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# Combined Hyperbaric Oxygen Partial Pressure at 1.4 Bar with Infrared Radiation: A Useful Tool To Improve Tissue Hypoxemia?

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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Tissue hypoxia contributes to the pathogenesis of several acute and chronic diseases. Hyperbaric oxygen therapy (HBO) and whole-body warming using low-temperature infrared technology (LIT) are techniques that might improve hypoxemia. Combining HBO and LIT as hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) might be an approach that results in positive synergistic effects on oxygenation. LIT increases blood flow and could reduce HBO-induced vasoconstriction, and hyperoxia could compensate for the increased metabolic oxygen requirements mediated by LIT. Both LIT and HBO increase the oxygen diffusion distance in the tissues. HBOIR at 0.5 bar has been shown to be safe and feasible. However, physiological responses and the safety of HBOIR at an increased oxygen ( $O_2$ ) partial pressure of 1.4 bar or 2.4 atmospheres absolute (ATA) still need to be determined. The hope is that should HBOIR at an increased oxygen partial pressure of 1.4 bar be safe, future studies to examine its efficacy in patients with clinical conditions, which include peripheral arterial disease (PAD) or wound healing disorders, will follow. The results of pilot studies have shown that HBOIR at an overload pressure is safe and well tolerated in healthy participants but can generate moderate cardiovascular changes and an increase in body temperature. From the findings of this pilot study, due to its potential synergistic effects, HBOIR could be a promising tool for the treatment of human diseases associated with hypoxemia.

**MeSH Keywords:** **Blood Pressure • Body Temperature Regulation • Heart Rate • Hyperbaric Oxygenation • Infrared Rays**

**Abbreviations:** **ATA** – atmosphere absolute; **CO<sub>2</sub>** – carbon dioxide; **DBP** – diastolic blood pressure; **HBO** – hyperbaric oxygen therapy; **HBOIR** – hyperbaric oxygen therapy combined with low-temperature infrared radiation; **HR** – heart rate; **LIT** – low-temperature infrared technology; **O<sub>2</sub>** – oxygen; **pO<sub>2</sub>** – partial oxygen pressure; **SBP** – systolic blood pressure; **SpO<sub>2</sub>** – arterial oxygen saturation; **VAS** – visual analog scale

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## Background

Hyperbaric oxygen therapy (HBO) has been widely implemented as primary or adjunctive therapy for conditions ranging from cardiovascular disorders to the management of wound healing [1,2]. Breathing 100% oxygen at an elevated environmental pressure increases oxygen tension in tissues. An increase in pressure from normobaric conditions to 3 atmospheres absolute (ATA) enables an increase in the physically dissolved oxygen in arterial blood from 0.3 mL/dL to approximately 6 mL/dL [3]. Therefore, breathing under hyperbaric conditions raises the diffusion gradient between dissolved oxygen in plasma and tissue [4,5]. According to the Krogh tissue cylinder model of oxygen transport, oxygen diffusion distance in tissue improves under hyperbaric conditions, resulting in an increase in diffusion distance from the capillary at 3 ATA by a calculated factor of 4 [6,7]. As a consequence, the supply of oxygen to tissue regions suffering from hypoxia is facilitated. Tissue hypoxia is known to negatively impact on the course of several chronic diseases [8–11]. Therefore, HBO provides an efficient adjunct treatment strategy in a variety of chronic diseases with an underlying deficiency in tissue oxygenation.

## Why Combine HBO with Low-Temperature Infrared Technology (LIT)?

Standard pressure chambers are expensive and are currently only accessible to a small number of patients. Also, detrimental effects of HBO have been shown to include reactive vasoconstriction in organs and tissues induced by hyperoxia [12–14]. An increase in the oxygen diffusion gradient may compensate for this potential disadvantage. However, it remains unclear if reactive vasoconstriction could negatively affect the treatment outcome in different medical conditions. Therefore, the effectiveness of HBO may be substantially increased if the administration of oxygen at higher pressure is combined with a method that increases metabolism and oxygen diffusion distance, and induces vasodilation at the same time as increasing local blood flow and tissue perfusion.

An approach to improving the effectiveness of HBO is to use low-temperature infrared technology (LIT). During LIT, only a small area of skin is irradiated under thermo-neutral conditions (ambient temperature of 28–37°C) [15]. Hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) technology using the Sensocare® system (Physiotherm, Thaur, Austria) automatically regulates the intensity of infrared radiation according to the registered temperature of the skin on the back, which is measured continuously and is contactless. Therefore, regulation of the heat input is independent of any subjective pain response to heat. The signal from the temperature sensors is transferred to the control system, which,

in turn, automatically regulates radiation intensity and heat input to the body. The desired target temperature is reached after between 12–15 minutes, which enables the core temperature to increase slightly within a sub-febrile range at the onset of treatment due to the heat defense mechanisms of the body. Therefore, the central circulation is not disturbed. Heat is dispersed from the core to the body surface, inducing moderate whole-body warming with only a slight increase in core temperature [16,17].

Therefore, combining HBO and LIT could have a synergistic effect. In addition to HBO, whole-body warming also increases the diffusion distance of oxygen, and the augmented peripheral perfusion generated by LIT could attenuate hyperoxia-induced vasoconstriction. Also, increased metabolism, induced by LIT, with its associated rise in oxygen consumption, might be compensated for by hyperoxia, and the standard duration of HBO therapy could be reduced, resulting in improved patient safety.

Because a major part of healthcare costs arise from the management of chronic diseases, efficient and cost-effective innovative approaches, which are easily accessible and have no, or few, side effects are becoming increasingly important. Therefore, and for the first time, we recently evaluated the safety and feasibility of the combined application of HBO and LIT or hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) used for 45 minutes at a low working pressure of 0.5 bar, or 1.5 atmosphere absolute (ATA), on healthy participants. We have previously reported clinically insignificant increases in heart rate and skin temperature (+3°C), elevations in core temperature within the desired range (+0.2°C), and unchanged arterial blood pressure, without adverse effects or impairment of participant well-being, indicating that HBOIR at 0.5 bar in a healthy study population to be safe and feasible [18]. However, physiological responses at a working pressure equivalent to commonly used HBO pressures (1.4 bar) have not previously been assessed.

Because the evaluation of the safety and feasibility of HBOIR at 1.4 bar (for 45 minutes) might provide the basis to examine the efficacy of HBOIR in patients with chronic diseases, a pilot study was performed to test the effects of HBOIR at a pressure of 1.4 bar (2.4 ATA) on physiological parameters that included heart rate, blood pressure, core temperature, skin surface temperature, and oxygen saturation, and to assess the safety of HBOIR in healthy participants and their tolerance of the treatment.

In this study, a total of six healthy participants received ten consecutive HBOIR treatments at 1.4 bar. Pure oxygen was administered using a re-breather technology for 30 minutes. Infrared radiation transferred heat to the back region via the

automated Sensocare® system. Physiological and ambient parameters were continuously recorded. Also, perceived well-being was assessed before, and after each HBOIR session. The main findings of this study were that the ten consecutive HBOIR treatments at 1.4 bar were well tolerated by all participants, and no significant side effects or complications were reported by the six study participants. The heart rate ( $75 \pm 12$  bpm to  $82 \pm 13$  bpm) ( $p < 0.001$ ) and core body temperature ( $37.3 \pm 0.3$  to  $37.5 \pm 0.3^\circ\text{C}$ ) ( $p < 0.001$ ) increased slightly, but not significantly. Systolic blood pressure decreased ( $121 \pm 15$  to  $110 \pm 10$  mmHg) ( $p < 0.001$ ). The findings of this pilot study in six healthy volunteer participants generated moderate cardiovascular and thermal responses with good well-being scores during treatment (see Attachment).

### Support for the Safety and Expected Benefits of Combining HBO and LIT

Despite the significant increase in working pressure and the high number of consecutive applications, the effects on the cardiovascular system in the pilot study were comparable to those observed in our previous study that applied a working pressure of 0.5 bar [18]. Known hemodynamic and circulatory changes in both healthy and unhealthy people during HBO include bradycardia and increased arterial blood pressure, reduced heart rate at rest and during exercise, which have been mainly attributed to the elevated oxygen pressure [19]. However, a decrease in arterial blood pressure and normal heart rate at rest and during exercise have also been recorded during normobaric oxygen administration and can, therefore, be independent of additional increases in hyperbaric pressure [20]. It has been proposed that a bradycardic effect is mediated by baroreflex activation due to a hyperoxia-induced increase in arterial blood pressure, as a result of increased parasympathetic activity [21]. Also, hyperoxia decreases catecholamine levels [22,23], as well as sympathetic activity, which reinforces parasympathetic activity [21]. The increased peripheral vascular resistance due to hyperoxic vasoconstriction tends to induce arterial hypertension [12,13]. This finding is in contrast to the reduction in systolic blood pressure observed in this pilot study. A possible explanation for this reduction in systolic blood pressure is that the increased blood flow induced by LIT reduced peripheral vascular resistance. If this was the case, then LIT might offset the potential vasoconstriction induced by the physiological effects of increased oxygen during HBOIR.

During standard HBO therapy, an increase in heart rate is primarily considered to be a warning sign of oxygen toxicity [24], which is a concern in HBO studies [25]. However, when using HBOIR, an increase in heart rate is interpreted to be a compensatory response to the vasodilatory effect induced by the thermal application [26]. The moderate observed increase in heart

rate at 1.4 bar is comparable to that observed in our previously published study, where a lower pressure of 0.5 bar was used [18]. During diving, exposure to a  $pO_2$  greater than 1.6 bar is known to be a risk factor for acute oxygen toxicity [27]. However, a higher  $pO_2$  can be tolerated during HBO therapy, but oxygen toxicity may arise at lower levels when exposure is prolonged.

In this pilot study, heart rate responses below and above a  $pO_2$  of 1.6 bar were similar, and the exposure time was limited to approximately 30 minutes, and oxygen toxicity was not expected, as exposures to hyperbaric oxygen were performed at rest in a hyperbaric chamber and not underwater, which is known to decrease the time of onset of oxygen toxicity [28]. Also, in this pilot study, changes in  $pO_2$  did not correlate with those in heart rate and systolic blood pressure, and heart rate and blood pressure changes were moderate, indicating that the applied levels of  $pO_2$  did not adversely affect heart rate or blood pressure, which are two physiological variables that are sensitive indicators of the acute onset of hyperoxia. Therefore, the findings of this pilot study of the use of HBOIR in six individuals, and under the conditions of the study, were that the treatment was acceptable.

The slight increase in core temperature observed in the pilot study was within the sub-febrile range ( $\leq 38^\circ\text{C}$ ), and was necessary to achieve a synergistic effect of HBO and LIT. The increase in temperature was facilitated by the special heating system with irradiation of only a small area of the body ( $< 15\%$  of the overall skin surface) [18], used in combination with a moderate environmental air temperature (thermoneutral temperature) in the chamber. Heat input to the body was raised slowly and adjusted in response to the heat-induced alteration in blood circulation. Heat transfer to the skin by infrared radiation was expected to be reduced during increased atmospheric pressures. However, the sensors used regulated the skin temperature independent of the changes in atmospheric pressure. The automatic regulation of heat input might have important implications for the future of the safe application of this system on patients suffering from chronic diseases, who may also have sensory disorders and who may be taking medication. Also, as the HBOIR system is contactless and records in real time, skin temperature is prevented from rising to above  $43^\circ$  for more than 3 minutes, which means that any effect on the heat defense reaction of the skin is marginal and thermal damage to the skin from a burn or heat can be avoided [29–31]. It is also important to note that the erythema observed on the backs of the participants immediately after treatments disappeared within one hour after leaving the chamber. In the pilot study, changes in heart rate, blood pressure and core temperature during HBOIR did not differ between treatments, which indicated that consistent physiological reactions could be achieved over ten consecutive HBOIR treatments with a 24-hour time interval between treatments.

The physiological responses recorded in this study contrast with those observed during conventional thermal treatments, such as sauna applications. During HBOIR, only marginal increases in core temperature are observed. However, during sauna applications (80-100°C) ambient temperatures are higher and thermal absorption by the body exceeds heat dissipation, resulting in an altered thermoregulation. Hence, blood supply to the inner body initially decreases to prevent a fever. After a certain exposure time, relative central volume depletion occurs, followed by a rapid increase in core temperature up to 39°C, as the blood flow to the inner body is enhanced [32,33]. Therefore, the cardiovascular strain can be high during sauna applications [26].

With regard to the findings in the pilot study, which involved six study participants, we did not expect any positive changes in participant well-being, as the treatments were performed on a group of healthy participants. However, the scores for perceived well-being increased overall, and quite significantly during some of the treatments. Importantly, well-being did not decrease during any of the treatments. These findings, together with the positive ratings during the treatments obtained by the VAS regarding pain, anxiety, and comfort indicate that HBOIR is not an unpleasant treatment. As for the climate in the chamber, increases in ambient temperature are as expected so the heat dissipation in the participants was not disturbed.

## Attachment (Pilot Study)

### Patients and Methods

Six healthy participants, three women and three men, mean age 37±18 years, mean height 175±8 cm, mean body mass index (BMI) 22.8±3 kg/m<sup>2</sup>, volunteered to take part in the pilot study. Participants were recruited through online platforms and mailing lists at local universities in and around the cities of Hall in Tirol and Innsbruck, Austria.

Inclusion criteria for the pilot study included a requirement of healthy male or female participants, between 21–70 years-of-age, who fulfilled the suitability criteria for diving. Exclusion criteria included women who were pregnant or lactating, and men and women who suffered from coronary artery disease, cardiac insufficiency, bronchial asthma or chronic obstructive pulmonary disease (COPD), acute allergies; chronic infections; inflammatory diseases or injuries, who had a history of drug or alcohol abuse, claustrophobia, or who had acute diseases during the test procedure, including simple infections, such as rhinitis or cough. Participants were excluded who had participated in a clinical trial within 30 days prior to the study, or who did not or could not comply with requirements of the study procedures. Participants were requested not to dive, fly, or climb

### Future Perspectives

HBOIR at an overload pressure of 1.4 bar results in moderate changes to the cardiovascular system and generates whole-body warming induced by small core temperature increases in a group of healthy participants. Aside from appearing to be a safe approach, HBOIR is very well tolerated and does not impair well-being during repeated exposures. These positive findings provide the basis for further studies to examine the efficacy of the HBOIR system in patients with medical conditions such as peripheral arterial occlusive diseases or wound healing disorders. We consider HBOIR to be a promising alternative means to improve hypoxemia in various conditions with the potential to be easier accessible than standard HBO.

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to high altitudes (>2,000 m) on the day before the start of treatment, as well as during the entire study period. Also, the use of a solarium or other heat applications, such as a sauna or a thermal bath, were to be avoided on each treatment day.

To evaluate the inclusion and exclusion criteria, participants underwent a clinical examination that included blood pressure measurement, spirometry and electrocardiogram (ECG) within one month before the study. An incremental symptom-limited exercise test on a bicycle ergometer (including ECG) had to be performed by all participants aged 40 years or more. Also, a medical interview took place before each HBOIR testing.

The study conformed to the requirements of the ethical standards of the Declaration of Helsinki, 1978, and with the Austrian Standards for Clinical Investigation of Medical Devices for Human Participants (ÖNORM EN ISO 14155). The Ethical Committee of the Medical University of Innsbruck approved the study design (AN 5232; 329/4.13.346/5.17). Written informed consent was obtained from all the study participants.

## Study Protocol Using the Hyperbaric Chamber with Low-Temperature Infrared Technology (HBOIR)

Ten treatment (tr) sessions were performed over a period of two working weeks (ten days). Participants were exposed to a monoplace hyperbaric chamber (volume of 1,200 liters) equipped with infrared technology using the Sensocare® system (Physiotherm, Thaur, Austria) using an overload pressure of 1.4 bar [18]. Prior to each treatment, the hyperbaric chamber was preheated to an ambient temperature of 30°C. Infrared radiation was directly applied to the back of the sitting participants using Sensocare® technology (see below).

During each treatment session, there was permanent audio-visual contact with the participants. Progressive pressurization was carried out using standardized diving cylinders (15 liters) filled to a pressure of 225 bar by a portable air compressor, the Bauer Junior 2 (Bauer, Munich, Germany). The pressure of the chamber was regulated and controlled by a technician. On reaching an overload pressure of 1.4 bar, which usually occurred after 5–10 minutes, depending on the ability of the participant to achieve and tolerate pressure equalization, the application was undertaken for a scheduled period of 45 minutes. After adjustments were made for the individual participants, including radiation levels, heart rate, respiratory rate, blood pressure, participant habituation, for a maximum time of 15 minutes, pure oxygen (O<sub>2</sub>) (100%) was administered via a re-breather for the remaining application time, for a minimum duration of 30 minutes.

After the 45-minute period, at a constant overload pressure of 1.4 bar, the chamber was decompressed. Participants were advised not to take off their facial mask during the decompression phase (2–5 minutes). The pressurization and decompression profiles were approved by the participant beforehand and further regulated by direct contact. After leaving the chamber, participants were observed for one hour in the study center. In case of emergency or appearance of pre-determined symptoms, the chamber could be decompressed in less than 2 minutes. The application could also be stopped if any problems occurred during pressurization, particularly continuous pain in the paranasal sinuses or the inner ear.

## Physiological Parameters

Heart rate was continuously recorded during each HBOIR exposure, using three chest and two waist Compact 7 cables (Medical Econet, Oberhausen, Germany). Also, core temperature using a rectal probe, oxygen saturation (SpO<sub>2</sub>) measured using a pulse oximeter, and non-invasive measurements of systolic and diastolic blood pressure were recorded during

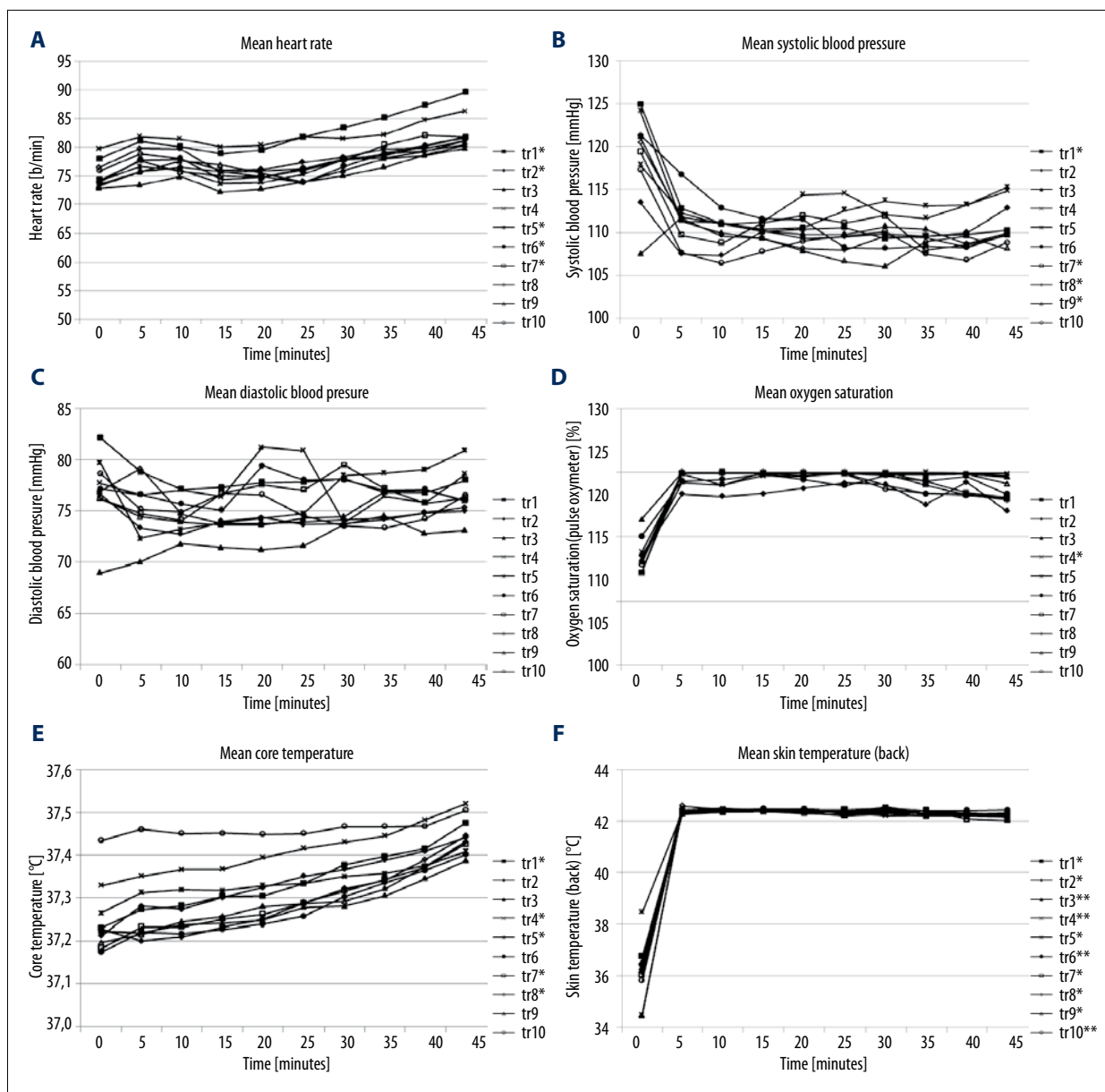
each treatment using the Compact 7 cables (Medical Econet, Oberhausen, Germany). Visual examination of the skin on the back of each participant was conducted by a physician immediately after exposure, and again one hour later. Heart rate, blood pressure, SpO<sub>2</sub> and core temperature were stored in the memory of the monitor and transferred to a personal computer after each HBOIR session.

## Measurements in the Hyperbaric Chamber

Climate changes in the chamber were monitored by continuous measurement of carbon dioxide concentration, air humidity and temperature using the EE80-5CT3/T04 sensor (E&E Electronic, Engerwitzdorf, Austria), air pressure using the GMUD MP pressure sensor (Greisinger Electronic GmbH, Regenstauf, Germany), and oxygen concentration using the Greisinger OXY 3690 MP, which is an atmospheric air oxygen transmitter-including electrode that measures the oxygen concentration in air (OXY 3690 MP) (Greisinger Electronic GmbH, Regenstauf, Germany).

## Hyperbaric Infrared Chamber

An infrared heater (Rückenstrahler Schwarz) (AP1-4S, Physiotherm, Thaur, Austria) was placed at the front of the HBOIR 1200 chamber (Holzner Druckbehälter GmbH, Peißenberg, Germany) and was used to reach a thermoneutral air temperature (30°C) within the chamber prior to the start of the treatment. A TÜV.SV.10.882.8.D/G.0.31/AZ pressure limiter (Armaturen GmbH, Mönchweiler, Germany) controlled the maximum working pressure in the chamber. A Drägersorb 800 Plus soda lime cartridge in an active ventilation system (Dräger Medical GmbH, Lübeck, Germany) was used to remove the exhaled CO<sub>2</sub> from the chamber. Oxygen was supplied using a Submatix Quantum re-breather (Submatix GmbH & Co.KG, Erfurt, Germany) with a Submatix X100 MF oxygen-integrated pressure reducer (Submatix GmbH & Co.KG) connected to an oxygen cylinder located outside the chamber. The partial pressure of oxygen in the supplied air was measured in the breathing loop of the re-breather by an oxygen controller. The amount of oxygen in the air, as determined by the re-breather, was slightly below 100%, as nitrogen was exhaled into the re-breathing system. The re-breathing technique was used for safety reasons, to prevent the oxygen content in the chamber increasing above critical values. Also, the implementation of the re-breather with an embedded CO<sub>2</sub> absorber avoids reduction in oxygen consumption and any significant increase in the amount of CO<sub>2</sub> exhaled into the chamber.



**Figure 1.** Physiological responses to hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR). (A) Mean heart rate. (B) Mean systolic blood pressure. (C) Mean diastolic blood pressure. (D) Mean oxygen saturation. (E) Mean core temperature. (F) Mean skin temperature (back). Physiological responses during the ten hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) treatment cycles for six participants, treatment (tr) days 1–10. Means of the results for all participants on the respective treatment days are shown and were calculated over a 5-minute period, except for systolic and diastolic blood pressure (5-minute interval measurements). \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , for significant changes from baseline to the end of treatment.  $N=6$  for each time point.

### Sensocare® Infrared Radiator with Integrated Infrared-Temperature Sensors

Using the Sensocare® system (Physiotherm, Thaur, Austria), the maximum skin temperature in the directly irradiated region was set at 42.5°C. Longterm, or repeated, exposure to temperatures above the intrinsic skin temperature of 43°C was avoided to

prevent and acute burns or chronic thermal damage to the skin. The infrared system is equipped with an inert thermal heating element. Thus, depending on the participant's thermoregulatory capability, the infrared system will allow the skin temperature to rise to 45.5 °C for a maximum of only 3 minutes. Considering that each 0.9°C incremental increase in skin temperature above 43°C halves the tolerance time, the maximum

**Table 1.** Cardiovascular, respiratory, and thermal changes during hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) at treatment (tr) days 1–10.

	tr 1	tr 2	tr 3	tr 4	tr 5	tr 6	tr 7	tr 8	tr 9	tr 10
<b>Heart rate (b/min)</b>										
Baseline	78±11	74±14	73±13	80±11	74±12	74±13	74±13	77±12	73±7	76±11
End of treatment	90±13*	81±12*	79±15	86±16	80±15*	82±15*	82±13*	81±9	80±13	82±11
<b>Systolic blood pressure (mmHg)</b>										
Baseline	125±15	113±17	108±15	118±12	124±19	121±18	119±14	120±18	121±18	117±16
End of treatment	110±9*	113±12	107±13	115±11	115±18	110±16	110±9*	110±11*	108±12*	108±10
<b>Diastolic blood pressure (mmHg)</b>										
Baseline	82±13	77±10	69±8	78±4	80±12	77±11	76±8	77±9	76±13	79±10
End of treatment	78±9	75±10	70±5	79±10	81±18	76±11	76±11	75±9	76±12	77±9
<b>Oxygen saturation (%)</b>										
Baseline	98±0.7	98±0.5	99±0.5	98±0.5	98±0.6	99±0.5	98±0.6	98±0.7	98±0.5	98±0.6
End of treatment	99±0.3	99±0.5	99±0.1	99±0.2*	99±0.1	99±0.3	99±0.5	99±0.5	99±0.2	99±0.5
<b>Core temperature [°C]</b>										
Baseline	37.2±0.3	37.2±0.3	37.2±0.3	37.3±0.2	37.3±0.4	37.2±0.4	37.2±0.3	37.2±0.2	37.2±0.2	37.4±0.3
End of treatment	37.5±0.4*	37.4±0.3	37.4±0.3	37.5±0.3*	37.4±0.4*	37.4±0.3	37.4±0.3*	37.5±0.1*	37.4±0.2	37.5±0.2
<b>Skin temperature (back) (°C)</b>										
Baseline	36.8±2.9	36.2±2.4	34.5±1.2	34.5±1.5	37.9±2.0	36.4±0.8	36.0±2.2	36.2±1.0	36.5±1.9	35.8±1.6
End of treatment	42.3±0.5	42.3±0.5*	42.2±0.5**	42.2±0.6**	42.2±0.4*	42.4±0.1**	42.0±0.5*	42.2±0.5**	42.2±0.5*	42.2±0.5*

Data are presented as mean ±SD. \* p≤0.05, \*\* p≤0.001: significant changes from baseline to the end of treatment during each treatment (tr).

**Table 2.** Participant well-being during hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) at treatment (tr) days 1–10.

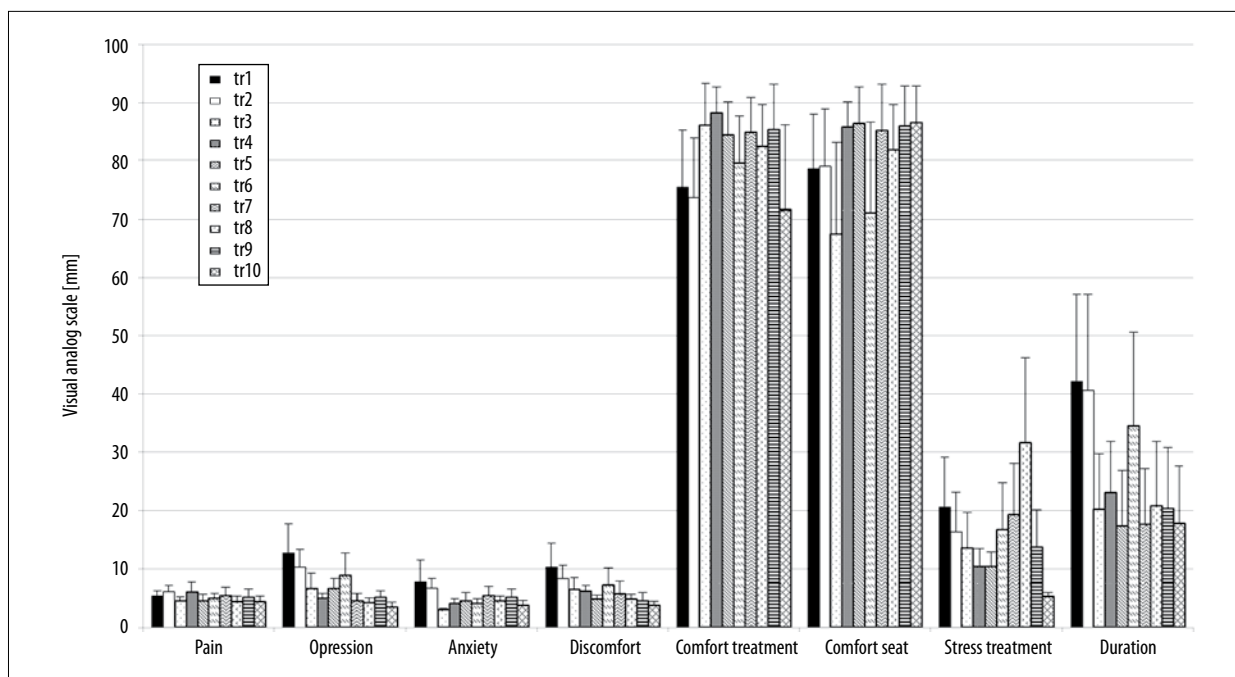
	tr 1	tr 2	tr 3	tr 4	tr 5	tr 6	tr 7	tr 8	tr 9	tr 10
<b>Well-being</b>										
Before treatment	8±16	71±20	79±25	84±15	76±22	94±15	86±18	82±16	81±26	81±27
After treatment	91±15*	94±11*	91±8	88±15	89±11	97±9	95±14	97±10*	95±17	98±19*

Ratings of the general condition of the pilot study participants two hours before and one hour after each treatment (tr). Data are presented as mean ±SD. \* p≤0.05 indicates a significant change. N=6 for each time point.

tolerable temperature over the period of 45 minutes is about 46°C [30]. Therefore, such short-term increases in the intrinsic skin temperature can be tolerated. However, for safety reasons, the system immediately turns off if 45.5°C is reached. The skin surface temperature (measured on the back) and radiation data were continuously recorded using fully electronic control with 1+LED MAX (Rawe Electronic GmbH, Weiler-Simmerberg, Germany) and automatically transmitted to a personal computer.

## Participant Well-Being

The 'Basler Befindlichkeitsfragebogen,' a multidimensional, self-rating system evaluating mental state (Cronbachs alpha: 0.88–0.79) [34], which was completed by the participants with regard to their general condition two hours before, and one hour after, each treatment. Also, the perception of the participants of pain, anxiety, discomfort, comfort, and stress, as well



**Figure 2.** Perceptions of the participants during hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR). Mean visual analog scale (VAS) scores determined after each treatment day for six participants treatment (tr) days 1–10. Data are presented as means  $\pm$  SEM for all participants on the respective treatment days. Visual analog scale (VAS), 0–100 mm. (N=6).

as the duration of the treatment were documented on a 100-mm visual analog scale (VAS) following each HBOIR session.

## Statistical Analysis

Data were analyzed using the SPSS statistical software package 24 (IBM, Vienna, Austria). Probability values  $\leq 0.05$  (two-tailed) were considered as statistically significant. Wilcoxon Matched Pairs Test was used to detect changes in each treatment. The delta ( $\delta$ ) of changes within each treatment were calculated and then tested for differences between treatment days using Friedman's Test. Data were presented as mean  $\pm$  standard deviation (SD) (two-tailed). The distribution normality of the variables was determined using the Kolmogorov–Smirnov test (KS-test). Values over a period of 5 minutes were averaged for evaluation of the data, except blood pressure, core temperature, and re-breather  $pO_2$ , which were recorded at 5-minute intervals. Relationships between changes in heart rate, systolic blood pressure, and  $pO_2$  were calculated with Spearman's rank correlation coefficient.

## Detailed Results of the Pilot Study

Each participant performed all ten prescribed hyperbaric infrared sessions. The exposures were well tolerated and

accomplished without any complications or adverse effects. No problems in pressure equalization during pressurization of the chamber up to 1.4 bar occurred or were reported by the participants. Cardiovascular, respiratory and thermal responses are presented in Figure 1A–1F, and Table 1.

## Cardiovascular and Respiratory Responses

Heart rate increased from baseline (time before pressurization of the chamber) to the end of treatment, and was particularly significant during treatments 1, 2, 5, 6 and 7 (tr 1, tr 2, tr 5, tr 6, tr 7) with the mean change being  $75 \pm 12$  to  $83 \pm 13$  bpm ( $p < 0.001$ ) (Figure 1A). There was no significant difference in the pattern of change in heart rates between the ten testing days. The extent of heart rate changes did not differ during the course of the treatments. Systolic blood pressure significantly decreased relative to the baseline only during tr 1, tr 7, tr 8 and tr 9, with the mean change being  $121 \pm 15$  to  $110 \pm 10$  mmHg ( $p < 0.001$ ) (Figure 1B). Changes in systolic blood pressure (SBP) were not observed between treatments. Diastolic blood pressure did not vary significantly from baseline to the end of the exposure, and there were no recorded differences between the individual testing days (Figure 1C). An increase in oxygen saturation from baseline to the end of the treatment was only significant during tr 4 (Figure 1D). There were no significant changes in  $SpO_2$  between treatment days.



**Table 3.** Changes in chamber parameters during hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) at treatment (tr) days 1–10.

	tr 1	tr 2	tr 3	tr 4	tr 5	tr 6	tr 7	tr 8	tr 9	tr 10
<b>Air temperature (°C)</b>										
Minute 5	32.4±2	32.3±3	30.3±1	29.8±1	34.5±2	30.5±2	30.9±2	30.3±2	30.8±2	30.3±2
End of treatment	36.2±2*	35.9±2*	35.6±1*	34.7±2*	30.1±2*	35.2±2*	35.5±2*	34.5±2*	35.0±2*	34.6±1*
<b>Air humidity (%)</b>										
Minute 5	61±9	62±10	54±7	54±8	51±5	45±8	51±9	52±8	49±8	53±5
End of treatment	72±10*	73±7*	71±4*	74±6*	69±9*	69±7*	69±10*	73±8*	69±10*	72±8*
<b>Carbon dioxide:</b>										
Minute 5	583±102	706±105	611±96	618±72	536±142	645±73	679±127	617±50	594±143	603±46
End of treatment	1328±1758	321±285*	448±594	644±1079	548±896	475±606	443±279	477±506	274±200*	325±194*
<b>Oxygen concentration (%)</b>										
Minute 5	20.5±0.1	20.4±0.2	20.4±0.3	20.3±0.2	20.2±0.2	20.4±0.2	20.5±0.2	22.4±0.1	20.4±0.4	20.2±0.2
End of treatment	22.2±0.2*	22.3±0.2*	22.5±0.2*	22.6±0.5*	22.8±0.6*	22.6±0.3*	22.7±0.5*	22.8±0.5*	22.4±0.4*	22.7±0.4*
(min–max)	20.6–23.9	20.7–23.6	20.6–23.1	20.7–23.2	20.6–23.4	20.6–23.3	20.7–23.9	20.6–23.4	20.6–23.3	20.7–23.4
<b>Chamber pressure (mbar)</b>										
Minute 5	1334±138	1360±78	1382±35	1384±30	1382±33	1380±36	1378±41	1380±34	1377±41	1378±45
End of treatment	1396±11	1402±4	1405±6	1402±4	1402±7	1403±6	1403±5	1403±5	1400±6	1402±5
<b>Partial oxygen pressure [bar]</b>										
minute 15	1.22±0.2	1.33±0.3	1.45±0.2	1.58±0.2	1.55±0.3	1.54±0.2	1.52±0.2	1.53±0.2	1.51±0.2	1.58±0.2
End of treatment	1.56±0.3	1.73±0.2#	1.80±0.2#	1.92±0.2#	1.90±0.3#	1.83±0.4	1.73±0.2	1.71±0.3	1.90±0.1	1.72±0.2
(min–max)	1.03–1.88	0.76–2.10	1.21–2.16	1.44–2.25	1.24–2.19	1.17–1.86	1.20–1.99	1.28–2.07	1.26–2.01	1.33–1.80

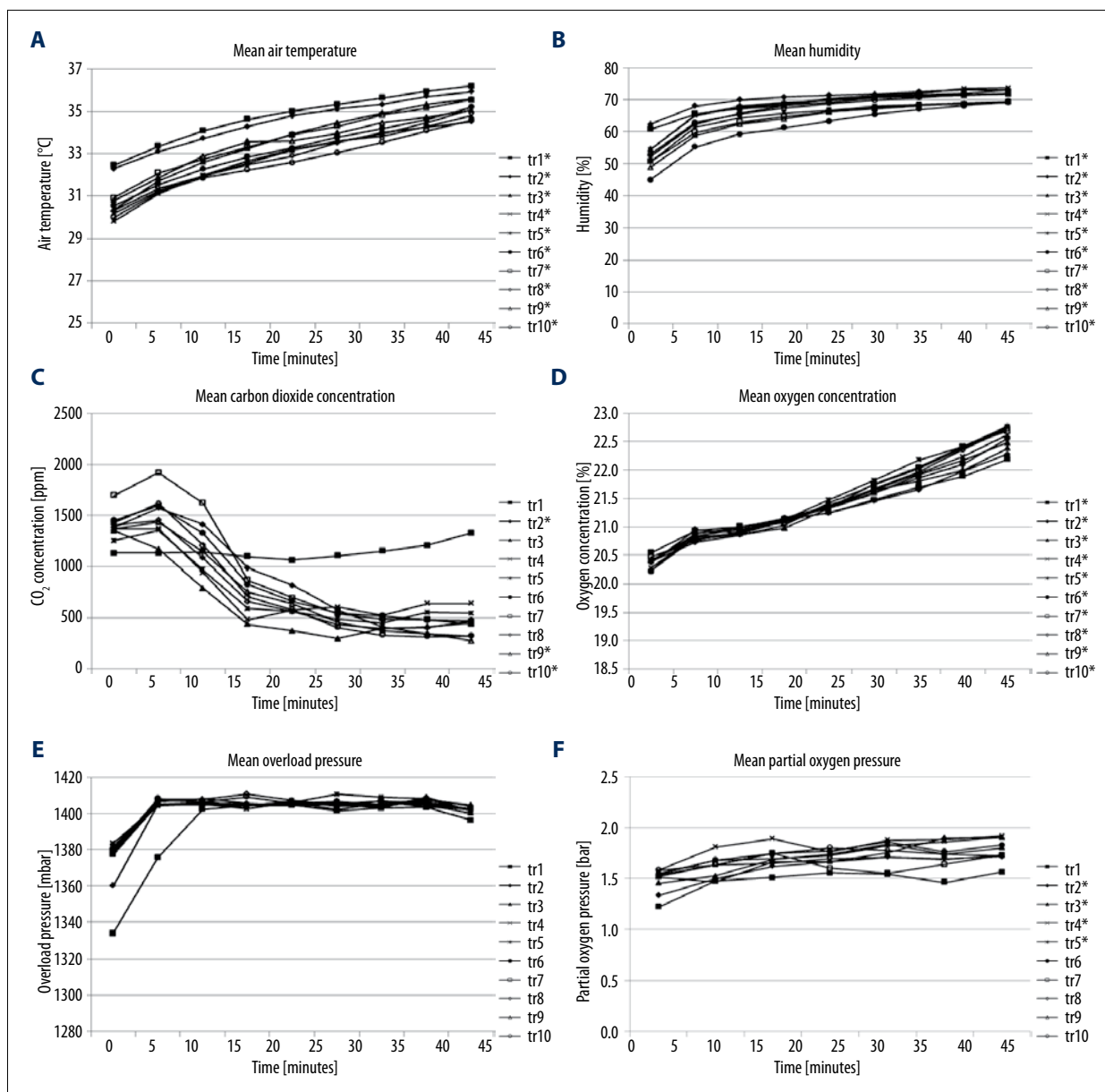
Data are presented as mean ±SD. \* p<0.05 indicates significant changes from the time when the chamber was pressurized (minute 5) to the end of treatment. # p<0.05 indicates significant changes from the time when oxygen administration had started in all participants (minute 15) to the end of treatment.

## Thermoregulatory Responses

The hyperbaric infrared exposures induced slight increases in body temperature, which became statistically significant during tr 1, tr 4, tr 5, tr 7, and tr 8, with the mean change: being 37.3±0.3 to 37.5±0.3 °C (p<0.001) (Figure 1E). No differences were recorded between the treatment days. Skin temperature in the back area significantly increased during each treatment (tr 1–tr 10) but showed no significant changes between treatments (Figure 1F). The target skin temperature was reached, at the latest, 5 minutes after the chamber was pressurized with the mean change being 42.4±0.3°C. A moderate reddening of the skin of the back of the participants in the irradiated region was observed immediately after the participants left the chamber. The redness was no longer apparent one-hour post-treatment.

## Perceived Participant Well-Being

The scores for perceived well-being significantly increased during tr 1, tr 2, tr 8, tr 10 (p<0.05) (Table 2). The visual analog scale (VAS) ratings did not significantly change between treatment days. Splitting the 100 mm scale of the VAS into quartiles, pain, anxiety, discomfort, and stress were rated during tr 1–tr 10 within the lowest quartile (<25%) with means of 5±1, 7±3, 5±1, 6±2, and 16±7, respectively. Overall comfort during the treatment and, specifically that of the seat, were rated within the highest quartile (>75%) with means of 81±6, and 81±7, respectively (Figure 2).



**Figure 3.** Changes in ambient parameters during hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR). (A) Mean air temperature. (B) Mean humidity. (C) Mean carbon dioxide concentration. (D) Mean oxygen concentration. (E) Mean overload pressure. (F) Mean partial oxygen pressure. Ambient parameters in the chamber during the ten hyperbaric oxygen therapy combined with low-temperature infrared radiation (HBOIR) treatment cycles for six participants, treatment (tr) days 1–10. Means for all participants on the respective treatment days are shown and were calculated over a 5 min period. \*  $p \leq 0.05$  for significant changes from minute 5 to the end of treatment. Data are presented for the period of time when the chamber was pressurized (minute 5) with an overload pressure of 1.4 bar. Data for partial oxygen pressure are shown for the time when oxygen administration was initiated in all participants (minute 15). (N=6).

### Ambient Parameters in the Chamber

Changes in chamber parameters from the time when the chamber was pressurized to the end of the treatments (tr) 1–10 are presented in Table 3 and Figure 3. There was a significant rise in the air temperature, with a mean change of  $4.5 \pm 1.8^\circ\text{C}$ , during

all sessions (tr 1–tr 10). The patterns of change did not differ between treatments. Also, humidity significantly increased by  $18.0 \pm 10\%$  during each exposure. There were no differences between the testing days. The  $\text{CO}_2$  concentration significantly decreased in tr 2, tr 9 and tr 10, with a mean change of  $-1084 \pm 293$  ppm; the oxygen concentration increased during

each testing day with a mean change of  $+2.2\pm 0.5\%$ . Changes in  $\text{CO}_2$  and oxygen concentration did not significantly differ between treatment days. Chamber pressure significantly increased at the beginning of each session and remained high until chamber decompression during all the HBOIR exposures. Re-breather  $\text{pO}_2$  significantly increased from  $1.5\pm 0.2$  bar to  $1.8\pm 0.2$  bar during tr2, tr 3, tr4 and tr 5. Changes in  $\text{pO}_2$  did not correlate with changes in heart rate and systolic blood pressure during any of the treatment days (tr 1–tr 10) ( $p>0.05$ ).

## Technical Remarks

When participants started breathing into the re-breather, nitrogen was exhaled into the re-breathing system, resulting in

decreased re-breather  $\text{pO}_2$  levels. As a consequence, 100% oxygen breathing was not possible. Exhalation of nitrogen decreased over time, but was present during the entire application phase. To obtain constant re-breather  $\text{pO}_2$  levels during the HBOIR application, both the re-breathing system and the application of a facial mask needed to be optimized. Also, a slight increase in oxygen concentration below critical values in the chamber was observed, which might be explained by slight leaking from the masks when participants exhaled. However, in future follow-up studies the system will be improved accordingly, to maintain constant oxygen concentrations during HBOIR.

## Conflict of interest

None.

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