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Complementary-therapeutic stimulation of deficient autorhythmic arteriolar vasomotion by means of a biorhythmically physical stimulus on the microcirculation and the immune system in 50-year-old rehabilitation patients

Abstract: As part of a placebo-controlled study series, a random sample of 50-year-old rehabilitation patients was examined to determine whether the complementary use of a physical treatment method to stimulate arteriolar vasomotion would improve the therapeutic success of established measures for the purposes of physical conditioning. The result showed that both the microcirculatory blood-flow regulation and the (cellular) immune response could be affected in a therapy-relevant manner through additional physical vasomotion stimulation.

Keywords: complementary therapy; physical conditioning; physiotherapy; rehabilitation.

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Introduction

The multimorbidity of older patients, for whom increased susceptibility to infections is significant, poses many problems. Older multimorbid patients are mostly treated in multiple ways (drug-based). This simultaneous administration of several medically indicated prescribed drugs raises questions:

For a number of drugs, there is only inadequate knowledge about the required doses for older people and their age-related reduced organ functions. Research is required on the interactions between different drugs taken at the same time with each other and the organism. The problem of adverse drug effects only too often becomes unpredictable in the case of multi-drug therapy.

In addition to further research efforts in the field of pharmacology, the other main focus is on developing effective, targeted physical treatment measures that can complement the established drug-based measures, as well as the generally effective and recognized physiotherapeutic treatment measures in terms of therapy optimization.

It is now generally recognized that disturbances in microcirculation – regardless of whether they are the cause, consequence or side effect of a macrocirculatory disturbance – can gradually become independent and assume a dynamic of their own in shaping the course of the condition, often independently of further macrocirculatory events. The most important regulatory mechanism of microcirculation and, thus, of the blood supply to organs is arteriolar vasomotion. The different microvessel diameters and their rhythmic changes in diameter influence the different segregation effects between blood plasma and blood cells with respect to microcirculation, and mainly determine the distribution of the plasma-blood-cell mix in the capillary networks. The higher-level, regulated vasomotion processes occur in the large-caliber arteriolar sections that contain the corresponding receptors for neural commands and humoral agents. Spontaneous autorhythmic vasomotion, with its own biorhythm, takes place in the small-caliber arteriolar sections that are immediately upstream from the capillary networks [1–6].

The efficiency of the blood-flow regulation and its regulatory range, i.e., its degree of adaptability with respect to changing metabolic requirements of the tissue to be supplied, does not only affect nutrition, but also the transport of cellular and humoral factors of the immune system. The consequences of metabolically inadequate nutrition and
impaired immune responses include limitations or even dysfunctionality of the organ to be supplied [2, 6].

Thus, effective treatment options for the physical and targeted stimulation of a deficient arteriolar vasomotion are not only of great importance in preventive medicine, but are also of great interest with respect to complementary therapy.

The vasomotor processes in the large-caliber and small-caliber arteriolar sections exhibit different biorythms; they can reinforce regulations together, or compensate each other for deficits within certain limits. A problem arises when the two vasomotion effects are not in harmony with each other, as may happen in the case of chronic stress. It is not rare for many older, multimorbid patients to be affected by this [2, 6].

For the large-caliber arteriolar section, there are drug-based therapy options (transfer of chemical energy); the locally regulated spontaneous autorhythmic vasomotion in small-caliber arteriolar sections, however, does not have corresponding receptors, which is why it cannot be influenced directly through pharmacological means.

Given today’s scientific-technical expertise, it is possible to transfer physical energy via a specific biorythmically defined stimulus to stimulate deficient spontaneous vasomotion [7].

Terms of reference

A biometrically defined random sample of older rehabilitation patients, as part of a placebo-controlled study series, was to be subjected to valid measurements of representative characteristics of microcirculation and the immune system by way of high-resolution methods to examine the extent to which the complementary use of a biorythmically defined stimulus for physical stimulation of spontaneous arteriolar vasomotion could contribute to prevention as well as improving the therapeutic success of established treatment concepts.

Materials and methods

The tests were done on a total random sample of 24 male rehabilitation patients (Table 1), on the basis of a GCP-compliant definition of inclusion and exclusion criteria.

General treatment: physical conditioning of individuals exposed to chronic stress and infections through mild daily exercise and walks; counseling for a health-conscious lifestyle.

The total sample was divided randomly into two equal sub-samples:
- **Control (placebo)** n=12 Physical conditioning *without* additional treatment for physical stimulation of spontaneous arteriolar vasomotion.
- **Verum** n=12 Physical conditioning *with* additional treatment for physical stimulation of spontaneous arteriolar vasomotion.
- Treatment period 30 days.

The complementary treatment was performed with the treatment device “Bemer Plus” (commercially available from the company Bemer International AG, Triesen).

In the case of the Bemer system, physical stimulation of spontaneous autorhythmic arteriolar vasomotion in connection with metabolically inadequate blood-flow regulation is achieved by means of a specific biorythmically defined stimulus, with the energy transfer being realized via a weak electromagnetic field (flux density ≤100 µTesla). The complex stimulus signal contains a stimulation signal in line with the mean physiological vasomotion rhythm of three vasomotion movements per minute.

Application of the complementary treatment

Application of the complementary treatment daily 2×12 min, approx. 2–3 h apart (mat, intensity level 3), always at the same time.

The patients in the control group were placed on the Bemer treatment mat, like the patients in the verum group, but for control-group patients the mat was not turned on (without telling the patients).

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): Day 0 (determination of initial values prior to the start of treatment), subsequently on Day 5, Day 10, Day 15, Day 20, Day 25 and Day 30.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Constitutional characteristics of the patients.</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>Body mass, kg</td>
</tr>
<tr>
<td>50.8±3.4</td>
<td>83.2±4.5</td>
</tr>
</tbody>
</table>
Collection of measured values under constant conditions

Measurements were 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, because it is tissue that is representative of the circulation and is among the immunologically most active areas of the organism.

- Defined subcutaneous tissue region (abdomen, caudal area in the epigastric angle).
- Penetration depth of measurements approx. 2.5 mm to approx. 3.5 mm.

Only non-invasive measurement methods were used [2, 8, 9]. In the defined target tissue (volume V=1200 µm³), contiguous microvascular networks with vessel diameters d≤200 µm were captured.

For each patient, a respective initial value was defined at the measuring time t=0 in a specific daily volume: 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) made it possible to determine spectrometric and dynamic characteristics in microvascular networks with vessel diameters 7 µm≤d≤200 µm. Information on validation and measurement specifications is provided in the literature [10–13].
- The reflection spectrometry unit (Spex system, USA) was combined with the microscopic unit via a commercially available interface (Zeiss Axiocvert, Germany; Nikon Diaphot, Olympus IMT-2, Japan). In microscopic target volumes, it allowed for relative measurements of changes in the concentration of excitable organic substances (computer-based evaluation of spectra). For information on the validation of the method and the measurement specifications (particularly regarding white balance), refer to the literature [14].
- As the imaging measurement method, a vital-microscopic unit was used in a combined incident-transmitted-light method with secondary computer-based image processing (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) [2, 6, 9].

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).

Figure 1 shows the block diagram of the test facility.

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

- **Area under the envelope of the amplitude-frequency spectrum of the arteriolar (spontaneous) vasomotion, A_{AVM}**
  Expressed as the percentage change compared with the respective baseline at the measuring time t=Day 0, which was set equal to zero. 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 flow Q_{ven}**
  Particle flow (blood-cell flow) in defined venules and/or changes in the flow (stated as percentage changes relative to the initial values at the measuring time t=0).

- **Number of the blood-cell-perfused nodes in a defined tissue volume unit, nNP**
  The number of blood-cell-perfused nodes (branching sites) were counted in the defined target network as a measure of the state of distribution of the blood in the microcirculation. \(v_{RBC}=80 \text{ µm/s}\) was defined as the boundary flow velocity of the red blood cells.
The evaluation was performed on the basis of + or − (compared to the initial value n=60). Borderline cases were evaluated with +0.5 or −0.5 (stated as percentage changes relative to the initial values at the measuring time t=0).

- **Venular oxygen saturation ΔpO₂**
  Difference (absolute) 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=Day 0.

- **Number of transmigrated white blood cells in a defined tissue volume unit V, nBC/V**
  V=1200 µm³.
  Expressed as the percentage change compared with the respective baseline at the measuring time t=Day 0.

- **Concentration of ICAM-1, cICAM-1**
  Determined in relative units (0–10).
  Expressed as the percentage change compared with the respective baseline at the measuring time t=Day 0.

### Statistics

For the statistical analysis of the measured data obtained, a non-parametric test method for small random samples was used that is among the most precise biometric methods. The Wilcoxon rank sum test at the significance level α=5% was used. The critical values for T were taken from the literature [15].

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=t.

### Results

Figures 2A, B and 3A, B show selected examples of vital-microscopic findings from the subcutaneous target tissue in a patient of the verum group to illustrate the success of treatment. Figures 4–9 show the measured data obtained of the investigated characteristics for both sub-samples.

Figure 4 shows the measured values for the characteristic “area under the envelope of the amplitude-frequency spectrum of arteriolar vasomotion AᵥM”.

From Day 5 to Day 30 of the treatment, there were significant characteristic changes both in the control and verum groups compared to the initial values. In the same period, the measured values for the control and verum groups were significantly different from each other.

The characteristic behavior of AᵥM was determined on the basis of the determination of the spontaneous
arteriolar vasomotion frequency in both sub-samples in the subcutaneous target tissue on Day 0 (initial values):

Vital-microscopic determination of the vasomotion oscillation by way of measuring the vessel diameters at a defined measuring point at equidistant measuring times (Table 2).

On Day 30 of the treatment, the control group exhibited an increase in spontaneous vasomotor activity by 8.6%±2.51% over the initial values; a much greater increase was observed in the verum group at 30.6%±2.50%.

The measured data on the characteristic “venular flow $Q_{ven}$” and the results of the statistical analysis correspond to the measured data evaluated for the characteristic $A_{AVM}$ (Figure 5). In the control group, the venular outflow increased by Day 30 by only 5.5%±1.78% relative to the associated initial values. In the verum group, venular outflow had increased by 32.8%±2.58% as of Day 30.

A similar characteristic behavior was also observed for the characteristic “number of blood cell-perfused nodes nNP” (Figure 6). On Day 30 of the treatment, the number of blood-cell-perfused capillaries in the control group had only increased by 4.4%±1.76%, while the verum group saw a rise by 34.8%±2.48%. From Day 5 to Day 30 of the treatment, the measured data differed from the respective initial values significantly for both sub-samples, as well as over the same period from each other.

The measured data on the characteristic “venular oxygen saturation $\Delta pO_2$” can be seen in Figure 7. In the control and verum groups, the measured data were significantly different from the respective initial values from Day 5 to Day 30, and over the same period the measured data of the two sub-samples also differed significantly from each other.

As of Day 30 of the treatment, venular oxygen saturation had increased by 38.5%±1.93% in the verum group, but only by 3.1%±1.03% in the control group.

Figure 8 shows the measured data on the immunological characteristic “number of transmigrating white blood cells in a defined tissue volume unit $V$, $nBC/V$”. Over the 30-day treatment interval, only a small increase in the number of transmigrating leukocytes was observed in the control group (4.6%±1.47%). Patients of the verum group exhibited a different characteristic behavior. The number of transmigrating white blood cells increased up to Day 10 of the treatment significantly by 59.3%±3.45%, then dropped off again, and on Day 30 achieved significantly lower values than on Day 0 (–3.8%±2.11%).

The measured data on the intracellular adhesion molecule ICAM-1 showed a characteristic behavior similar to nBC/V. In the control group, a significant increase in ICAM-1 had been observed up to Day 30 of the treatment (8.9%±1.84%). In verum-group patients, ICAM-1 increased up to Day 10 by 69.5%±3.48%, then dropped off again, and on Day 30 of the treatment reached significantly lower values than on Day 0 (–4.5%±2.66%).

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

Discussion

The study results are interpreted as follows in accordance with the accepted views of the current state of knowledge in the field [5, 6, 16, 17]:

The measured results obtained provide statistically sound statements about the fact that the physical
stimulation applied achieved a prophylactically and complementary-therapeutically relevant influence on spontaneous arteriolar vasomotion among the verum-group patients examined. This affects not only the arteriolar inflow into the capillary networks of the subcutaneous target tissue, but also the venular outflow. This is of particular prophylactic importance, because disorders of the microcirculation mostly begin in the venules.

The expansion of the local regulatory range for the blood supply as a result of the stimulated spontaneous arteriolar vasomotion, which was demonstrated to have been achieved in verum-group patients through the use of the Bemer system, manifests itself in an increase of the capillaries of the microvascular networks perfused with the plasma-blood-cell mix, which improves the diffusion conditions for the metabolism. This produces a greater
microcirculatory reserve for the appropriate blood flow. Another consequence of the improved arteriolar blood-flow regulation, as was demonstrated following the complementary use of the Bemer system, is an increase in the oxygen saturation of the microcirculation.

The dynamic characteristics of the functional state of the microcirculation determine also the microhemodynamic boundary conditions for the initial steps of a (cellular) immune response – the flooding and distribution of the white blood cells in the microvascular networks, the
roll-off phenomena at the endothelium, the adhesion processes, and finally the transmigration of the white blood cells into the tissue. Based on the measured results on the transmigration behavior of the leukocytes, it has been shown that the additional use of the Bemer system creates a stronger infection defense and/or reduced susceptibility to infections. A rapid-onset, significant rise in the number of transmigrating leukocytes could be demonstrated only in verum-group patients as a sign of increased (cellular) immune responses; the subsequently reduced transmigrations are expressions of the successful defense response. For control-group patients, also exposed to infections, however, only minor transmigrations of white blood cells could be detected over the treatment period.

In conclusion, it is found that the therapeutic success of prophylactic and rehabilitative treatment concepts can be enhanced through the complementary use of the Bemer system. A prophylactic or complementary-therapeutic use of biorhythmically defined physical vasomotion stimulation.

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.

Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

Summary
As part of a placebo-controlled study series involving a random sample of 24 male rehabilitation patients aged approx. 50 years, high-resolution measurement methods were used to document microcirculatory and immunological functional characteristics in order to examine whether and to what extent the additional use of physical stimulation of deficient arteriolar vasomotion could enhance the therapeutic success of established measures of physical conditioning. The result of the tests showed that both representative characteristics of microcirculatory blood-flow regulation and cellular immune responses in the subcutaneous target tissue studied could be affected in a therapy-relevant manner through additional physical vasomotion stimulation. This speaks in favor of a prophylactic and complementary-therapeutic use of biorhythmically defined physical vasomotion stimulation.

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.

Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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