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Results of the Berlin HOT/UVB Comparative Study in Patients with Peripheral Arterial Occlusive Disease

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Results of the Berlin HOT/UVB Comparative Study in Patients with Peripheral Arterial Occlusive Disease

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Zusammenfassung

Die photobiologischen Verfahren hämatogene Oxidationstherapie (HOT) und Ultraviolettbestrahlung des Eigenblutes (UVB) wurden hinsichtlich ihrer therapeutischen Wirksamkeit bei Patienten mit peripheren arteriellen Durchblutungsstörungen der unteren Extremitäten im Stadium II nach Fontaine (pAVK II) miteinander verglichen. Begleitend wurden neben paraklinischen und gerinnungsserologischen Daten auch hämodynamische sowie hämorrheologische Parameter zur Klärung möglicher Wirkungsmechanismen erhoben. Beide Therapiegruppen setzten sich jeweils aus 15 männliche Patienten mit einer durchschnittlichen Klaudikatio-Distanz von 178 ± 108 m (HOT) bzw. 213 ± 147m (UVB) zusammen. Nach einer Serie von jeweils 10 Behandlungen innerhalb von 4 Wo-chen verbesserte sich die Klaudikatio-Distanz signifikant ($p < 0.05$) um 94% in der HOT-Gruppe bzw. 83% in der UVB-Gruppe. Bezüglich des Therapieeffektes (Verbesserung der Laufleistung) konnten zwischen den zwei Therapieverfahren keine Unterschiede gesichert werden. Signifi-kante Veränderungen der untersuchten paraklinischen Parameter wurden unter der HOT/UVB-Therapie nicht festgestellt.

Code: arterielle periphere Durchblutungsstörungen - photobio-logische Therapie - Hämorrheologie

Summary

Results of the Berlin HOT/UVB Comparative Study in Patients with Peripheral Arterial Occlusive Disease

Both photobiological hematogenic oxidation therapy (HOT) and therapy by retransfused ultraviolet irradiated own blood (UVB) were compared with regard to their therapeutic efficacy in patients with peripheral arterial occlusive disease of the lower extremities in stage II by Fontaine. In parallel to paraclinical and coagulation data, hemodynamic as well as hemorheological parameters were investigated to clarify possible mechanisms of action of these therapies. Fifteen male patients were enclosed in the corresponding patients groups with a mean walking distance of 178 ± 108m (HOT) and 213 ± 147m (UVI), respectively. The claudication distances were significantly improved after 10 series of therapy by 94% in the HOT group and by 83% in the UVI group, respectively. A significant difference in the improvement of walking distances could not be detected between both therapeutic methods. Significant alterations in observed paraclinical parameters were not observed.

Code: peripheral arterial occlusive disease - photobiological therapy - hemorheology

Introduction

The difficulty in the treatment of stage II peripheral arterial occlusive disease according to Fontaine (PAD II) indicates the need to use non-drug measures in addition to the options in surgical and interventional radiology as well as pharmacology. For the latter, the photobiological treatment processes of ultraviolet own blood irradiation (UVB) or hematogenic oxidation therapy (HOT) can be considered (11).
The main area of indication for both photobiological processes can be seen in the treatment of patients with PAD II. Relevant experience and results have been repeatedly reported in the literature (11). There is still no reliable evidence to date about the mechanism of action. Ideas on the possible effects of UVB and HOT were also derived, among others, from observations of changes in hemorheological parameters, the plasma protein composition and the blood count (1, 8, 11, 13). A comparison of the two photobiological processes has not yet been described in the literature.
The aim of this clinical study, therefore, was to compare the efficacy of both photobiological processes in patients with PAD II and to uncover new aspects to the mechanism of action of these therapeutic procedures by way of a corresponding collection of paraclinical, functional diagnostic and hemorheological parameters during therapy.

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Methodology

Selection of patients
Thirty patients with PAD II were treated. The patients were assigned to the UVB or HOT group (15 patients each) based on their ergometric treadmill performance in order to make the initial situation with respect to the walking distance comparable in both patient groups (see. Fig. 1, Tab. 2). Exclusion criteria included diabetes mellitus and inflammatory arterial disease under immunosuppressive therapy.
The patients were encouraged not to change their habits during the course of the study and to maintain their usual walking distance during the day. According to the study design, the following medications were discontinued four weeks before the start of therapy: vasodilators (especially pentoxifylline, xanthinol nicotinate, etc.), vitamin E, vitamin C, non-corticoid anti-rheumatics, and corticoid-containing preparations. Other medications, in particular cardiological medications and high blood pressure medications, but also anticoagulants, were not changed. The behaviour of the coagulation parameters was listed and interpreted separately in these patients (see Tab. 3).

Therapy procedures
Hematogenic oxidation therapy: The treatment was performed with the Oxysan device and the disposable sets made by Eumatron GmbH, Munich. The blood taken from the cubital vein (about 40 ml) was anticoagulated with pyrogen-free sodium citrate in a 4:1 ratio and collected in a receptacle. Then the blood was foamed with medical oxygen, passed through a quartz tube at a UV source (Osram low-pressure lamp, 10 watts) and collected again in a receptacle. Finally, the treated blood was reinfused to the patient. The treatment time was about 40 minutes (11).
Ultraviolet irradiation of own blood: In this treatment, the FMR-10 blood irradiation device made by Präcitronik in Dresden was used. The extracted venous blood (40 ml whole blood) was anticoagulated during extraction with 10 ml of pyrogen-free sodium citrate solution. The blood is passed by the UV lamp (253.7 nm) during collection. With the reinjection of the blood, the blood is irradiated again. The treatment time is about 10 minutes (11). In both therapy groups, a series of 10 treatments (2 treatments per week) were performed.

Methods
Treadmill ergometry: Following internationally recognized principles, two forms of walking distances at a belt speed of 4 km/hour and an incline of 5% were measured:
1. The pain-free walking distance S_1 (onset of pain in one of the legs) and 2. The claudication distance S_2. Before the study, the patients had already exercised on the treadmill ergometer (Lauferergotest made by Jaeger, Würzburg) several times (at least 3 times) to avoid the adaptation effect as an apparent treatment effect.

Hemodynamic function diagnostics: The following diagnostic procedures were used for the classification of the severity and the localization of the circulatory disorders: oscillography, venous occlusion plethysmography and ultrasound-Doppler-blood pressure measurements. Before or after the study, each patient in this study underwent an arteriography to investigate the possible indication for a surgical intervention.
Rheological examinations: Blood is one of the non-Newtonian fluids, that is, the viscosity depends on the magnitude of the acting shear forces. Therefore, the flow properties of the blood on the one hand were characterized by the apparent viscosity of whole blood, and on the other hand, by the main determinants of whole blood viscosity such as hematocrit, plasma viscosity, erythrocyte aggregation and deformability (6). All studies were carried out at a temperature of 25.0 °C.
Whole blood viscosity: With native as well as standardized hematocrit of 0.45, the patients' blood was measured in a viscometer with a Couette measuring system (measuring system DIN 452, LS-40, Contraves AG, Zurich) in the shearing gradient range of $0.05s^{-1}$ to $125s^{-1}$. For interpretation of the blood rheology, the viscosity values at $0.05s^{-1}$ (predominance of erythrocyte aggregation ability) as well as at $100s^{-1}$ (predominantly influenced by erythrocyte deformability) were used (6).
Erythrocyte filterability: The determination of erythrocyte deformability was based on the filterability of washed erythrocyte suspensions. The measurements were performed with a semi-automated hemofiltrometer according to the principle of gravity (initial pressure p = 165 Pa, cellulose filter F 1388, suspension hematocrit 0.60, made by Rentsch in Pirna). The standardized filtration time from 4-5 measurements of each sample - relativized to the calibration time - was calculated as the filterability index F1 (4, 6).
Plasma viscosity: The plasma viscosity was determined using a modified Ubbelohde capillary viscometer at a temperature of 25.0 ± 0.1° C from the processing times for the blood plasma and water as calibration fluid (2). The hematocrit was determined using a microhematocrit centrifuge (5 min at 10,000 × g).
Erythrocyte aggregation: The aggregation of erythrocytes was determined via a light backscattering technique. The blood sample with a normalized hematocrit of 0.45 is disaggregated in the slot of a Couette measuring system at high shearing gradients (> $128s^{-1}$). The backscattered light from the disaggregated erythrocytes oriented in the flow is detected by a photodetector. After the rapid stop, the erythrocytes are disoriented and the back scattering intensity is maximized. The red blood cells begin to aggregate, so that the backscatter intensity decreases due to the decreasing total backscatter area. For the characterization of the stationary aggregation behaviour of the erythrocytes, the curve of the measured backscattered light intensity was adjusted nonlinearly and the aggregation index determined from the functional parameters (5, 6).

Paraclinical: The following groups of parameters were also monitored: blood count (hemoglobin, leukocyte count, thrombocyte count, MCV, MCHC), liver enzymes (GOT, GPT, γ-GT); transcutaneous partial oxygen pressure (arterialized capillary blood, from instep vein), electrolytes (Na, K, Ca), kidney values (creatinine, urea, uric acid), coagulation serology (fibrinogen, quick, PTT).
Statistics: The changes in the parameters within the therapy groups were statistically supported by the Wilcoxon test ($\alpha \leq 0.05$) and the changes between the therapy groups were statistically supported by the t-test.

Study design: Table 1 summarizes the dates of the diagnostic examinations defined in the study protocol.

Table 1. Study design of the Berlin HOT/UVB comparative study in patients with PAD II.

Examinations	Before	After 4 HOT/UVB	After 10 HOT/UVB	4 weeks after end of therapy
History, ECG	x			
Subjective therapy assessment		x	x	x
Treadmill ergometry	x	x	x	x
Hemodynamic diagnostics	x		x	x
Paraclinical	x	x	x	x
Rheological examinations	x	x	x	x

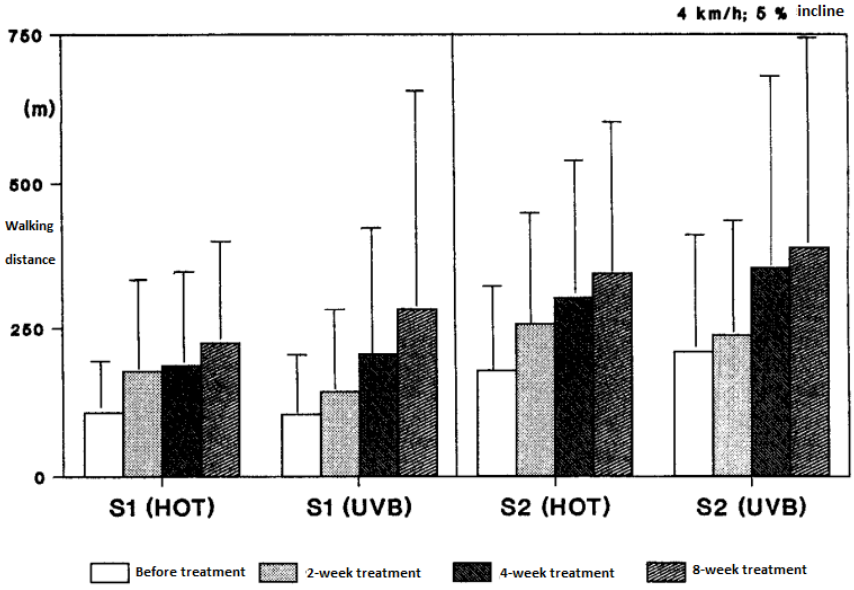

Figure 1. Comparative representation of the pain-free walking distance S_1 and the claudication distance S_2 under HOT and UVB as a function of the examination date.

Table 2. Ergonometric (treadmill), paraclinical and hemorheological parameters as a function of the treatment duration.

Parameter		Before HOT/UVB therapy	After 2-week HOT/UVB therapy	4 weeks after HOT/UVB therapy
Pain-free walking distance S_1	HOT	109.7 ± 63.8 m	179.1 ± 109.1 m	225.0 ± 121.6 m
	UVB	106.3 ± 71.6 m	145.1 ± 97.1 m	284.4 ± 298.9 m
Claudication distance S_2	HOT	178.3 ± 107.6 m	257.2 ± 138.4 m	345.3 ± 191.9 m
	UVB	213.2 ± 147.1 m	239.6 ± 140.8 m	391.1 ± 360.7 m
Hematocrit	HOT	0.45 ± 0.06	0.44 ± 0.05 m	0.46 ± 0.04
	UVB	0.45 ± 0.03	0.45 ± 0.04	0.45 ± 0.03
Leukocytes	HOT	8.23 ± 3.39 Gpt/l	8.09 ± 4.51 Gpt/l	7.76 ± 3.10 Gpt/l
	UVB	8.23 ± 2.20 Gpt/l	8.33 ± Gpt/l	8.04 ± 1.57 Gpt/l
Thrombocytes	HOT	239 ± 73 Gpt/l	225 ± 59 Gpt/l	246 ± 68 Gpt/l
	UVB	252 ± 43 Gpt/l	256 ± 44 Gpt/l	270 ± 42 Gpt/l
Plasma viscosity	HOT	1.74 ± 0.14 mPas	1.73 ± 0.13 mPas	1.71 ± 0.12 mPas
	UVB	1.75 ± 0.08 mPas	1.75 ± 0.07 mPas	1.77 ± 0.12 mPas
Filterability index	HOT	11.3 ± 1.6	12.1 ± 2.1	10.6 ± 0.9
	UVB	11.7 ± 2.2	12.1 ± 2.5	10.8 ± 1.5
Aggregation index	HOT	0.56 ± 0.09	0.53 ± 0.09	0.54 ± 0.08
	UVB	0.52 ± 0.09	0.51 ± 0.07	0.53 ± 0.09
Apparent blood viscosity $0.05s^{-1}$	HOT	92.0 ± 10.1 mPas	102.4 ± 7.2 mPas	101.4 ± 7.4 mPas
	UVB	92.9 ± 13.4 mPas	102.7 ± 12.9 mPas	96.4 ± 9.9 mPas
Apparent blood viscosity $100s^{-1}$	HOT	6.22 ± 0.38 mPas	6.03 ± 0.21 mPas	6.17 ± 0.27 mPas
	UVB	6.26 ± 0.39 mPas	6.54 ± 0.44 mPas	5.99 ± 0.29 mPas

Results

As clearly shown in Figure 1 and Table 2, the walking performance was significantly improved as early as the 2nd week of HOT or UVB therapy. A further increase in walking distance was observed even four weeks after completion of the study. With comparable initial values for the pain-free walking distance S_1 and claudication distance S_2 in both groups, both therapies resulted in a comparable, not significantly different increase in the walking performance (see Fig. 2 for a comparative representation of the individual values).
The success of the therapy is also reflected in the improved general condition and increased resilience of the patients. The scientific part of the study focused on diagnostic as well as concomitant therapy check-ups. In the hemodynamic studies, no changes were observed in the course of the treatment series. None of the patients experienced acute deterioration of macrocirculation (results not shown).

In the whole range of paraclinical parameters (blood count, liver enzymes, transcutaneous oxygen partial pressure, electrolytes, kidney values, coagulation serology) no changes among the therapeutic measures could be determined, especially since the initial values were in the normal range on average, as is clearly shown in Table 2 in the example using leukocyte and thrombocyte counts.
Like the paraclinical values, the initial hemorheological values were in the upper normal range (Tab. 2). The tendency of the changes in all rheological parameters of the blood samples after four treatments (2nd week of treatment) cannot be statistically supported.

Discussion

The improvements in walking performance for both therapy groups (there is no significant difference in the S_1 and S_2 walking distances between UVB therapy and HOT in this study) are comparable with those found by other authors in the photobiological treatment of leg circulatory disorders.

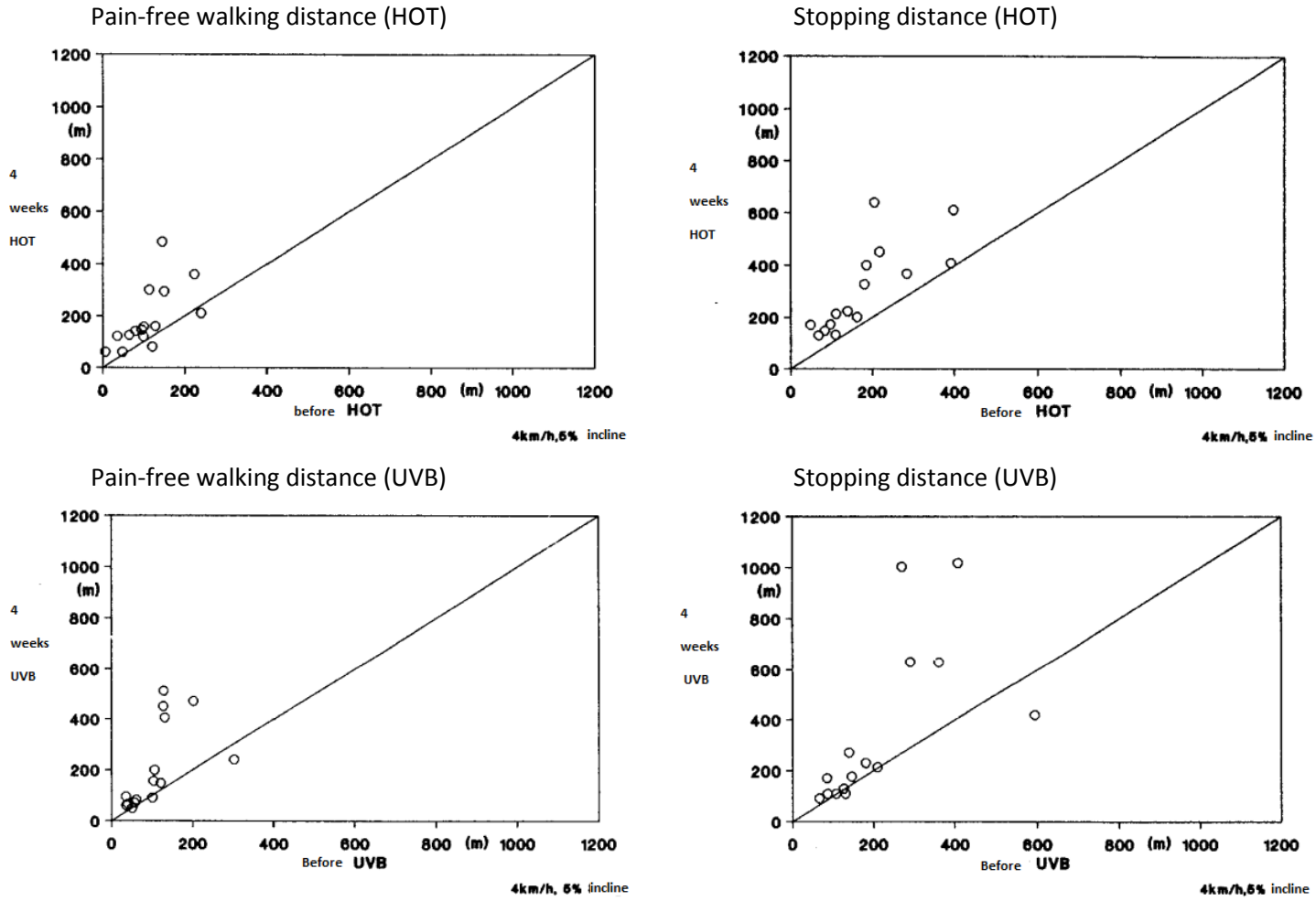

Figure 2. Intra-individual comparison of the pain-free walking distance S_1 and the stopping distance S_2 before the start of therapy compared to 4-week therapy.

In 12 UVB patients with an average initial walking performance of 430 m, *Pöhlmann* was able to achieve a 163% improvement with a controlled (but not standardized) walking distance. For a total of 18 patients, *Scherf* et al. reported a 170% improvement in the S_1 distance and a 155% improvement in the S_2 distance. Interesting is the fact that at comparable initial values with medicinal therapy (flunarizine, pentoxifylline) no significant improvements in walking performance could be achieved than those achieved with photobiological therapy. *Reich* and *Gillings* observed a 68% prolongation of the claudication distance after 24 weeks of treatment with pentoxifylline. In another study (7) the effect of flunarizine and pentoxifylline on the claudication distance is estimated at 43% or 18%, respectively. Sports therapy (3) also does not result in significant improvements in the walking distance in comparison to HOT and UVB.

In the study, no change in plasma protein values and fibrinogen was observed; these were initially in the standard or upper range. This is also reflected in the largely constant plasma viscosity and aggregation values. Other authors (13) reported a significant decrease in fibrinogen in stage II-IV PAD patients after UVB. The normalization of fibrinogen levels in this study is certainly primarily due to the healing of the ulcerations and not primarily a result of UVB, since wound treatment was carried out at the same time.

One issue in the use of HOT/UVB is the possible contraindication in the case of anticoagulant therapy. Both treatment groups included patients who were treated with marcumar. As is apparent from Table 3, an unchanged marcumar dose did not significantly decrease the coagulation parameters under HOT or UVB.

In contrast to our own earlier work (1) and other authors (8, 13) no significant changes in blood flow properties were observed in the UVB group. This also applies to the HOT group. The cause is considered to be the fact that the initial values of the hemorheological parameters were in the upper normal range and thus no "further normalization" is to be expected. Only the trend that all hemorheological parameters basically showed a change at the two-week therapy examination date (with reset at the end of therapy) was striking, which suggests a possible reaction of the body in terms of a general activation by the photobiological therapy.

In summary it can be stated that both HOT and UVB lead to significant improvements in the walking performance of PAD patients. The walking distance increase is comparable to that achieved with conservative treatment methods (medication, sports therapy, hemodilution). The absence of changes in the examined paraclinical and functional diagnostic parameters suggests that in further studies the inclusion criteria must also include pathologically increased parameters in order to obtain evidence about the mechanisms of action of the photobiological therapies.

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Table 3. Comparison of coagulation-serological parameters in patients with (UVB: 6 pat./HOT: 7 pat.) and without anticoagulant therapy.

Parameter		Before HOT/UVB therapy	After 2-week HOT/UVB therapy	4 weeks after HOT/UVB therapy
Marcumar patients				
Fibrinogen	HOT UVB	3.17 ± 0.89 g/l 3.13 ± 0.49 g/l	2.84 ± 0.84 g/l 3.55 ± 0.80 g/l	2.72 ± 0.49 g/l 3.05 ± 0.63 g/l
Quick	HOT UVB	32.3 ± 7.7 % 32.8 ± 12.1 %	17.4 ± 7.6 % 24.7 ± 7.2 %	23.0 ± 5.0 % 26.0 ± 6.9 %
PTT	HOT UVB	40.6 ± 7.9 s 69.0 ± 53.2 s	58.0 ± 12.8 s 54.2 ± 11.7 s	45.3 ± 13.6 s 52.9 ± 16.3 s
Patients without anticoagulant therapy				
Fibrinogen	HOT UVB	2.71 ± 0.47 g/l 2.88 ± 0.96 g/l	2.90 ± 0.81 g/l 2.88 ± 0.96 g/l	2.69 ± 0.25 g/l 3.02 ± 0.64 g/l
Quick	HOT UVB	95.0 ± 5.9 % 96.1 ± 5.5 %	88.7 ± 11.2 % 93.3 ± 10.0 %	88.7 ± 10.6 % 91.3 ± 13.1 %
PTT	HOT UVB	39.9 ± 13.6 s 37.3 ± 8.7 s	40.9 ± 15.7 s 36.4 ± 2.0 s	36.1 ± 5.5 s 34.6 ± 3.3 s

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