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Influence of a specific, biorhythmically defined physical stimulus on deficient vasomotion in small-caliber arterioles in the subcutis in patients with diabetic polyneuropathy

Abstract: As part of a placebo-controlled study series on a random sample of patients with diabetic polyneuropathy and trophic skin lesions on the edge of the foot, functional characteristics of the local microcirculation and immune system were measured to check the complementary-therapy success of biorhythmically defined vasomotion stimulation. Over a 30-day treatment period, complementary-therapy success was demonstrated for an additional physical vasomotion stimulation to increase the therapeutic success of established treatment concepts.

Keywords: complementary therapy; diabetic polyneuropathy; microcirculation; spontaneous arteriolar vasomotion.

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Introduction

The clinical pictures of polyneuritis and polyneuropathy represent extensive disorders of the peripheral nervous system and are divided into four main groups based on their causes: the inflammatory forms in a more narrow sense – triggered either by immunological or bacterial and/or viral infections, that is, vascular polyneuropathy – including collagenoses, toxicity-caused polyneuropathy and polyneuropathy with endocrinological-metabolical causes – including hereditary forms. The clinical picture reveals two main types: symmetric and asymmetric manifestation types. In the case of the symmetric manifestation type, one must distinguish between the symmetric-sensory and symmetric-paretic types. The asymmetric manifestation type can be divided into focal polyneuropathy as well as distal, symmetric-sensory deficits and reflex disorders. Diabetic polyneuropathy often starts with the latter manifestation type. As symptoms progress, the condition mostly transitions to the symmetric-paretic manifestation type with symmetric motor deficits. Typical signs and symptoms of a (largely treatment-resistant) diabetic polyneuropathy include trophic skin changes, sometimes with extensive ulceration of the foot.

With respect to the pathogenesis and effective treatment options for polyneuritis and polyneuropathy, there is still a great deal of research to be done. Since these clinical pictures are very likely not to represent separate diseases, but one organ manifestation among possibly many others, treatment is geared to the underlying condition (optimization of blood sugar control, possibly intensified insulin treatment). In addition, a number of measures to treat symptoms are used. It is not rare to encounter treatment resistance and indication for amputation.

Based on current knowledge, the clinical picture of diabetic polyneuropathy is accompanied by microcirculatory disorders, which can gradually become independent, develop a dynamic of their own and influence the course of the disease. In this context, arteriolar vasomotion, the most important regulatory mechanism of microcirculation, plays a prominent role. Most likely, this affects in the early stages of the condition mainly the vasomotion regulated at a higher level in the large-caliber arteriolar sections, which contain the corresponding receptors for neural commands and humoral agents. The spontaneous autonomic vasomotion in the small-caliber arteriolar sections that are immediately upstream from the capillary networks makes up only initially more or less effectively the disorders of its higher-level large-caliber arteriolar sections, and gradually behaves in its function for the blood-flow regulation in a manner...
that is metabolically inadequate and thus deficient. This does not only affect nutrition, but also the transport of the cellular and humoral factors of the immune system. The consequences of metabolically inadequate nutrition and impairment of immune responses are ulcerations and/or necroses at the most prominent locations for diabetes-related circulation problems (especially the subcutis in the foot) [1–3].

As concerns effective treatment options to stimulate deficient arteriolar vasomotion, one cannot expect causal-therapeutic success, but certainly success with respect to complementary therapy. This can help optimize the treatment by way of attenuating the symptoms and, at least, slow down the progression of the condition. For the large-caliber arteriolar section, there are pharmacological treatment options (transfer of chemical energy). The small-caliber arteriolar section, given its locally regulated spontaneous autorhythmic vasomotion, does not respond to direct pharmacological treatment because of its lack of receptors. In terms of physical energy transfer, a specific, biorhythmically defined stimulus is recommended for spontaneous vasomotion: the “oscillatory system of the small-caliber arteriole” is stimulated, in a formally analog manner to a (damped) resonator, in the direction of physiological regulatory ranges.

Terms of reference

As part of a placebo-controlled study series involving a biometrically defined random sample of patients suffering from diabetic polyneuropathy and trophic skin lesions along the edge of the foot, the task was to examine, using valid measurements with high-resolution methods of investigation, whether and to what extent the complementary use of a biorhythmically defined physical stimulation of spontaneous arteriolar vasomotion could help improve the therapeutic success of established treatment concepts.

Materials and methods

The study comprised a total random sample of 18 male patients with diabetic polyneuropathy (Table 1) who were treated as outpatients over the study period.

GCP-compliant definition of inclusion and exclusion criteria.

Main diagnosis: Diabetic polyneuropathy.
Adult-onset diabetes, trophic skin lesions on the foot (ulcer area approx. 3 cm²).

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Body mass, kg</th>
<th>Body length, cm</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>67.2±4.3</td>
<td>78.4±2.9</td>
<td>174.7±3.1</td>
<td>♂</td>
</tr>
</tbody>
</table>
patients was the “Bemer Plus” (commercially available from the company Bemer International AG, Triesen, FL).

Application of the complementary treatment: daily \(2 \times 10\) min, approx. 6 h apart (mat, intensity level 3), always at the same time (approx. 11:00 AM and approx. 5:00 PM).

**Measuring time points**

The measurements were taken at equidistant measuring time points over the 30-day treatment interval (on each measurement day 1 h after the second treatment, approx. 6:00 PM):

- Day 0 (determination of initial values prior to the start of treatment), subsequently on Day 1, Day 10, Day 20 and Day 30.

**Collection of measured values under constant conditions**

Measurements taken with patients lying down, under constant macrocirculatory and temperature-regulatory conditions. No alcohol, coffee, tea or cola beverage 2 h prior to the examinations. At least 6 h of sleep every day, no biotropic weather conditions over the observation period.

**Target tissue and subcutis**

The subcutis was chosen as the representative target tissue for the detection of functional characteristics of microcirculation:

- Defined subcutaneous tissue region (affected foot region, edge area of ulcer wound, approx. 8 mm from wound edge).
- Penetration depth of approx. 2.5 mm to approx. 3.5 mm.

The measurement methods used for therapy control were non-invasive [1, 4–8]. In the defined target tissue (volume \(V=1200\) \(\mu\)m\(^3\)), contiguous microvascular networks with vessel diameters \(d \leq 200\) \(\mu\)m were captured.

For each patient, a respective initial value was defined at the measuring time \(t=0\): 60 blood-cell-perfused nodes (branching sites of microvessels) within a contiguous microvascular network.

- The instrument system for the laser Doppler microflow measurement and white light spectroscopy (LEA, Giessen, Germany) allows for the determination of spectrometric and dynamic characteristics in microvascular networks with vessel diameters 7 \(\mu\)m \(\leq d \leq 200\) \(\mu\)m. Information on validation and measurement specifications is provided in the literature [5, 8–10].
- The reflection spectrometry unit (Spex system, USA) was combined with the microscopic unit via a commercially available interface (Zeiss Axiowert, Germany; Nikon Diaphot, Olympus IMT-2, Japan). In microscopic target volumes, it allows for relative measurements of changes in the concentration of excitable organic substances (computer-based evaluation of spectra). The validation of the method and the measurement specifications (especially for white balance) are presented in detail in the literature [11].
- As the imaging measurement method, a vital-microscopic unit was used in a combined incident-transmitted-light method with secondary computer-based image processing to study the subcutaneous microcirculation (incident-transmitted-light microscopes with prismatic joints for lens mounting, Zeiss, Germany; Nikon, Olympus, Japan). The findings were documented by means of 35 mm Cine film (Agfa-spezial, high-resolution) and the high-speed camera system ARRI (Arnold & Richter, Germany) with 60–90 frames per second. The image-to-image analysis was performed by means of the transfer system Cipro (Cipro, USA) and the computer system IBAS 2000 (interactive image analysis system Kontron, Germany; Mipron software, Medical Image Processing) [1, 3, 6, 7].
- Specific incident-light microscopy under defined lighting conditions (Zeiss, Technival) for computer-based determination of the area of the wound (planimetry).

The measured data were collected in the same tissue region at each measuring time. For this purpose, the measurement region was marked at the first measuring time (Day 0), and the respective target network was stored on the computer. The microvessel representations at subsequent measuring times were compared with the initial findings on Day 0 by means of a digital subtraction program. The comparison criterion was the least differential signal (near zero).

The following characteristics of the functional state of the microcirculation were measured in the subcutaneous target tissue:

- **Area under the envelope of the amplitude-frequency spectrum of the arteriolar (spontaneous) vasomotion, \(A_{\text{VM}}\).**
Expressed as the percentage change compared with the respective baseline at the measuring time \( t = \text{Day 0} \), which was set equal to zero. Methodological approach: Determination of the time-distance function of the arteriolar vessel-wall oscillation by measuring precisely the vessel diameter at a defined measurement location at equidistant time points (10/s), Fourier analysis of the composite oscillation, representation of the amplitude-frequency spectrum.

- **Venular oxygen saturation** \( \Delta p_{O_2} \) (difference in the oxygen saturation of the hemoglobin in the afferent arterioles and efferent venules of the target network). Expressed as the percentage change compared with the respective baseline at the measuring time \( t = \text{Day 0} \), which was set equal to zero.

- **Number of adherent white blood cells on a defined venular inner wall area** \( A, n_{WBC/A} \).
  \( A = 18,000 \mu m^2 \).

- Concentration of ICAM-1, \( c_{\text{ICAM-1}} \). Specified in relative units (0–10).

**Statistics**

The statistical analysis of the measured data was done using a non-parametric test method for small samples. The Wilcoxon rank sum test at the significance level \( \alpha = 5\% \) was used. The critical values for \( T \) were taken from the literature [12].

For each sub-sample, the initial values at the time \( t=0 \) were checked against the measured values at subsequent measuring times. Furthermore, the measured data of both sub-samples were compared at the same measuring times \( t \).

**Results**

Figure 1 (A and B) illustrates two states of the arteriolar vasomotion at consecutive observation times on the basis of an example of vital-microscopic findings.

The measured data obtained from the two sub-samples (control, verum) regarding the microcirculatory and immunological characteristics studied are summarized in Figures 2–5 (means and standard deviations).

In all characteristics studied, no significant differences between the two sub-samples were observed on measurement day 0.

Figure 2 shows the measured values for the characteristic “area under the envelope of the amplitude-frequency spectrum of arteriolar vasomotion \( A_{\text{VM}} \)”. No significant characteristic changes were observed in the control group over the 30-day observation interval when compared to the initial values. In contrast, the measured data obtained from the verum group showed significant differences to the initial values from Day 1 to Day 30. On Day 30 of the treatment, an increase in vasomotor activity by 7.58% (5.45) was observed. A statistical comparison of the measured values control versus verum revealed significant differences from Day 1 to Day 30.

The measured data on the characteristic “venular oxygen saturation \( \Delta p_{O_2} \)” exhibit a corresponding characteristic behavior (Figure 3). There are no significant characteristic changes in the control group when compared to the initial values; in the verum group, the measured data are significantly different from the initial values from Day
Over the same period, the measured data in both sub-samples differ significantly from each other. On Day 30 of the treatment, the venular oxygen saturation in the verum group had increased by 5.51% (5.09).

Figure 4 shows the measured data on the immunological characteristic “number of adherent white blood cells on a defined venular inner wall area A, nWBC/A”. No significant characteristic changes were observed in the control group when compared to the initial values. A significant increase in the adhesion behavior of white blood cells was observed in the verum group from Day 1 to Day 30 of the treatment. On Day 30 of the treatment, the number of adherent white blood cells increased by 7.36% (5.81) relative to the corresponding initial values.

Figure 5 contains the measured data on the intracellular adhesion molecule ICAM-1. A small, significant decrease in the concentration was observed in the control group from Day 10 to Day 30 of the treatment. By contrast,
the ICAM-1 concentration levels increased significantly in the verum group from Day 1 to Day 30 of the treatment. A statistical comparison of the measured values demonstrated significant differences between the sub-samples control and verum on Day 20 and 30 of the treatment.

On measurement day 0 and Day 30 of the treatment, the skin area (wound area on the foot) affected by ulceration was measured in both sub-samples. The planimetric findings are shown in Table 2 (means and standard deviations). The measured data in the control group do not differ significantly from the initial values. In contrast, the reduction of the ulcer area in the verum group was significant.

### Discussion

The present measurement results show a slight improvement in the functional state of the subcutaneous microcirculation and cellular immune response in the peripheral area of the foot wound in patients of the verum group following the complementary application of the treatment device “Bemer Plus”, as opposed to control-group patients.

There was no indication of adverse effects of the complementary device system Bemer Plus.

The increase in venular oxygen saturation observed in the verum group is attributed to the stimulation of the spontaneous arteriolar vasomotion as a result of the complementary Bemer treatment. The influence of the spontaneous arteriolar vasomotion on the segregation effects of blood cells and blood plasma in the microvascular networks and, thus, on the functional state of the microcirculation was already demonstrated by other studies [3, 13, 14].

Associated with the improved flow conditions of the plasma-blood-cell mixture in the microcirculation are also microhemodynamically more favorable boundary conditions for the unhindered sequence of cellular (and humoral) immune responses, as the measured data on the leukocyte adhesion behavior and ICAM-1 in verum-group patients demonstrate [3, 13–16]. The increased adhesion of white blood cells in verum-group patients (significant characteristic differences), compared to control-group patients, indicates increased immunological activities in the tissue of the wound edge, and is reflected in a slight decrease in the ulceration in patients who received complementary treatment.

Considering the amounts of the characteristic changes observed in verum-group patients, one should note that the conventional treatments administered to both sub-samples were not successful for the control group in respect of the characteristics studied over the observation period. Keeping in mind that diabetic polyneuropathy is among the most common forms of polyneuropathy and that, furthermore, drug-based and physiotherapeutic treatment options of conventional medicine are limited for this clinical picture, and not rarely culminate in an indication for amputation, even relatively minor microcirculatory characteristic changes justify the complementary-therapeutic use of the Bemer system.

In conclusion, it is found that the therapeutic success of established (drug-based and physiotherapeutic) treatment concepts can be enhanced through the complementary use of the Bemer system. A prophylactic or complementary-therapeutic use of the treatment device Bemer Plus seems promising also in connection with other conditions of limited or impaired microcirculation.

Finally, it should be noted that the presented measured data were obtained from a particular sample, and will therefore require further clinical scrutiny. Furthermore: The present study results were obtained by using a specific treatment unit, and are therefore not readily transferable to any other treatment devices.

### Summary

To test whether and to what extent the complementary use of a biorhythmically defined physical stimulation of deficient spontaneous arteriolar vasomotion would improve the therapeutic success of established treatment concepts, a biometrically defined random sample of patients with diabetic polyneuropathy and trophic skin lesions at the edge of the foot, as part of a placebo-controlled study series, were subjected to measurements of characteristics of the functional state of microcirculation and the immune system. The measurements were carried out by means of high-resolution methods. Over a 30-day treatment and/or observation interval, it was possible to demonstrate a

### Table 2 Area of ulceration on the affected foot.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Verum</th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
<td>1.42</td>
<td>-4.70</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>2.98</td>
<td>2.85</td>
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</tbody>
</table>

Percentage changes on Day 30 of the treatment compared to the baseline on Day 0.
complementary-therapeutic success of the biorhythmically defined physical vasomotion stimulation used in the random sample studied.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Overall research funding played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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