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## Effects of various physical treatment methods on arteriolar vasomotion and microhemodynamic functional characteristics in case of deficient regulation of organ blood flow. Results of a placebo-controlled, double-blind study

**Abstract:** As part of a placebo-controlled study, high-resolution measurement methods were used to examine, on the basis of representative functional characteristics of microcirculation, whether and to what extent six different, commercially available, physical treatment devices were suitable for influencing, through complementary therapy, deficient blood-flow regulation. Of the six commercially available devices tested, two proved to be ineffective and three not effective enough to be therapeutically relevant. Only in one device was it possible to show a complementary-therapeutic effect: the device uses a specific, biorhythmically defined stimulus for vasomotion.

**Keywords:** complementary therapy; physical conditioning; stimulation of organ blood flow; vasomotion.

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### Introduction

Microcirculation is the most important part, functionally speaking, of human blood circulation. It is here that the transport phenomena of cell nutrition occur (exchange of O<sub>2</sub> and CO<sub>2</sub> per diffusionem, transport of substrate and metabolic end product in the transcapillary fluid exchange), as well as the initial steps of immune responses (transport of plasmatic factors of the immune system, roll-off, adhesion and transmigration processes of white blood cells). The functional state of microcirculation and its regulatory range (so-called microcirculatory reserve) are, thus, decisive for the functioning and/or performance

of organs and the immune system. Disturbances in microcirculation are less often limitations on the overall volume of blood that flows through organic tissue in a given time unit than they are problems in distributing the plasma-blood-cell mix in the microvascular networks. The most important regulatory mechanism of microcirculation and/or the blood supply of organs is arteriolar vasomotion. The rhythmic diameter changes influence the segregation phenomena between blood plasma and blood cells in muscle-reinforced microvessels, and thus 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. These diameter variations and their distance-time functions (vascular wall oscillations) are the result of the shear-force-dependent formation and release of nitrogen monoxide in connection with the tone regulation facilitated by the endothelium [1–7].

The vasomotor processes in the large-caliber and small-caliber arteriolar sections exhibit different biorhythms. Physiologically, 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 [8, 9]. For the large-caliber arteriolar section, drug-based treatment options are available (transfer of chemical energy). Locally regulated spontaneous autorhythmic vasomotion in the small-caliber arteriolar sections cannot be influenced directly by pharmacological means, but physical energy can be transferred through a specific, biorhythmically defined stimulus as a therapeutic method in case of deficient spontaneous vasomotion [8].



Thus, effective treatment options for the physical and targeted stimulation of deficient arteriolar vasomotion are not only of great importance in preventive medicine, but are also of great interest with respect to complementary therapy for the purpose of improving the therapeutic success of established drug-based treatment measures.

### Terms of reference

A random sample of approx. 50-year-old test subjects, as part of a placebo-controlled study series, was subjected to valid measurements of representative characteristics of microcirculation by way of high-resolution investigative methods in order to examine whether and to what extent complementary uses of different, commercially available physical treatment devices could be successful in the physical stimulation of spontaneous arteriolar vasomotion and, thus, in the reduction of deficits in the blood supply of organs by way of prophylaxis, as well as whether and to what extent they could help improve the therapeutic success of established treatment concepts.

### Materials and methods

The tests were performed on a biometrically defined random sample of 12 male patients (Table 1) exposed to moderate chronic stress and mixed infections (mild rhinitis, otherwise without pathological findings as per family physician). The inclusion and exclusion criteria were defined in a GCP-compliant manner. The patients did not undergo any drug-based or other medical or physiotherapeutic treatments during the study interval.

Over intervals of 12–14 days, test subjects were subjected to a total of 6 different 3-day treatments with different commercially available treatment devices that, according to the respective manufacturers, were capable of having a therapy-relevant effect on the organ blood flow (and/or microcirculation). In addition, a placebo device was available. Table 2 provides information on the test equipment used.

**Table 1** Constitutional characteristics of the patients.

	Age, years	Body mass, kg	Body length, cm
Mean	51.3	79.0	175.5
Standard deviation	1.9	4.1	2.6

### Test equipment

Test device 1: Ineffective, deceptively similar replica of a treatment device (placebo device). When pressing the power button, battery-powered LEDs feigned a function of the dummy.

Test devices 2–6: Various time-repetitive waveforms (electromagnetic fields of low flux density) without specific stimulation signal.

Test device 7: Biorhythmically defined pulse configuration for stimulating the higher-level, regulated and especially spontaneous arteriolar vasomotion (electromagnetic field of low flux density,  $\mu\text{T}$  range).

### About using the test equipment

The equipment was applied with the patients lying down on the mats supplied by the respective manufacturers. The settings were medium (electro-)magnetic flux densities (according to manufacturer's specifications), which corresponded to level 3 of the test device 7 (verified by flux density measurements prior to start of the study).

The treatments were administered in a 3-day treatment interval 2× daily 10 min at intervals of 2 h (between 3:00 PM and 6:00 PM).

Table 3 provides information on the measuring time points.

To eliminate systematic errors or other factors distorting the measured results and their statistical analysis, the test equipment, measured value surveys and data analyses were randomized (strict random allocation of test subjects to the test equipment according to randomization list, determination of sequence of test equipment to be used for each test subject by random selection). The operation of the treatment devices, including all measured value surveys and analyses of measured data, were performed by different people. Neither the investigator nor the test subject had any knowledge, both prior to and during the examinations, of the respective test equipment

**Table 2** Test equipment.

Test device	Trade name
Test device 1	Placebo device
Test device 2	Magneter
Test device 3	Impulser
Test device 4	Terramagnon
Test device 5	SENTIPLUS Professional
Test device 6	iMRS
Test device 7	BEMER Classic

to be used (including the placebo device) according to the randomization list.

#### About the boundary conditions in collecting the measured values

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 of approx. 2.5 mm to approx. 3.5 mm.

Only non-invasive measurement methods were used. In the defined target tissue (volume  $V=1200 \mu\text{m}^3$ ), contiguous microvascular networks with vessel diameters  $d \leq 200 \mu\text{m}$  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 following non-invasive systems for collecting measured values were used:

- Laser Doppler microflow measurement and white-light spectroscopy (LEA, Germany). Spectrometric measurement and dynamic characteristics in microvascular networks with vessel diameters  $7 \mu\text{m} \leq d \leq 200 \mu\text{m}$ . Information on validation and measurement specifications is provided in the literature [2, 10–14].

- Reflection spectrometry unit (System Spex, USA). Connected to microscopic unit (Zeiss Axiovert, Germany; Nikon Diaphot, Olympus IMT-2, Japan) via a commercially available interface. Allows in microscopic target volumes for relative measurements of changes in concentration levels of excitable organic substances (computer-based evaluation of spectra). The validation of the method is proven [14, 15].
- 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 Cipro system (Cipro, USA) and the computer system IBAS 2000 (interactive image analysis system Kontron, Germany; Mipron software, Medical Image Processing) [2, 7, 9, 16].

The measured data were collected in the same tissue region at each measuring time. In this context, the representation of the target network at the first measuring time point (Day 0) 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).

For the following representative characteristics of the functional state of microcirculation, measured values were collected in the subcutaneous target tissue:

- Area under the envelope of the amplitude-frequency spectrum of the arteriolar (spontaneous) vasomotion,  $A_{VM}$ .
- Expressed as the percentage change compared with the respective baseline at the measuring time  $t = \text{Day } 0$ , which was set equal to zero.

**Table 3** Equidistant measuring time points in 3-day treatment interval.

Day 0	Determination of initial values one day prior to start of the study
Day 1	Collection of measured values immediately after the 2nd treatment on 1st day of treatment
Day 2	Collection of measured values immediately after the 2nd treatment on 2nd day of treatment
Day 3	Collection of measured values immediately after the 2nd treatment on 3rd day of treatment
Day 4	Collection of measured data on determining the wearing off of characteristic changes after the end of treatments.



Steps: 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. Determination of the area under the envelope 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) was counted in the defined target network as a measure of the state of distribution of the blood in the microcirculation.  $v_{RBC}=80 \mu\text{m/s}$  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  $\Delta pO_2$ .  
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  $t=\text{Day } 0$ .

The required constancy of boundary conditions in obtaining measured values was monitored by accompanying measurements of systemic characteristics (heart rate, systemic blood pressure, respiratory rate, body core temperature).

## 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  $\alpha=5\%$  was used. The critical values for T were taken from the literature [17].

For each sub-sample (the respective test device application), the measured values at the time  $t=0$  were checked against the measured values at subsequent measuring times. In addition, the measured values of all sub-samples

studied (test device applications 1-7) were compared to each other at the same measuring times  $t=t$ .

## Results

The statistical analysis of the measured data obtained showed for all characteristics studied a significantly different characteristic behavior following the use of the respective test equipment. The best results were obtained after using test device 7, compared to the test devices 1-6. Figure 1 shows an example of vital-microscopic findings from the subcutaneous target tissue in a test subject on the 3rd day of treatment with the test device 7.

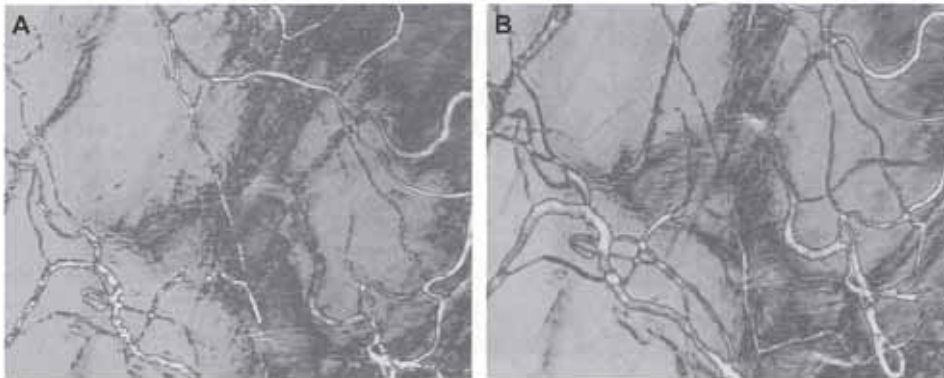
The measured data on the characteristic "number of blood-cell-perfused nodes nNP" yield information on the distribution state of the plasma-blood-cell mix in the microvascular networks. They are represented as a graph for the test devices 1-7 in Figure 2.

After application of the placebo device (test device 1), no significant characteristic changes were observed in the entire observation interval. Minor significant characteristic changes from the initial values were detected for the test devices 2 and 4 on Day 2 and 3 of the treatment. The characteristic changes found for the two test devices on Day 2 and 3 of the treatment were significantly different from the values of the placebo device at the same measuring times, but they did not differ significantly from each other. A day after the treatment had ended (Day 4), the measured data for the test devices 2 and 4 were again in line with the initial values. The biggest characteristic changes compared to the initial values were approx. 3%.

After application of the test devices 3, 5 and 6, significant characteristic changes from the respective initial values occurred on Day 1 and 3 of the treatment, and reached their highest levels at approx. 7% on Day 2 of the treatment. On Day 4 of the measurements, no significant differences from the respective initial values were detected. The measured data for the test devices 3, 5 and 6 differed significantly from those of the test devices 2 and 4 on Day 2 and 3 of the treatment.

The measured data obtained for test device 7 were significantly different from all other test devices tested from Day 1 to 4 of measurements; from Day 1 to 4 they had differed significantly from their initial values. The following measured data were obtained after application of the test device 7: Day 1/14.5%±1.48%, Day 2/22.6±1.88, Day 3/27.1±1.92, Day 4/18.5±1.85.

Figure 3 shows the measured data for the test devices 1 to 7 on the microhemodynamically important characteristic "venular flow  $Q_{ven}$ ".

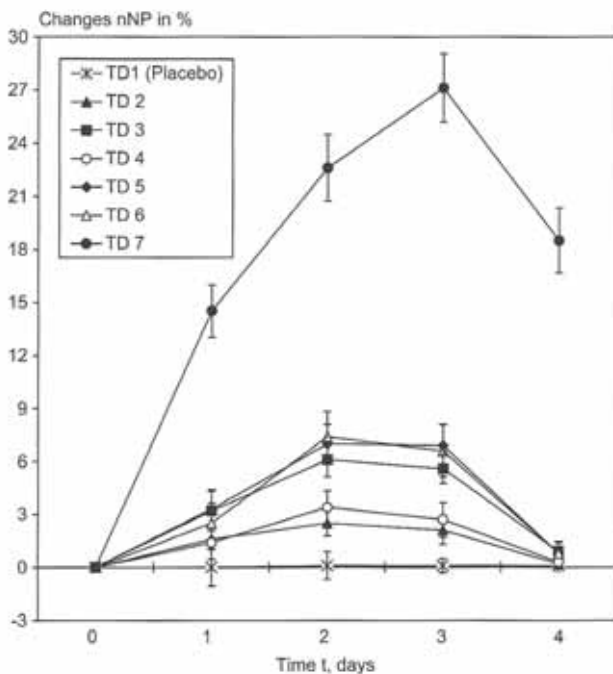


**Figure 1** Example of vital-microscopic findings from the subcutaneous target region of a test subject who was treated with test device 7, at two different observation times (pseudo color translation of primary figures; blood-cell-perfused microvessels are highlighted in yellow). Distribution state of the plasma-blood-cell mix in the microvascular network of the subcutis (arterioles, capillaries, venules). (A) Day 0 (baseline prior to treatment). (B) State on Day 3 of the treatment.

The results of the statistical analysis correspond to the evaluated measured data for the characteristic nNP. Convincing measured data were obtained only after using the test device 7. Compared to the initial values (Day 0), the venular flow increased significantly on Day 1 by  $13.3 \pm 1.86\%$ , on Day 2 by  $19.6 \pm 1.95\%$ , on Day 3 by  $23.3 \pm 1.99\%$ , and even a day after the end of the treatment

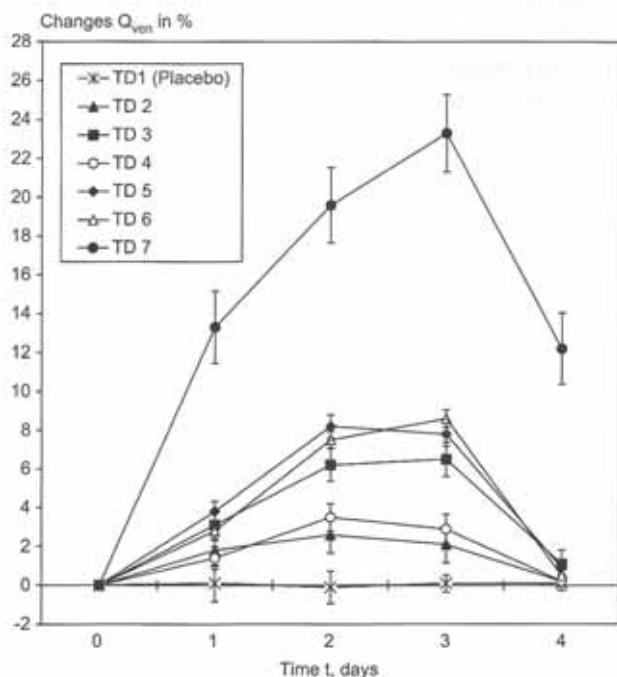
(Day 4), it still differed significantly from the initial values by  $12.2 \pm 1.85\%$ .

Figure 4 shows an example of vital-microscopic findings from a test subject illustrating the changes in the distribution change of the plasma-blood-cell mix and microhemodynamics in the subcutaneous target network after a 3-day treatment using the test device 7.



**Figure 2** Measured values on the characteristic "number of blood-cell-perfused nodes in the defined network unit, nNP" (means and standard deviations) following application of the test devices 1 to 7 (TD 1 to 7).

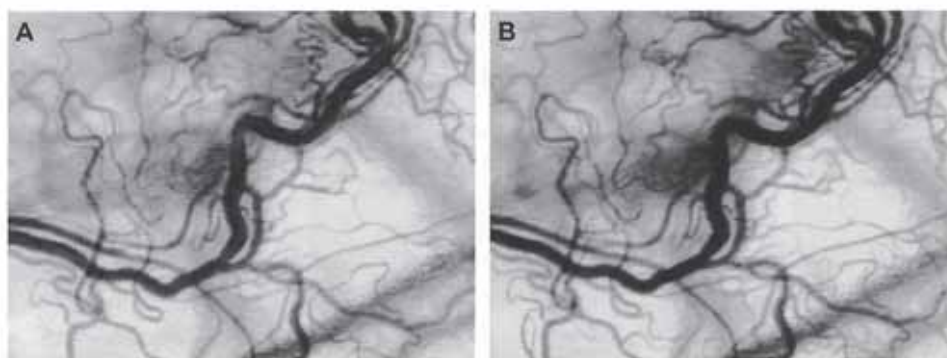
Ordinate: Changes in %. Abscissa: Measurement time points (d).



**Figure 3** Measured values on the characteristic "venular flow  $Q_{ven}$ " (means and standard deviations) following application of the test devices 1 to 7 (TD 1 to 7).

Ordinate: Changes in %. Abscissa: Measurement time points (d).





**Figure 4** Example of vital-microscopic findings from the subcutaneous target region of a test subject who was treated with test device 7, at two different observation times.

Microhemodynamic functional state of the plasma-blood-cell mix in the microvascular network of the subcutis (arterioles, capillaries, venules). (A) Day 0 (baseline prior to treatment). (B) State on Day 3 of the treatment.

The measured data on the characteristic “venular oxygen saturation  $pO_2$ ” can be seen in Figure 5. The characteristic changes for  $pO_2$ , too, exhibited characteristic behavior similar to the characteristics  $nNP$  and  $Q_{ven}$ .

After use of the test devices 2 and 4, venular oxygen saturation was up significantly only by approx. 2 to 3% on Day 2 of the treatment, and on Day 4 of the measurements, it reached the initial values again. For the test devices 3, 5 and 6, significantly higher characteristic changes were detected compared to the test devices 2 and 4 (for test device 5 on Day 3  $9.5 \pm 1.60\%$ ), but these characteristic changes, too, had dropped to the initial values again on Day 4 of the measurements.

In the application of the test device 7, the characteristic amounts were significantly different from the initial values from Day 1 to Day 4 of the measurements, and exceeded the characteristic amounts measured for all other test devices: Day 1/ $15.5 \pm 1.92\%$ , Day 2/ $25.4 \pm 1.84\%$ , Day 3/ $28.4 \pm 1.85\%$ , Day 4/ $12.8 \pm 1.61\%$ .

Figure 6 shows the measured values for the characteristic “area under the envelope of the amplitude-frequency spectrum of spontaneous arteriolar vasomotion  $A_{VM}$ ”.

The characteristic changes obtained after the use of the test devices 2 and 4 reached a maximum of 1% and are therefore irrelevant. For the test devices 3, 5 and 6, significant changes in the characteristic amounts were detected from Day 1 to Day 3 relative to the respective initial values. The biggest characteristic changes found were: Test device 3 on Day 2  $2.2 \pm 0.75\%$ , test device 5 on Day 3  $3.4 \pm 1.46\%$ , test device 6 on Day 3  $2.8 \pm 1.13\%$ .

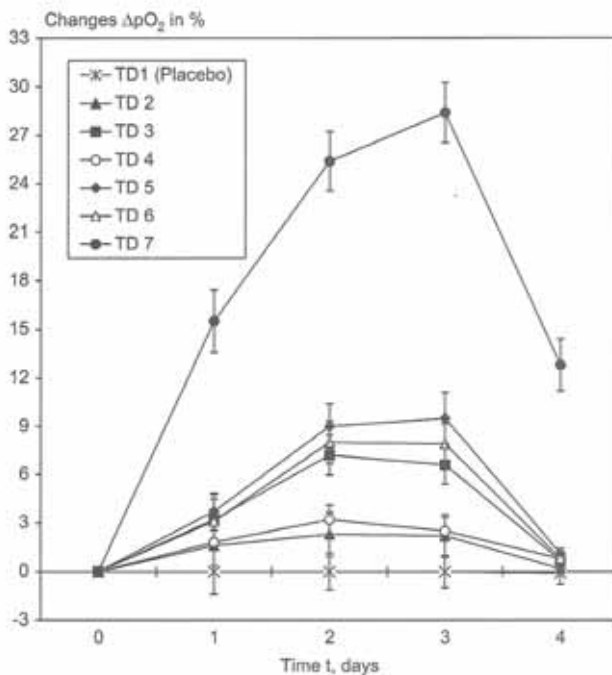
The characteristic amounts measured after the use of the test device 7 were significantly different from their initial values from Day 1 to Day 4, as well as from the measured data of all other test equipment: Day 1/ $6.6 \pm 1.23\%$ , Day 2/ $9.7 \pm 1.28\%$ , Day 3/ $12.4 \pm 1.68\%$ , Day 4/ $7.1 \pm 1.34\%$ .

Adverse effects were not detected with any of the test devices used.

## Discussion

The physical treatment methods used in medical practice or recommended, such as the methods mentioned in the manual of medical therapies and other guidelines, are almost exclusively general systemic or symptomatological measures, the justification of which is beyond doubt [18]. However, the range of effective physical treatment methods for the targeted influencing of specific regulatory processes, particularly in connection with deficient organ blood flow, is currently still very limited. In addition to further research efforts in the fields of pharmacology and physiotherapy, the other main focus is on developing effective, targeted physical treatment measures that can complement the established drug-based measures and recognized physiotherapeutic treatment measures in terms of therapy optimization. In this context, it is about enabling the body's own regulatory mechanisms to correct the disorder that has occurred as much as possible through effective, targeted physical stimulation in the event of a deficit. In case of a deficient organ blood flow, this can be influenced physically through targeted therapy only by means of an effective stimulation of arteriolar vasomotion, particularly spontaneous arteriolar vasomotion [1, 2, 4, 6, 7, 16].

The measured results obtained provide statistically reliable statements about whether and to what extent the different commercially available test devices examined can be effective in the physical influencing of regulatory deficits in the organ blood flow and whether and to what extent they may justify complementary-therapeutic use. Aside

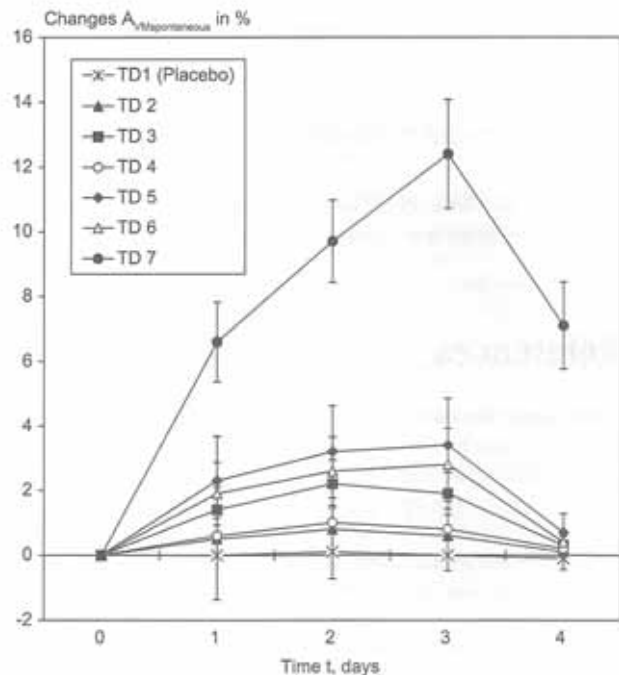


**Figure 5** Measured values on the characteristic "venular oxygen saturation  $pO_2$ " (means and standard deviations) following application of the test devices 1 to 7 (TD 1 to 7). Ordinate: Changes in %. Abscissa: Measurement time points (d).

from the placebo device, two test devices proved to be virtually ineffective (TD 2 and TD 4). For three test devices, only a very small effect on spontaneous arteriolar vasomotion could be detected in the target tissue and, consequently, only minor effects on the distribution state, venular flow, and venular oxygen saturation (TD 3, TD 5 and TD 6).

Only when the test device 7 (Bemer Classic, biorhythmically defined physical stimulation) was used, was it possible to achieve a prophylactically and complementary-therapeutically relevant effect on spontaneous arteriolar vasomotion. The expansion of the local regulatory range for the blood supply as a result of the stimulated spontaneous arteriolar vasomotion, which was achieved 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. As a further consequence of the improved arteriolar blood-flow regulation, increased oxygen saturation occurs in the microcirculation. The increase in the venular flow, too, is of therapeutic significance, because disturbances in microcirculation mostly start in the venules.

Improvements in the functional state of microcirculation also affect the transport of plasmatic and cellular factors of immune responses and, thus, enable the initial



**Figure 6** Measured values on the characteristic "area under the envelope of the amplitude-frequency spectrum of spontaneous arteriolar vasomotion  $A_{VM}$ " (means and standard deviations) following application of the test devices 1 to 7 (TD 1 to 7). Ordinate: Changes in %. Abscissa: Measurement time points (d).

steps of immune responses (infection defense) to progress as unimpeded as possible.

The amounts of characteristic changes achieved with the test device 7 are not sufficient for causal therapy, but the Bemer system, with its biorhythmically defined stimulus for the physical stimulation of spontaneous, autorhythmic arteriolar vasomotion in connection with metabolically inadequate blood-flow regulation, is suitable for effective prophylactic and complementary-therapeutic use.

## Summary

As part of a placebo-controlled study series, random test subjects were subjected to high-resolution measurement methods to capture microcirculatory functional characteristics to examine whether and to what extent the use of different commercially available physical treatment devices could contribute to the effective stimulation of deficient blood flow in organs.

The examinations showed that only a targeted, biorhythmically defined stimulus could affect arteriolar vasomotion and, thus, microcirculatory blood-flow regulation in a therapeutically relevant manner, and was suitable for prophylactic and complementary-therapeutic use. Of six



commercially available treatment devices, only one met this requirement.

#### 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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