Evaluation of the Carbon Dioxide-balneotherapy on the Microcirculation and Oxygen Tension in Peripheral Arterial Occlusive Disease

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Summary
The effects of immersion of the lower leg and foot in fresh water and in CO$_2$-enriched water (1200 mg CO$_2$ per kg water; succinate + sodium bicarbonate: Kao-Bub®) on cutaneous circulation, vasomotion and oxygen tension (PO$_2$) were measured by laser Doppler flowmetry and transcutaneous oximetry. On the first of two consecutive days patients were randomly assigned to have the lower extremities immersed in either fresh water or CO$_2$-enriched water under standardised conditions (temperature, 34°C; depth, 35 cm; immersion time, 20 min) with concurrent measurement. On the second day patients were switched to the other bath type. For both sets of measurements probes were attached symmetrically to the dorsum of each foot. 18 patients with mild, bilateral, peripheral, occlusive arterial disease (intermittent claudication, femoral or iliac type) were included in the study.

During immersion in CO$_2$-enriched water the Doppler laser signal and vasomotion amplitude rose by 300%, while PO$_2$ increased by 10%. These increases were still apparent during the latter part of the measurement period, following withdrawal of the limbs from the bath, while patients were seated and supine. During immersion in fresh water and thereafter the Doppler laser signal was unchanged and the PO$_2$ increase was considerably less marked.

We were thus able to demonstrate vasodilation and increased oxygen utilisation (Bohr effect) resulting from topical CO$_2$ application, and hence that the use of topical CO$_2$ has an objective basis.

Key words: Laser Doppler flowmetry, transcutaneous oximetry, CO$_2$-enriched water, fresh water
INTRODUCTION
Both in physical solution and chemically bound carbon dioxide is a permanent and everpresent component of the body. In its gaseous form it permeates readily through membranes. At rest the body produces around 250 ml/min of CO₂ as a metabolic end product, of which some 2.7% is eliminated via the skin under normal atmospheric conditions. Increases in CO₂ concentration in the medium surrounding the body, as is the case during immersion in CO₂-enriched water, lead to percutaneous infiltration (30 ml/min/m² in a saturated aqueous solution) due to the altered gradient [21]. Intracorporeal variations in CO₂ concentrations affect both blood flow (tissue perfusion) and oxygen dissociation, and in fact the shift in the oxygen dissociation curve first described by Bohr was CO₂-induced [2, 5, 13, 18, 19]. Topical carbon dioxide, applied either as a gas or in aqueous solution, has a hyperemic effect on the skin [11]. However, while the effects of percutaneous application have been repeatedly investigated, there have been few controlled studies using modern, reliably validated methods. Following the advent of semi-quantitative Doppler flowmetry (LDF) and transcutaneous oximetry non-invasive measurement of skin blood flow and oxygen tension is now possible. These techniques have been modified to allow direct measurement under water. The principles of the laser Doppler technique and transcutaneous oxygen monitoring have been fully described and evaluated [10]. Using these techniques it is now possible to investigate specific effects of carbon dioxide therapy and differentiate them from the thermal and hydrostatic effects of immersion in water alone.

MATERIALS AND METHODS
In the periods before fixation of the measuring probes (laser Doppler flowmeter, and oximeter) and after completion of measurements, ankle systolic pressure (posterior tibial and dorsalis pedis) and brachial systolic pressure were obtained simultaneously by two investigators using Doppler ultrasound equipment.

Two periflux Pf 1b laser Doppler flowmeters (Perimed, Stockholm) were attached to probes fixed 2.5 cm proximally to the first interdigital folds of each foot using conventional, non-heating plastic holders and adhesive rings. The LDF filter was set to a time constant of 0.2 sec, the system bandwidth to 4 kHz and the output gain to X10. Electrical calibration for zero blood flow was performed for all recordings and the maximum output of a given level (defined electrically) was taken as 100%. The output was fed to a pen recorder (Gould 2400, Cleveland, Ohio). The analog output of the equipment gives the relative changes in cutaneous blood flow and vasomotion, not absolute values. Transcutaneous oxygen tension (PO₂; mm Hg) was determined using two Servomed SMK 365 oximeters (Hellige, Freiburg) attached to probes (core temperature, 44°C) fixed 5 cm proximally to the fourth interdigital folds of each foot. For technical details and evaluation of the technique the reader is referred to Huch et
Measurements on the dorsum of the foot were carried out bilaterally, symmetrically and simultaneously. Identical probe positioning on both measurement days was achieved by standardisation of measurement zones and body position, both supine and seated. The probes and holders covered an area of 13 cm² on each foot. Environmental conditions were standardised, with room temperature maintained at 23°C, relative humidity at 60% and air movement at <0.1 m/s. Medication, physical activity, physical therapy and food intake were also standardised on both days and measurements were carried out at the same time on each day.

Arterial blood pressure was measured in the 10th minute of the preliminary, bath and postbath phases using a Riva-Rocci device with the cuff applied to the right arm at heart level.

Patients were randomised for immersion of the lower extremities in either fresh water or CO₂-enriched water on the first of the two measurement days (Day 1), each patient then switching to the other bath type for measurement on Day 2. Attachment of the probes and warm-up of the O₂ probes (average warm-up time, 20 min ± 2 min) was followed by a 20 min preliminary phase. After these measurements were made in air for 20 min with the patient supine (foot with attached probe at heart level), then for 10 min with the patient seated (probe 80-85 cm below heart level), after steady state was reached (Fig. 1).

This was followed by the immersion phase. Patients' legs and feet were immersed in both types of bath for 20 min to a depth of 35 cm; the bath temperature was maintained at 34°C. Succinate and sodium bicarbonate (Kao-Bub®) were used to chemically produce a CO₂ enrichment of 1200 mg/kg water. Following withdrawal of the limbs from the bath measurement was continued for 10 min with the patient seated, then for 20 min with the patient supine.

The mean values obtained during the 20th pre-immersion supine, 10th pre-immersion seated, 20th immersion, 10th postimmersion seated and 20th postimmersion supine minutes, respectively, were used for comparative analysis. The measurement data are presented as arithmetic means ± SEM. Statistical evaluation was by analysis of variance.

Fig. 1. Experimental procedure.
PATIENTS
18 patients aged 42-76 (67±2) yr with bilateral arterial occlusion (aortoiliac or femoropopliteal) of both lower extremities were enrolled. The clinical diagnosis had been confirmed functionally before enrolment by Doppler ultrasound, strain-gauge plethysmography with suprasystolic occlusion and reactive hyperemia and morphologically by angiography within the preceding 12 months.
The average pain-limited walking distance was 285±35m (standardized at 120 steps/min); the mean Doppler ultrasound index (ankle systolic pressure/systemic BP) was 0.79±0.04.

RESULTS
Arterial blood pressure, measured non-invasively in the right arm, was not affected by the immersions. No intra-individual blood pressure differences were observed.
There was no change in ankle systolic pressure in either absolute terms nor in relation to brachial systolic pressure (Doppler index).

Laser Doppler Measurements
Comparable readings were obtained during the pre-immersion phases. In the 20th min of the supine measurement phase the laser Doppler output (in volts) was 0.18±0.03 before CO₂ immersion and 0.19±0.04 before fresh-water immersion. In the 10th min of the seated phase the output was 0.14±0.03 V before CO₂ immersion and 0.15±0.04 V before fresh-water immersion (Fig. 2).
Output remained stable during immersion in fresh water, measuring 0.16±0.05 V in the 20th min. During immersion in CO₂-enriched water laser Doppler output increased threefold within 193±27 sec to 0.48±0.3 V, following an average delay of 128±14 sec (i.e., without any change from pre-immersion levels), and remained this level for the remainder of the immersion phase.
The signals obtained during seated and supine measurement following the fresh-water bath were unchanged from preliminary-phase levels. However, following the CO₂ bath they remained elevated, by comparison with preliminary-phase levels and with the corresponding fresh-water control measurements, reaching 0.24±0.03 V seated (p<0.005) and 0.32±0.02 V (p<0.001) supine at 10 min.
This increase following immersion in CO₂ enriched water was accompanied by a rise in vasomotion amplitude, recorded using a 0.02 sec time constant (Fig. 3). The fresh-water bath had no effect on vasomotion. The increase in amplitude, compared with the corresponding pre-immersion phases, was maintained after withdrawal from the CO₂ bath (p<0.005). The measurement profile reproduced in Figure 4 shows the typical pattern which was observed all cases.

Transcutaneous oxygen tension
Comparable mean oxygen tension values (in mmHg) were obtained before immersion,
Fig. 2. Laser Doppler readings (volts) obtained from the unwarmed dorsum of the foot in the pre-immersion (20th min supine, 10th min seated in ambient air at 23°C), immersion (20th min) and postimmersion (10th min seated and 20th min supine: ambient air at 23°C) periods before, during and after immersion of the lower extremities in fresh water and CO₂-enriched water, respectively (temperature, 34°C; depth, 35 cm; immersion period, 20 min; CO₂ concentration, 1200 mg/kg); x ± SEM, n = 36.

Fig. 3. Laser Doppler vasomotion amplitude (mV), using a time constant of 0.2 sec, recorded in the unwarmed dorsum of the foot before (10th min seated in ambient air at 23°C) and during immersion (20th min) in fresh water and CO₂-enriched water, respectively.
at 28±3 (pre-CO₂) and 29±4 (pre-fresh water) after 20 min supine, and 58±2 (pre-
CO₂) and 59±4 (pre-fresh water) after 10 min seated.
During the CO₂ bath PO₂ increased significantly, compared with the pre-immersion
phase, to 72±3 mmHg after 20 min immersion. The pattern of increase was not quite
as clear as that of the laser Doppler readings: in 7 limbs (aortoiliac disease) no change
at all was detected and in another 6 steady state had not be reached at 20 min; on average
a clear increase over pre-immersion values was observed after 7±2 min, with end points
reached after 15±2 min.
In the fresh-water bath PO₂ showed a non-
significant increase to 63.3 mmHg after 20 min.
10 min after the CO₂ bath mean seated PO₂ was
68±3 mmHg, 10% above pre-bath levels (p<0.005), but comparable to those reached follow-
ing the fresh-water bath (64±4 mmHg). Subse-
quently, supine measurements at 20 min post-
immersion also failed to reveal any significant
differences in PO₂, which was 39±4 following

**Fig. 4.** Example of a laser Doppler flow
recording.

**Fig. 5.** Transcutaneous oxygen tension (mmHg, skin temp. 44°C) in the
dorsum of the foot in the pre-immersion (20th min supins, 10th min seated : in ambient air at 23°C), immersion (20th min) and postimmersion (10th min seated and 20th min supine : ambient air at 23°C) periods before, during and after immersion of the lower extremities in fresh water and CO₂-enriched
water, respectively (temperature, 34°C ; depth, 35 cm ; immersion period, 20
min ; CO₂ concentration, 1200 mg/kg).
DISCUSSION

CO₂ gas obtained from fumaroles (natural volcanic vents) and CO₂-enriched water have long been used for the empirical treatment of arterial disease and cutaneous circulatory disorders [9]. In recent years some of the effects of these percutaneous treatment methods have been scientifically documented [1]. Controlled animal experiments (vs fresh water) have demonstrated that both cutaneous and muscular blood flow and oxygen tension increase during immersion [12]. A study of healthy volunteers which used invasive methods to measure heat conduction showed that whole-body immersion in a CO₂ bath at body temperature resulted in increased muscular blood flow [4]. In patients with occlusive arteriopathy an increase of total blood flow in the extremities was achieved by topical application of CO₂ gas restricted to the areas of hemodynamic impairment [17]. Serial whole-body CO₂ gas baths led to improved peripheral oxygen utilisation in patients with cardiovascular disease [14]. In a controlled study vs fresh water it was shown that a series of CO₂-enriched water baths produced long-term improvement in blood-flow characteristics by reducing hematocrit and blood viscosity [3]. In another controlled study the same improvement in walking distance was achieved with CO₂ gas baths as with a course of special exercise training, the accepted therapeutic standard in stage II peripheral occlusive arteriopathy [15].

It must be pointed out that while Doppler ultrasound measurement of ankle systolic pressure is suitable for diagnostic purposes, strain-gauge plethysmography with measurement of reactive hyperaemia following suprasystolic occlusion is more sensitive, permitting quantification of macrocirculatory blood-flow variations. However, this intervention has the disadvantage of influencing transcutaneous PO₂ and the laser Doppler signal [7]. In addition, the pain produced by four applications of occlusive pressure for three minutes each proves intolerable for many patients, resulting in a high dropout rate (authors' unpublished results). In view of this, occlusion was not carried out. In view of these findings we decided to investigate the effects of immersion in CO₂-enriched water on cutaneous blood flow and oxygen tension, as compared with those of fresh-water immersion (taking into account hydrostatic, hydrodynamic and thermal effects, i.e. the change in the heat-exchange coefficient accompanying the transition from air to water) [6]. Such investigations involving patients have only recently become possible thanks to new developments in non-invasive measurement techniques. Invasive measurement under water presents hygienic and thus ethical problems. Only a short time after the introduction and validation of laser Doppler technology studies were conducted using a specially designed measurement chamber in order to quantify and differentiate the effects of CO₂ treatment and temperature in humans [20]. In a subsequent controlled study using modified equipment and serial measurement with a laser Doppler flowmeter it was shown that immersion in CO₂-enriched water increased cutaneous
blood flow in both healthy subjects and patients with arterial and venous circulatory disorders, while fresh water had no effect \[7,8\].

This immediate effect was confirmed quantitatively and qualitatively in the present study. In addition we observed an increase in tcPO2. Possible explanations are a hypercapnia-induced rise in capillary blood flow, a drop in cutaneous oxygen consumption or a right shift of the O2 dissociation curve during partial immersion (theoretically-Bohr effect-to be expected, and already demonstrated during whole-body immersion), indicating improved oxygen utilisation.

However, this effect did not persist beyond the period of actual immersion. It is nonetheless both theoretically and clinically relevant, particularly in the case of those patients for whom there are no other therapy options.

Owing to the method of attachment of the probes there was no water-skin contact at the point(s) of measurement, i.e., an area of some 13 cm² remained dry. Moreover, the change of body position necessary for immersion may also by expected to have had some influence on the readings obtained, resulting (in the ambient air) in a hydrostatically-mediated increase in PO2 and reduction in the laser Doppler signal compared with those obtained with the patient supine \[10\].

The immediate and longer-lasting effects which have been identified can help us to understand the efficacy of topical CO2 therapy. We believe that prospective, randomised and controlled studies of total extremity and muscle blood flow are now required in order to demonstrate that these effects are clinically relevant and long-term following repeated application.

Our results also show that renewed evaluation of empirical treatment methods can be useful, helping to quantify effects and identify possible mechanisms of action. From a therapeutic point of view, in the treatment of occlusive arteriopathy it is essential that blood flow and PO2 be increased, especially in advanced disease of the extremities.

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