms referring to the previous week are measured. Specifically, they ask about impairment caused by activity of Raynaud's phenomenon, digital ulcerations, gastrointestinal complaints, respiratory/lung problems and general disease-related complaints. Use of a visual analogue scale allows assessment of changes in subjective parameters that are otherwise difficult to compare and is easy for subjects to understand and perform [136]. Patients were asked to place a mark on an unscaled graph 10 cm long, with the extremes "0" for no impairment and "10" for very severe impairment, according to their self-assessment.

4.2.1.2 Skin findings

Modified Rodnan Skin Score (MRHS)

The MRHS is a common, suitable and well validated method for assessing skin thickness [48,49,50-52]. Seventeen body areas are assessed by the examiner through clinical palpation using a four-point ordinal scale. "0" corresponds to normal, "1" to mild, "2" to moderate and "3" to severe scleroderma of the respective skin region (Fig. 5) [49]. After addition of all values, the range is from 0 (no skin thickening) to 51 (grade 3 changes in all 17 regions). The regions examined are the fingers, hands, forearms and upper arms, feet, lower legs and thighs, face, chest and abdomen [49].

Fig. 5: MRHS examination form. Score 0-3 per region: 0 = normal, 1 = mild, 2 = moderate, 3 = severe skin thickening. Regions include face, anterior thorax, abdomen, upper arms, forearms, hands, fingers, thighs, lower legs and feet; right and left sides are recorded separately where appropriate. Total sum = MRHS.

4.2.2 Therapeutic measures

The present study prospectively evaluated the efficacy of two new therapeutic procedures, DEEP OSCILLATION® and biofeedback, with respect to SSc-related symptoms. Comparison with the control group was intended to show whether the therapies used had an influence on the parameters investigated.

4.2.2.1 Deep Oscillation (DEEP OSCILLATION®)

Deep Oscillation (TO) is an electromechanical treatment method in which electrostatic attraction and friction are used to achieve a deep resonance oscillation in tissue.

Fig. 6: HIVAMAT® 200 / manual lymph drainage supported by Deep Oscillation (image: © PHYSIOMED).

Using the therapy devices Hivamat® 200 or Deep Oscillation® (Physiomed Elektromedizin AG, Laipersdorf, Germany), an electrostatic field of low intensity (U = 100-400 V; I = 150 microamperes) is established between the hands of the therapist or a hand applicator and the patient's tissue. Therapy can be performed by a therapist wearing vinyl gloves as an insulating layer, making it possible to combine the method with manual therapeutic techniques, especially manual lymph drainage (MLD) in oedema therapy [122,125,137]. For this purpose therapist and patient are connected to the device (voltage source) by an electrode. While the patient holds the electrode rod in the hand, the electrode is attached to the therapist's arm as an adhesive electrode (Fig. 7). Polarity is not considered. At the selected frequency (5-200 Hz), the patient's tissue is electrostatically attracted and released again. This produces a deep and sustained resonance oscillation. Very weak electrical current impulses in the microampere range also act during the therapy.

Patients receiving Deep Oscillation were treated 12 times over four weeks with manual lymph drainage. This therapy was supported by Deep Oscillation on the hand, forearm and facial region.

Each therapy session lasted one hour. First, 15 minutes of central preparation in the form of manual lymph drainage were performed; another 15 minutes were used at a frequency of 100 Hz for both upper extremities; afterwards the facial region was also treated for 15 minutes at a frequency of 30 Hz. The application was performed using manual lymph drainage grip techniques.

Twelve persons, ten women (83.34%) and two men (16.67%), belonged to this intervention group by randomization.

Fig. 7: Manual lymph drainage with Deep Oscillation / HIVAMAT® 200 therapy device.

4.2.2.2 Biofeedback

Biofeedback therapy was performed using skin sensors that measure skin conductance (SC), skin temperature (TEMP), respiratory rate, muscle activity and the blood volume pulse (BVP) on the fingers or face.

Under screen display of the above measured values, relaxation exercises, breathing exercises, stress tests and visualization exercises were carried out. The aim of treatment was to improve perception of the autonomic reaction state and to learn conscious influence over it.

As in the Deep Oscillation group, patients received a one-hour biofeedback treatment three times weekly for four weeks.

After a short acclimatization to room temperature of approximately 24 degrees C ± 1 degree, the following parameters were recorded while relaxation exercises in the form of progressive muscle relaxation according to Jacobson were performed [138,139]:

- skin conductance (SC) on fingers II and IV of the left hand (in microSiemens);
- temperature on finger II (fingertip) of the right hand (in degrees C);
- pulse/heart rate on finger IV (fingertip) of the right hand (as frequency in beats per minute and amplitude in %);
- muscle activity (EMG) on the right forearm (in microvolts);
- respiratory rate using a breathing belt around the chest (breaths per minute).

The ProComp Infinity™ Encoder from Thought Technology Ltd., Montreal, Canada, was used for the recordings. Screen display and recording were performed with BioGraph Infiniti Version 3 software from the same company.

At the end of the relaxation phase, patient and physiotherapist viewed the curves of the recorded parameters on the screen.

Patients were also asked to use the learned relaxation technique at home.

The biofeedback group included 11 patients. The proportion of women was 90.1% (n=10) and that of men 9.1% (n=1).

No risks are known for Deep Oscillation when the exclusion criteria are observed. No risks are known for biofeedback therapy either.

Control group

During the three-month study period the control group received none of the interventions and continued the therapies already used before study entry. In the sense of a waiting-list group, the subjects in this group were given the option of being treated with one of the two interventions after completion of the study.

Of the 11 patients in the control group, 10 were female (90.9%) and one was male (9.1%).

4.3 Study design

The study was conducted as a monocentric, three-arm, single-blind, randomized, controlled study on the efficacy of two new therapeutic procedures.

The examiners were blinded. Double blinding was not feasible because of the therapeutic procedures used.

Figure 8 illustrates the study design and shows the exact time course of examinations, measurement instruments and therapies.

Fig. 8: Study design. From the scleroderma outpatient clinic (10/2004 to 02/2008), 220 patients were screened, 76 patients were recruited, and after inclusion and exclusion criteria 34 patients were included. After patient information and consent, patients were allocated to control (n=11), Deep Oscillation (n=12) and biofeedback (n=11). T1 was therapy start; interventions were no therapy, DEEP OSCILLATION® or biofeedback for four weeks with 12 treatments where applicable. VAS, MRHS, stress test and Raynaud diary were recorded at T1, therapy end T2 and follow-up T3 after 12 weeks.

4.4 Data protection

Data were documented in a questionnaire, an examination form and computer software. Data processing was carried out according to the provisions of the Berlin Data Protection Act (Act on the Protection of Personal Data in the Berlin Administration, Berlin Data Protection Act - BlnDSG, 17 December 1990, most recently amended by the Act of 3 July 1995). Consent to data inspection and transfer was obtained separately from consent to study participation.

The randomization table for group allocation of subjects was prepared by staff of the Institute of Medical Biometry of Charité - Universitätsmedizin Berlin. Before randomization, each patient was informed orally and in writing by the treating physician about the nature, aims, expected benefits and possible risks of the study and gave informed consent.

A positive vote of the Ethics Committee of Charité - Universitätsmedizin Berlin was available at the beginning of the study (EA 1/100/05; NCT00946738).

4.5 Statistical analysis

The results were analysed using SPSS (Statistical Package of Social Science), version 16.0 for Windows.

Data were analysed as an intention-to-treat analysis for all randomized subjects, regardless of treatment discontinuation and protocol violations. Missing values were not replaced.

Assuming non-normally distributed variables, non-parametric tests were used for statistical analysis. For descriptive analysis, the median was chosen because it is particularly suitable for presenting small numbers of subjects and asymmetrical distributions. If no significant results occur in a small study population, they cannot be definitely excluded; however, the presence of significant results must be rated as particularly meaningful [140-143].

Testing for equal distribution between groups was performed for quantitative data with the non-parametric Kruskal-Wallis test. Qualitative data were analysed using the chi-square test [142,143].

To test differences in means between different groups across several dependent variables, a multivariate analysis (MANOVA with repeated measures) was used. Only in the case of significant deviations between means was a Dunnett T3 post-hoc test used to determine which means differed.

To examine the influence of secondary target parameters, multiple linear regression analysis was performed. It is used to determine how changes in independent variables affect the dependent variable [140-143].

Using the equation created, the absolute score change between the time points after four weeks of therapy and follow-up after 12 weeks and the baseline value was calculated. The VAS 1 baseline score, age, disease duration, baseline MRHS and season at the time of examination were used as potential confounding factors. Multi-categorical variables were dichotomized for easier interpretation of the analysis. If the dichotomized characteristic is present, the result factors of the linear regression analysis represent the associated score change. In addition to the assumption that the interventions are superior to the control group, possible superiority of one intervention over the other was also considered. For this purpose the variable "therapy" was dichotomized into the two new variables "Deep Oscillation" and "biofeedback". The analysis was performed by the backward method. In this method the equation begins with all included variables; variables without predictive value are then excluded stepwise.

In multiple linear regression with stepwise exclusion, the probability of error was 10%. In all other calculations, a probability of error of 5% was assumed.

4.6 Critical appraisal of methods

Because this study examined the efficacy of two different physiotherapeutic methods, blinding was not possible. Although a control group without the physiotherapies performed in the study was formed, the validity is limited because these patients did not expect improvement from a new therapy. For non-pharmacological studies, placebo-controlled and blinded designs are very difficult to carry out and represent a general problem for assessing therapeutic success of physiotherapeutic measures [144].

Standardization of measurement methods is problematic especially in relation to Raynaud's phenomenon. Temperature differences during the examination period can influence results because Raynaud symptoms are particularly subject to seasonal temperature fluctuations [67]. Recruitment of subjects from 2004 to 2008 could not always take place in the same season. In addition, the examinations of individual subjects had to be conducted in different seasons because the study period lasted 12 weeks.

Standardization was also difficult in the assessment of the Modified Rodnan Skin Score (MRHS), since for optimal validity only one person should perform the examinations [49]. For personnel reasons this could not be guaranteed over the entire study period.

5 RESULTS

5.1 Description of the baseline population

Apart from disease duration and the Modified Rodnan Skin Score (MRHS), there were no significant differences between the three groups at the start of therapy (Table 5).

Table 5: Relevant baseline clinical parameters of the patient collective (Deep Oscillation = TO).

Number of patients: overall 34, control 11, TO 12, biofeedback 11.

Female sex: overall 30 (88%), control 10 (91%), TO 10 (83%), biofeedback 10 (91%).

Age in years, median [min-max]: overall 57 [28-71], control 58 [51-66], TO 55 [32-71], biofeedback 53 [28-70]; p=0.337.

Disease duration in years: overall 4.5 [0-26], control 1.5 [0-8], TO 9 [1-26], biofeedback 6 [4-20]; p=0.004.

SSc type: limited overall 23 (68%), control 9 (82%), TO 6 (50%), biofeedback 8 (73%); diffuse overall 9 (27%), control 1 (9%), TO 5 (42%), biofeedback 3 (27%); p=0.013.

Valentini score, median [min-max]: overall 1.3 [0-3.0], control 1.0 [1.5-3.0], TO 1.5 [0-3.0], biofeedback 1.5 [0.5-3.0]; p=0.324.

MRHS, median [min-max]: overall 4.0 [0-45], control 2.0 [0-7], TO 7.5 [2-45], biofeedback 4.0 [0-22]; p=0.031.

Smoking status: former smokers 2 (6%) overall; smokers 2 (6%) overall.

Ulcerations: overall 4 (12%), control 1 (9%), TO 2 (17%), biofeedback 1 (9%).

Previous physiotherapy: overall 20 (59%), control 5 (46%), TO 8 (67%), biofeedback 7 (64%); p=0.254.

Season at therapy start: spring 10 (29%), summer 7 (21%), autumn 9 (27%), winter 8 (24%); p=0.899.

A chi-square test for equal distribution of the parameters SSc type, smoking status and ulcerations could not be performed because of the small number of cases. However, inspection of the medians suggested equal distribution.

The Raynaud diaries mentioned in the study design were not analysed because documentation was completed by only four subjects.

5.2 Influence of the therapies on SSc-related symptoms and skin findings

5.2.1 Subjective SSc-related symptoms - VAS (primary endpoint)

Subjective disease-related symptoms were assessed using the five visual analogue scales. The questions concerned impairment due to Raynaud symptoms (VAS 1), ulcers (VAS 2), gastrointestinal symptoms (VAS 3), lung problems (VAS 4) and overall complaints (VAS 5) during the preceding seven days. At therapy start (T1), at therapy end after four weeks (T2) and during follow-up after 12 weeks (T3), subjects were asked to enter their current subjective feeling on an unscaled graph 10 cm long. "0" meant no impairment and "10" very severe impairment.

At therapy start (T1), there were no significant differences between the groups for the individual VAS. Table 6 compares the values and shows equal distribution in the Kruskal-Wallis test.

Table 6: Baseline VAS values, median [min-max] as score points.

VAS 1: control 3.83 [0-7.5], Deep Oscillation 6.44 [0-8.2], biofeedback 4.89 [0-8.6], p=0.197.

VAS 2: control 3.17 [0-6.9], Deep Oscillation 5.43 [0-9.9], biofeedback 0.48 [0-9.6], p=0.471.

VAS 3: control 4.44 [0-6.2], Deep Oscillation 2.35 [0-8.7], biofeedback 3.89 [0-9.4], p=0.859.

VAS 4: control 4.30 [0-6.9], Deep Oscillation 6.04 [0-8.5], biofeedback 1.39 [0-5.2], p=0.126.

VAS 5: control 5.17 [0-6.5], Deep Oscillation 6.74 [0-9.0], biofeedback 2.39 [0-8.4], p=0.070.

In the descriptive statistics for Raynaud symptoms (VAS 1, Table 7), the control group showed an increase in the median from baseline to the end of the therapy phase (week 4) by 1.71 points. In the Deep Oscillation group, by contrast, a score reduction of 0.16 points was observed. Biofeedback therapy achieved a reduction of the median by 3.35 points to 1.54, the lowest value overall.

A similar development was seen in the differences between medians from therapy start to follow-up in week 12. An increase of 1.21 points was calculated in the control group, whereas reductions were seen in both therapy groups: 0.74 points with Deep Oscillation and 1.65 points with biofeedback.

Table 7: Descriptive statistics for Raynaud complaints (VAS 1), n, median [min-max].

T1: control 11, 3.83 [0-7.5]; Deep Oscillation 11, 6.44 [0-8.2]; biofeedback 8, 4.89 [0-8.6].

T2: control 8, 5.54 [0-7.4]; Deep Oscillation 11, 5.83 [0-8.7]; biofeedback 10, 1.54 [0-8.4].

T3: control 7, 5.04 [0-7.1]; Deep Oscillation 9, 5.70 [0-7.9]; biofeedback 8, 3.24 [0-9.2].

A different trend was seen for score changes regarding ulcerations (VAS 2, Table 8). Here a decrease in scores at therapy end and follow-up was calculated for the control group as well as for both intervention groups. In the control group there were strong fluctuations. The value decreased by 2.14 points after four weeks and by 0.69 points at week 12. In the two intervention groups the values fell during therapy. With Deep Oscillation, a score reduction of 1.04 points was observed after four weeks; with biofeedback, 0.47 points. At follow-up after 12 weeks the values also decreased: by 3.56 points with Deep Oscillation and by 0.48 to 0.00 points in the biofeedback group.

Table 8: Descriptive statistics for ulcers (VAS 2).

T1: control 11, 3.17 [0-6.9]; Deep Oscillation 11, 5.43 [0-9.9]; biofeedback 8, 0.48 [0-9.6].

T2: control 8, 0.76 [0-5.9]; Deep Oscillation 11, 4.39 [0-6.5]; biofeedback 10, 0.07 [0-9.5].

T3: control 7, 2.48 [0-6.1]; Deep Oscillation 9, 1.87 [0-6.7]; biofeedback 8, 0.00 [0-8.7].

For gastrointestinal symptoms (VAS 3), Table 9 shows a score decrease of 2.43 points in the control group after four weeks. The biofeedback group also achieved a decrease (-0.87), whereas Deep Oscillation showed an increase of 2.04 points. At follow-up only biofeedback therapy still showed a moderate score reduction (-0.82). The values for the control group and Deep Oscillation rose by 0.40 and 4.17 points respectively.

Table 9: Descriptive statistics for gastrointestinal symptoms (VAS 3).

T1: control 11, 4.43 [0-6.2]; Deep Oscillation 11, 2.35 [0-8.7]; biofeedback 8, 3.89 [0-9.4].

T2: control 8, 2.00 [0-5.3]; Deep Oscillation 11, 4.39 [0-8.6]; biofeedback 10, 3.02 [0-9.4].

T3: control 7, 4.83 [0-6.2]; Deep Oscillation 8, 6.52 [0-7.7]; biofeedback 8, 3.07 [0-10.0].

Regarding lung problems (VAS 4) after four weeks, Table 10 shows a similar result for the control group: the score in this group decreased by 2.56 points. In the Deep Oscillation group a score reduction was also recorded (-1.87 points). For the biofeedback group there was an increase of +0.07 points. A similar, although less pronounced, trend was seen in the comparison of medians between therapy start and follow-up in week 12. Values decreased by 0.3 points in the control group and by 0.61 points in the Deep Oscillation group. At this examination time a decrease in the median was also seen in the biofeedback group, with the score falling by 0.02 to 0.00 points. Although no significant differences between the groups were found at therapy start, it should be noted that with a baseline value of 0.02 points in the biofeedback group there was hardly any possibility of lowering the value.

Table 10: Descriptive statistics for lung problems (VAS 4).

T1: control 11, 4.30 [0-7.0]; Deep Oscillation 11, 6.04 [0-9.0]; biofeedback 8, 0.02 [0-5.0].

T2: control 8, 1.74 [0-6.0]; Deep Oscillation 11, 4.17 [0-9.0]; biofeedback 10, 0.09 [0-5.0].

T3: control 7, 4.00 [0-7.0]; Deep Oscillation 8, 5.43 [0-9.0]; biofeedback 8, 0.00 [0-1.0].

VAS 5 reflects subjective impairment in relation to general disease-related complaints (Table 11). In the control group, point values remained relatively constant at both examination times. From therapy start to therapy end there was only an increase of 0.09 points, and at follow-up the score decreased by 0.13 points.

For Deep Oscillation, the median decreased over the entire examination period: from baseline to week four by 0.09 points and from baseline to follow-up in week 12 by 0.74 points.

In the biofeedback group, by contrast, the median increased over the entire examination period: by 0.15 from baseline to therapy end and by 0.63 from baseline to follow-up in week 12.

Table 11: Descriptive statistics for overall complaints (VAS 5).

T1: control 11, 5.17 [0-6.5]; Deep Oscillation 11, 6.74 [0-6.5]; biofeedback 8, 2.39 [0-8.4].

T2: control 8, 5.26 [0-6.3]; Deep Oscillation 11, 6.65 [0-6.3]; biofeedback 10, 2.54 [0-9.5].

T3: control 7, 5.04 [0-6.3]; Deep Oscillation 9, 6.00 [0-6.3]; biofeedback 8, 3.02 [0-9.4].

Inspection of these changes in medians suggests that both Deep Oscillation and biofeedback therapy had a positive effect on Raynaud symptoms (VAS 1). The value for Deep Oscillation decreased clearly after four and twelve weeks. Biofeedback therapy also achieved a clear score reduction at both examination times, exceeding three points at therapy end after four weeks. In the control group, by contrast, the values increased.

Deep Oscillation and biofeedback therapy also seem to have a positive effect on ulcerations (VAS 2). Both applications achieved a score decrease at both examination times. However, this effect was also observed in the control group.

Furthermore, biofeedback therapy also appeared to have a favourable influence on gastrointestinal symptoms (VAS 3). Here too, a decrease in score was recorded at both examination times, although less clearly.

These assumptions were tested for significant group differences and differences within the groups over the course of therapy by multivariate data analysis (MANOVA with repeated measures) (Table 12).

Table 12: MANOVA with repeated measures for VAS 1-5.

Group: VAS 1 p=0.008; VAS 2 p=0.912; VAS 3 p=0.439; VAS 4 p=0.865; VAS 5 p=0.707.

Time point: VAS 1 p=0.788; VAS 2 p=0.471; VAS 3 p=0.072; VAS 4 p=0.369; VAS 5 p=0.886.

Interaction: VAS 1 p=0.244; VAS 2 p=0.588; VAS 3 p=0.359; VAS 4 p=0.046; VAS 5 p=0.514.

For complaints related to Raynaud symptoms (VAS 1), highly significant differences between groups were shown (p=0.008).

For impairments in the sense of lung involvement (VAS 4), a significant difference was seen regarding the interaction (p=0.046). As Figure 9 illustrates, the line of estimated marginal means for the biofeedback group runs opposite to the lines for Deep Oscillation and the control group. This may mean that significant differences appear only in pairwise group comparison. Therefore, a Dunnett post-hoc test was then used for the individual therapy groups and the duration of treatment effect to determine whether significant differences resulted (Table 13). No significant differences were found for any group comparison or any examination time.

Table 13: Group comparison of differences for lung problems (VAS 4), Dunnett post-hoc test.

Control/Deep Oscillation: short-term effect T2-T1 p=0.949; long-term effect T3-T1 p=0.850.

Control/Biofeedback: short-term effect p=0.922; long-term effect p=0.703.

Deep Oscillation/Biofeedback: short-term effect p=0.815; long-term effect p=0.904.

For score changes regarding ulcerations (VAS 2), gastrointestinal complaints (VAS 3) and general disease symptoms (VAS 5), no significant differences were found within or between the examined groups over the course of therapy.

The highly significant group differences (p=0.008) in Raynaud-associated symptoms (VAS 1) were checked in a subsequent Dunnett post-hoc test for the individual therapy groups and the duration of treatment effect (Table 14, Fig. 10).

With regard to the baseline value for Raynaud's phenomenon (VAS 1), biofeedback therapy after four weeks of treatment showed a significant reduction in the burden due to Raynaud's phenomenon compared with the control group. The significance level was p=0.003. The change was highly significant. This improvement persisted eight weeks after therapy start. With p=0.024, this change was also in the significant range. Thus both a short-term effect and a long-term effect can be identified.

With Deep Oscillation therapy, a difference compared with the control group could also be shown at follow-up, although only a statistically significant tendency was present (p=0.054).

Table 14: Group comparison of differences for VAS 1 (Dunnett post-hoc test).

Control/Deep Oscillation: short-term effect T2-T1 p=0.150; long-term effect T3-T1 p=0.054.

Control/Biofeedback: short-term effect p=0.003; long-term effect p=0.024.

Deep Oscillation/Biofeedback: short-term effect p=0.106; long-term effect p=0.751.

Fig. 10: Score change from baseline for complaints related to Raynaud's phenomenon (VAS 1).

5.2.2 Skin findings - MRHS (secondary endpoint)

The skin findings were assessed by measuring skin thickness. Table 15 compares baseline values for the MRHS using the Kruskal-Wallis test. At therapy start, despite randomization, the values in the individual groups differed significantly.

Table 15: Comparison of baseline MRHS values as score points, median [min-max].

Control n=11: 2.00 [0-7]; Deep Oscillation n=12: 7.50 [2-45]; biofeedback n=10: 4.00 [0-22]; significance p=0.031.

Descriptive statistics for the MRHS (Table 16) showed an increase in the median for the control group from baseline to the end of the therapy phase (week four) by 3.5 points. In the Deep Oscillation group a score increase of 3.5 points was also observed. Biofeedback therapy, by contrast, achieved a reduction of the median by 2.0 points.

In comparison of the medians between therapy start and follow-up in week 12, the score in the control group fell by 5.5 to 0.0 points. A decrease was also recorded in the Deep Oscillation group (-2.0 points), while the median in the biofeedback group remained constant at 2.0.

Because MRHS values in the individual groups were not equally distributed, no further analysis of mean values was performed.

Table 16: Descriptive statistics for MRHS, n, median [min-max] as score points.

T1: control 11, 2.00 [0-7]; Deep Oscillation 12, 7.50 [2-45]; biofeedback 10, 4.00 [0-22].

T2: control 8, 5.50 [0-8]; Deep Oscillation 11, 11.00 [0-16]; biofeedback 9, 2.00 [0-19].

T3: control 7, 0.00 [0-15]; Deep Oscillation 10, 8.00 [0-19]; biofeedback 9, 2.00 [0-19].

5.3 Influence of secondary target parameters (linear regression)

The effects of the therapies on score changes of the Raynaud's phenomenon-associated VAS (VAS 1) were then examined in a multiple linear regression analysis (Table 17).

Neither the VAS baseline value, the MRHS at therapy start, nor the season during the examination had a confounding influence on the results.

For the short-term effect, the analysis for the score difference between therapy start and therapy end after four weeks showed an average increase across all three therapy groups of 5.808 (p=0.004). This score increase decreased with increasing age. Older patients therefore benefited more from the therapies. A decrease of -0.078 was calculated for each year of age (p=0.013).

In contrast, longer disease duration resulted in a poorer therapy result. Here there was an increase in the score difference of +0.009 per year (p=0.093).

Furthermore, improvement in the therapy result was observed when the patient had received biofeedback therapy. A decrease in the score difference of -4.253 was calculated (p=0.000). The change with biofeedback therapy was clearly greater than with Deep Oscillation. Deep Oscillation showed a reduction of only -1.969 in the source text's narrative, while Table 17 gives -2.666 (p=0.005).

For the long-term effect between follow-up after 12 weeks and therapy start, a similar constellation of values was found. The older a subject was, the better the therapy result. There was a decrease in score difference of -0.105 per year (p=0.004).

Subjects who had received biofeedback therapy also achieved improved therapy results in the long-term effect. The decrease in score difference was -3.270 (p=0.002). For Deep Oscillation a similar value to the short-term effect was found at -2.196 (p=0.013). The change with biofeedback therapy was still higher than with Deep Oscillation, though less clearly.

Disease duration had no significant influence on the long-term result.

Table 17: Multiple linear regression analysis, backward method. Positive values indicate an increase in the score difference, i.e. worsening; negative values indicate a decrease in the score difference, i.e. improvement.

Short-term effect: constant 5.808, p=0.004; age -0.078, p=0.013; disease duration 0.099, p=0.093; biofeedback -4.253, p=0.000; Deep Oscillation -2.666, p=0.005.

Long-term effect: constant 7.132, p=0.002; age -0.105, p=0.004; biofeedback -3.270, p=0.002; Deep Oscillation -2.196, p=0.013.

Equations:

Score difference (short-term effect) = 5.808 - 0.078 x age + 0.099 x disease duration - 4.253 x biofeedback - 2.666 x TO.

Score difference (long-term effect) = 7.132 - 0.105 x age - 3.270 x biofeedback - 2.196 x Deep Oscillation.

6 DISCUSSION

The present work is the first prospective randomized controlled study to examine the effect of Deep Oscillation (DEEP OSCILLATION®) and biofeedback therapy, compared with a control group, on symptoms in systemic scleroderma in patients with stable disease. Despite the small patient population, we were able to identify a positive effect of biofeedback therapy on SSc-associated Raynaud symptoms, suggesting high efficacy. Deep Oscillation seems to be somewhat less effective in this respect.

One possible explanation is that patients in the biofeedback group had more treatments over the total period because they were instructed to continue the learned method independently at home even after therapy ended at four weeks. This larger therapy interval could have contributed to the better efficacy in both the short-term and especially the long-term effect.

6.1 Deep Oscillation (DEEP OSCILLATION®)

Deep Oscillation is already used therapeutically in lymphoedema [121] and can supplement manual lymph drainage, which is often used in SSc patients [126]. A first controlled study showed a significant reduction of pain symptoms and swelling in patients with secondary breast lymphoedema through therapy with manual lymph drainage (MLD) supported by DEEP OSCILLATION® compared with MLD alone [121,122]. In patients additionally treated with Deep Oscillation, the pain score decreased significantly from therapy start to therapy end and to follow-up. As in the present study, therapeutic effects were assessed by symptom-associated visual analogue scales (VAS).

In our study we were able to confirm the positive effects of DEEP OSCILLATION® therapy on subjective symptoms. For Deep Oscillation, we recorded a tendency towards symptom reduction on the Raynaud-associated visual analogue scale at follow-up (p=0.054).

Further studies show a positive effect of DEEP OSCILLATION® on oedema-related skin swelling. In an uncontrolled study of 20 patients, Gasbarro et al. achieved a significant reduction in oedema circumference and thickness of the subcutis in patients with leg lymphoedema using the combination of manual lymph drainage and Deep Oscillation [125]. Theys et al. also showed a decrease in oedema through Deep Oscillation in combination with manual lymph drainage. In an uncontrolled study including ten patients with phleboedema or lymphoedema of the lower extremity, leg circumference decreased [126].

Biomechanical stimulation works with stimulation parameters similar to DEEP OSCILLATION®. Using this method, Klyscz and colleagues achieved significant improvement in the skin score (not described in detail) and the finger-floor distance in 6 of 8 patients with diffuse systemic scleroderma in an uncontrolled study [127].

In our study we could not show an influence on reduction of skin swelling or skin thickness. The Modified Rodnan Skin Score (MRHS) differed significantly between groups already at therapy start, so no further analysis was performed. For optimal validity of the MRHS, skin assessment should be performed by the same trained examiner [49]. This could not be maintained over the entire examination period in the present work. The significant differences in baseline MRHS values despite randomization may have been due to subjective differences in assessment. Some authors also assume that validity regarding slight but clinically relevant changes within one score is limited because of low sensitivity [53,54]. Although the MRHS is currently regarded as the most suitable instrument for assessing skin involvement in SSc [48-52], development of new objective assessment criteria for evaluating therapeutic success appears useful. In 2008 Kuwahara presented a new objective method for quantifying skin involvement: a sensor, the Vesmeter, measures hardness, elasticity and viscosity of the skin [54].

We attribute the tendency towards therapeutic benefit of Deep Oscillation on Raynaud-associated symptoms to a combination of different effects: stimulation of lymphatic drainage, reduction of muscle tone, pain reduction through mechanical stimulation of pain receptors, and mechanical influence on collagen metabolism. However, these mechanisms are currently still being examined in clinical studies. To date, in vitro experiments have shown only an immunostimulating and wound-healing-promoting effect [123,135].

A positive influence on wound healing, measured in this study indirectly by a visual analogue scale for complaints caused by ulcerations (VAS 2), could be confirmed only indirectly and without statistical significance. The control group showed strong fluctuations in score reduction; in both intervention groups the values fell during therapy and at follow-up. Indirectly, this indicates that Deep Oscillation contributed to improvement in the long-term result. However, at the beginning of the study acral ulcerations were present in only four subjects (12%), which limits the significance of this parameter.

In this study, Deep Oscillation did not meet expectations of an individualizable, mobile electrical massage therapy. Reasons may lie in the small study population and in different temperature influences at the measurement times, although this was not confirmed in the regression analysis.

Since the tendency towards a positive effect of DEEP OSCILLATION® therapy appeared only in the long-term effect, it is also conceivable that a longer therapy interval is needed to use and evaluate the effects optimally.

It should also be questioned whether the Modified Rodnan Skin Score (MRHS), because of the suspected low sensitivity to slight but clinically relevant changes within one score and because of variations due to different examiners, is suitable for follow-up assessment of skin findings in clinical observations. For further studies in this field, consideration should be given to adding an additional visual analogue scale for assessing swelling and tension of the skin.

Nevertheless, the result of a statistically tendential reduction in symptoms within an SSc-associated Raynaud symptom complex is consistent with the current state of research on Deep Oscillation and other electrostimulating procedures.

6.2 Biofeedback

For biofeedback therapy as an autonomically modulating measure, the literature already provides evidence that this treatment has favourable effects on both primary [129-131] and secondary [132,133] Raynaud's phenomenon.

Regarding secondary Raynaud's phenomenon, a retrospective data analysis of 23 patient records showed increased baseline digital temperatures after biofeedback training in all examined patients (time point not specified). Improvements in subjective symptoms (57%) and reduction of ulcerations (44%) were also detectable in long-term follow-up. Five of seven patients could still increase their digital temperatures within five minutes eighteen months after the last therapy session [132].

In our study these results regarding the efficacy of biofeedback therapy could be confirmed. Score changes on the Raynaud-associated visual analogue scale (VAS 1) show both a significant short-term effect (p=0.003) and a long-term effect (p=0.024) compared with the control group.

The positive effect on symptoms caused by ulcerations could not be clearly demonstrated in our study. Ulcerations were present in only four subjects. In both intervention groups the values fell during therapy and at follow-up, while in the control group they fluctuated. This permits the indirect conclusion that biofeedback therapy achieved a reduction of subjective symptoms in the long-term result. However, no significant differences within or between groups could be calculated for this.

Other relaxation techniques that modulate the autonomic system, such as hypnosis and autogenic training, are also recommended as supportive treatment methods for Raynaud's phenomenon in systemic scleroderma [134]. In a 1995 study of 12 SSc patients, vasodilatation of acral vessels was interpreted by the authors as an expression of reduced sympathetic activity of the autonomic nervous system after hypnosis therapy and autogenic training [134]. The mechanism of action of these methods relates to the fact that acral innervation is exclusively via noradrenergic sympathetic fibres that are connected to brain centres of emotional activity. Autonomic tension increases sympathetic tone and triggers vasoconstriction [68]. Biofeedback therapy in combination with relaxation techniques may cause a sustained reduction in sympathetic activity. Consequently, excessive vasoconstriction decreases, blood flow improves and the acral region warms.

This increased heat development through better blood circulation confirms the results of several studies that have examined the use of heat supply in SSc patients. In a study conducted in 2005 at the Department of Dermatology and Allergology of Charité - Universitätsmedizin Berlin including 58 patients, serial application of mild whole-body hyperthermia using infrared-A irradiation (wavelength 780-1400 nm) reduced acral rewarming time and thus improved Raynaud symptoms. The application also had positive effects on skin findings, lung function and general well-being [105]. Two studies by Meffert also report improvement in acral vascular reactivity in SSc patients through mild infrared-A whole-body hyperthermia [5,106].

Local heat applications can also be beneficial. Daily local application of a paraffin pack in combination with a hand exercise programme in a group of 17 patients with systemic scleroderma improved hand mobility, stiffness and skin elasticity [107]. In our study, no improvement in skin characteristics through biofeedback therapy could be found, but it should be noted that skin involvement in the subjects examined here was very low, with a median value of four points.

One limitation of this study is the use of a subjective symptom as the primary endpoint. Its assessment cannot be objectified by measurement methods and is highly susceptible to influence by the patient's desire for successful therapy. This possible placebo effect is generally difficult to prevent in all non-pharmacological studies because it is often impossible to realize a sham intervention [144]. Nevertheless, Deep Oscillation therapy, which has a greater potential for placebo effect, was not superior to biofeedback therapy. Potential nocebo effects, in which the patient's expectations and experiences lead to worsening of well-being, must also be considered regarding negative results in the control group.

Another problem was standardization of measurement methods. Because patient recruitment and examination times during the study extended over several months, measurements could not always be performed in the same season. A seasonal influence on acral blood flow is known from the literature. Watson described a possible improvement of Raynaud symptoms in the summer months by up to 50% [67]. This potential seasonal influence was taken into account in a multiple linear regression analysis. Despite measurements being distributed across different seasons, no influence on the therapy result was found.

The number of patients in this study was very small. In close cooperation with the Department of Rheumatology as a specialized centre for systemic scleroderma, a high number of 220 patients was screened, but only 34 could be included in the study. A main reason was comprehensive and specialized patient care within such a specialized centre. Many patients were already involved in other clinical studies or received specific therapies that contradicted the inclusion criteria of our study.

In summary, significant improvement of subjective complaints within an SSc-associated Raynaud symptom complex can be achieved through biofeedback therapy both as a short-term effect and as a long-term effect. Thus the present study confirms the current state of research in a prospective controlled study setting. Further studies over a longer observation period are needed to make statements about long-term efficacy.

Even though this work showed only a tendential benefit of Deep Oscillation, the good clinical experience with this treatment method should prompt further, larger controlled studies in this field.

Despite more severe and more progressive disease in the therapy groups, reflected in longer disease duration and higher MRHS, differences in changes were visible. This underlines the positive effects of the physiotherapeutic methods studied and justifies stronger integration into treatment concepts for SSc patients.

Furthermore, this study supports the demand for improved status indices for disease activity and disease-related damage and their follow-up observation, or suitable prognostic criteria, as well as for development of evidence-based recommendations for diagnosis and especially for a standard of therapy for systemic scleroderma.

7 SUMMARY AND OUTLOOK

Systemic scleroderma (SSc) is a rare chronic inflammatory systemic autoimmune disease of vascular connective tissue and belongs to the collagenoses. The clinical presentation, course and prognosis of the disease vary greatly and are difficult to predict [31]. Its main characteristic is fibrosis and, later in the course, sclerosis of the skin and of internal organs to varying degrees. In up to 90% of those affected the disease begins with Raynaud's phenomenon [4], in which vascular spasms triggered by cold or emotional stimuli first cause reduced tissue perfusion and later may lead to ulceration and necrosis, up to loss of fingers.

Drug treatment approaches aim to combat the inflammatory response, improve microcirculation and influence collagen metabolism [42,46]. Physical treatment methods are a valuable supplement to the therapeutic concept and have long been used, but so far have been examined only in small observational studies.

The present work is the first prospective randomized controlled study to examine the effect of Deep Oscillation (DEEP OSCILLATION®) and biofeedback therapy on SSc-related symptoms compared with a control group in patients with stable disease. Patients in the therapy groups were treated three times weekly over a period of four weeks, and a follow-up examination took place after 12 weeks.

We were able to confirm for the first time in a randomized controlled study design the pain-relieving effect of biofeedback therapy on SSc-associated Raynaud symptoms suspected in other retrospective and uncontrolled studies [132,133]. Despite the small patient population of 34 patients, we identified a positive effect of this therapy, suggesting high efficacy. Deep Oscillation seems to be somewhat less effective in this respect.

For the other complaints in systemic scleroderma, which in this study were recorded using the SSc-specific visual analogue scales and the Modified Rodnan Skin Score, no significant differences within or between the examined groups were found over the course of therapy. In future studies, extending follow-up would be interesting in order to reflect these therapy effects as well. It should also be discussed which change on a visual analogue scale should be regarded as a clinically relevant effect. Based on clinical experience, a change of 10% is assumed for this, but clinical studies on this issue are lacking.

The results shown here from the investigation of biofeedback and Deep Oscillation indicate sustained success of the physiotherapeutic methods studied, especially biofeedback therapy, in the treatment of secondary Raynaud's phenomenon. Long-term studies must show whether longer-term or even permanent reduction of Raynaud-associated symptoms can be achieved and to what extent the method must continue to be used. There is also the question whether one-time learning of the technique by the patient is sufficient or whether repeated training at regular intervals is necessary.

Because the Raynaud symptom complex in systemic scleroderma appears very early and represents a massive restriction of quality of life for patients, physiotherapeutic procedures should be more strongly integrated into treatment concepts for SSc patients.

Further intensive research is necessary to clarify the open questions and to optimize diagnostic methods and parameters for assessing therapeutic success.

The present work is intended to contribute to closing these gaps.

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APPENDIX

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CURRICULUM VITAE

For reasons of data protection, my curriculum vitae is not published in the electronic version of my work.

DECLARATION ON OATH

Declaration

"I, Birte Sporbeck, declare that I wrote the submitted dissertation entitled: 'On the influence of Deep Oscillation and biofeedback on subjective disease perception and tissue findings in scleroderma' myself and used no sources or aids other than those indicated; that I wrote it without the inadmissible help of third parties; and that I have not represented copies of other works, even in parts."

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