Functional changes in microcirculation during hyperbaric and normobaric oxygen therapy

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ABSTRACT

Objectives: Treatment of cutaneous wounds is one of the many applications of hyperbaric oxygen therapy (HBO). However, the complex regulation of skin microcirculation during different phases of HBO is not completely understood. We therefore investigated skin microcirculation and oxygenation during HBO and normobaric oxygen (NBO) exposure.

Methods: Seven healthy volunteers were investigated using measurements of transcutaneous oxygen pressure ($P_{tc}O_2$), tissue spectrophotometry and laser Doppler flowmetry recorded simultaneously in the hand and foot during HBO and NBO in 2- and 4-mm depths. We defined tissue hypoxia as a $P_{tc}O_2$ below 30 mmHg.

Results: At the hand, in 2 mm depth, NBO induced a mild vasoconstriction (-37%, p=0.07), but a significant increase in $P_{tc}O_2$ (+380%, p<0.001). HBO induced a mild vasoconstriction (-45%, p=0.08), significantly increasing $P_{tc}O_2$ (+1430%, p<0.001). Hand changes in 2 and 4 mm were comparable. Foot changes were smaller than at the hand and more pronounced in 4 mm than in 2 mm depth during NBO and compression. No episodes of tissue hypoxia occurred at any time.

Conclusions: In healthy subjects, NBO and especially HBO significantly improve tissue oxygenation, despite vasoconstriction. Differences in vascular regulation between hand and foot and especially at the latter site between 2 and 4 mm depth exist.

INTRODUCTION

Hyperbaric oxygen therapy (HBO) is used in several clinical settings for the treatment of diving accidents (1), osteomyelitis (2, 3), reperfusion injuries (4), carbon monoxide poisoning (5), clostridial myonecrosis (6, 7), radiation injury of bone and soft tissue (8), necrotizing soft tissue infections (9), crush injuries (10) and ischemic wound healing (11).

The latter application has raised controversies, but it also represents an interesting approach for the healing of treatment-refractory wounds. The mechanisms are related to angiogenesis (12), antibacterial effects (13) and improved collagen synthesis (14).

Under HBO, oxygen diffusion is optimized, along with the oxygenation of cells whose supply is jeopardized by trauma, inflammation, or disturbed blood circulation (15, 2). During HBO with 2.5 atmospheres absolute (2.5 ATA or 2.45 bar), a four- to fivefold increase in oxygen partial pressure in subcutaneous healthy and infected tissues can be measured (16). Systemic effects of HBO comprise an increase in peripheral resistance (about 30%) due to peripheral vasoconstriction (17) and a fall in heart frequency and cardiac output by approximately 20% (18, 4, 19). Overall, systolic, diastolic and mean arterial pressure remain constant (17).

The exact mechanisms of vasoconstriction under NBO and HBO are unclear as yet, although several hypotheses have been discussed (20). An increased generation of reactive oxygen species (ROS) inactivates the vasodilatating effect of nitric oxide (NO) (21), has direct vasoconstrictive effects (22), reduces the synthesis of vasodilatating prostaglandins (21) and promotes the secretion of vasocon-

strictive prostaglandins (23) and endothelin-1 (24). The influence of the sympathetic system on hyperoxia-mediated vasoconstriction is controversial (21, 25). It is interesting to note that hyperoxia-induced vasoconstriction, probably a function of blood flow regulation to tissues, might indirectly protect from harmful effects of increased oxygen availability (26).

How this response emerged remains to be elucidated, since the body throughout the evolution has never had to develop mechanisms to protect itself from harmful hyperoxic conditions. This may be just a coincidental interaction but nevertheless a helpful response that may help protect — *e.g.*, the brain from hyperoxygenation/seizures.

The regulation of microcirculation under HBO has been investigated at the level of retinal (17) and pancreatic (27) arteries, as well as at the thenar site. At the latter site, HBO induces a decrease in blood flow (BF) by 76.5%, while NBO reduces it by 37% (28). In another study, NBO induced a nonsignificant decrease in BF in feet of healthy subjects, as assessed by laser-Doppler, but accompanied by a significant increase in transcutaneous oxygen pressure ($P_{tc}O_2$).

No significant correlation was found between parameters of laser-Doppler and $P_{tc}O_2$ (29). In middle- or low-perfused skin (forearm), oxygen seems to only modestly influence microcirculation, while oxygen- induced decrease in blood flow is augmented in high-perfused areas (30). Thus theoretically, a too-pronounced oxygen-induced vasoconstriction might cause regional tissue hypoxia in some tissues. Taken together, available data suggests that:

1. Under normobaric and hyperbaric conditions oxygen administration increases tissue oxygenation despite vasoconstriction;
2. There are marked differences in regulation between the upper and lower extremities; and
3. There are also marked differences between well- and poorly perfused areas.

However, available information is extrapolated from different studies, and previous cutaneous measurements assessed superficial skin layers only (max 2 mm). Regulation of subcutaneous vascularization might differ from that of superficial skin layers. The understanding of the rheology of different skin layers in different regions is crucial for the interpretation of clinical data on wound healing under increased oxygen and pressure conditions. This constituted the main purpose of our study, along with the exclusion of hypoxic episodes ($P_{tc}O_2$ below 30 mmHg). In order to differentiate between the effects of oxygen, pressure and oxygen + pressure, our subjects were investigated during NBO, HBO (oxygen breathing), compression and decompression (air breathing).

MATERIALS AND METHODS

Seven healthy volunteers (mean age 39.2, range 26-60 years; sex-ratio M/W: 5/2; smokers/non-smokers: 3/4; no medication intake) were investigated using tissue $P_{tc}O_2$ measurement, spectrophotometry and laser-Doppler flowmetry. Oxygen saturation of hemoglobin (SO_2), BF and flow velocity (FV), were recorded simultaneously at the hand and foot during HBO and NBO.

Subjects were recruited from the staff of the University Hospital Duesseldorf and were investigated after giving written informed consent, in accordance to the declaration of Helsinki and after approval by the ethics committee of the Heinrich-Heine-University Duesseldorf.

Study design

Each subject was studied on one occasion in the afternoon (3-4 p.m.) at least four hours apart from food intake and smoking. Previous data of our laboratory have shown that this period is enough for microcirculation parameters to reach a steady state. Nicotine from smoking rapidly decreases microvascular reactivity, but returns to normal within minutes (31).

The study subject lay down on a cot within the HBO chamber for at least 15 minutes prior to the first measurement and remained in recumbent position throughout the investigation. Probes were kept in place during the entire investigation. We continuously recorded variables during the seven study sequences:

1. *Baseline 1 (BL1):* subjects breathing normal air under normobaric conditions for 10 minutes;
2. *NBO:* patients breathing 100% oxygen (delivered over a facial mask) under normobaric conditions for 15 minutes;
3. *Baseline 2 (BL2):* first recovery, subjects breathing normal air under normobaric conditions for 15 minutes;
4. *Compression (CP):* subjects breathing air, the ambient pressure being constantly elevated from 1 to 2.5 ATA during 10 minutes;

5. *HBO:* subjects breathing 100% oxygen under hyperbaric conditions (2.5 ATA) for 15 minutes;
6. *Decompression (DC):* subjects breathing air for 14 minutes, ambient pressure being constantly decreased from 2.5 to 1 bar; and
7. *Baseline 3 (BL3):* second recovery phase, subjects breathing air under normobaric conditions for 30 minutes.

Hyperbaric oxygen treatment

During HBO treatment in a pressure chamber, 100% oxygen was inhaled under elevated ambient pressure (2.5 ATA), and a significantly increased blood oxygen concentration was achieved by physical solution of oxygen in blood plasma. The concentration of oxygen within plasma can be increased by up to 12.5-fold by a pressure of 2.5 ATA (2).

Places of measurement

The laser-Doppler probe and the probes for $P_{tc}O_2$ measurements were applied on the thenar surface of the right hand and posterior to the right medial malleolus (foot). We chose the hand because it is a highly perfused area that underlies local humoral as well as local and systemic nervous regulation (32, 33). We therefore expected maximal hyperoxia-induced vasoconstriction at this site.

The perimalleolar area was chosen:

1. Because of its clinical relevance (it lies between the calcaneus, where ischemic lesions often occur, and the shank, where venous lesions are frequently located);
2. Because foot skin reaches one of the thinnest parts at this site, enabling reliable measurements of perfusion;
3. Because, as non-glabrous skin, this region also underlies neuronal regulation (33) comparable to the hand, though being an area of lower perfusion (4).

Laser-Doppler
(Micro-light-guide spectrophotometer)

Skin microcirculation was assessed simultaneously at the hand and the foot, using a micro-light-guide spectrophotometer (O2C, LEA Medizintechnik, Giessen, Germany) (34, 35). Briefly, the laser-Doppler transmits continuous wave laser light (830nm and less than 30mW) and white light (20W, 500–800 nm, and 1 nm resolution) to the tissue, where it is scattered and collected on the surface of the skin by detecting fibers, situated 2 and 4 mm apart from the light source of the probe. The light propagates within the tissue between illuminating and detecting fiber in a way that can be described as having a banana-like shape. The larger the separation between illuminating fiber and detecting fiber, the deeper/bigger the tissue sample responsible for the measured parameters (34, 36). A good penetration capacity of near-infrared spectrum (NIRS) light into the tissue has been previously reported (31, 37). Thus, our device enabled measurements in 2 mm (superficial skin) and 4 mm (deep skin and subcutaneous tissue) depth.

The collected light is split into its spectral components by charge-coupled device array and converted into an electrical signal that is digitally recorded on a personal computer. Data are analyzed by comparison with prerecorded deoxygenated and oxygenated hemoglobin spectra (35). Thus, from the analysis of white light, it is possible to measure postcapillar parameters such as oxygen saturation (SO_2) and relative amount of hemoglobin (rHb). The oxygen saturation is determined by the color of blood, while the tissue hemoglobin value is determined by the amount of light absorbed by the tissue. This enables the calculation of hemoglobin concentration per tissue volume and is independent from the vessel properties and hemoglobin quantity in the blood (34, 35).

The movement of erythrocytes causes a Doppler shift effect on the laser light, which is analyzed after reflection for blood flow velocity (FV). The product of moving erythrocytes times velocity of each erythrocyte makes the relative BF (35).

The O2C used in this study had two probes. One probe (at the hand) transmitted simultaneously the white light and the laser-Doppler light, thus enabling concomitant measurement of all above mentioned parameters. The second probe (at the foot) transmitted only the laser-Doppler light. Therefore only measurements of BF and FV were available. BF and FV were measured in 2 and 4 mm depths, rHb and SO_2 in 2-mm depth. BF, FV and rHb are expressed in arbitrary units (AU); and SO_2 is expressed in percents (35).

Transcutaneous oxygen tension

Measurements were performed as previously described (25) using three $P_{tc}O_2$ probes (TINA TCM4 Radiometer, Copenhagen, Denmark). Measurement is possible by use of a membrane-covered platinum (modified Clark) electrode. Initially, one calibration to air was performed before attaching probes to the skin. The probe was heated to 44.0°C, allowing maximal vasodilatation, and decreasing the arterial-to-skin surface oxygen pressure gradient. Consecutively a temperature correction to 37°C was automatically performed. A reference electrode was placed subclavicular to assess eventual systemic changes; the other two were placed near the laser-Doppler probes after cleaning the skin by gently rubbing it with gauze. A pretest heating period of 10 minutes was required to allow a steady state. $P_{tc}O_2$ data were digitalized and recorded on a computer every minute and are expressed as mmHg (38).

Statistical analyses

Data were analyzed using SPSS for Windows 12.0. Continuous variables are expressed as mean ± SEM, unless otherwise stated. Two-sided, paired Student's t tests were used to compare the effects of treatment phases on parameters. Parameters (rHb, SO_2, BF, FV, $P_{tc}O_2$) were calculated by averaging values from the last two minutes of each treatment phase. Only $P_{tc}O_2$ values were continuously analyzed in order to exclude tissue hypoxia. The level of significance was set at 0.05, and all tests were performed two-sided.

RESULTS

Blood flow (BF) and flow velocity (FV) were significantly higher at the hand compared to the foot in both 2mm: BF (104±26 vs. 17±4 AU) and FV (26±4 vs. 8.8±1.6 AU) and 4mm: BF (73±19 vs. 34±7 AU) and FV (31±5 vs. 11±2 AU) (values presented as hand vs. foot, $p<0.05$ for all). There was no difference in $P_{tc}O_2$ between hand (58.2±5.4 mmHg), foot (56.6±1.3 mmHg) and subclavicular region (62.3±7.2 mmHg). Further values will be presented separately at the hand and foot.

The hand level

(*For absolute values in 2mm, see Figures 1 A, B, C and D* — Page 386.)

NBO, compared to BL1 induced a mild vasoconstriction reflected by a borderline significant decrease in BF and FV (*Table 1*, Page 385), but these changes were accompanied by a modest increase in SO_2 and a significant increase in $P_{tc}O_2$ (*Table 2*, Page 385).

During the compression phase, compared to BL1, BF did not significantly change and FV tended to increase in 2 mm (*Table 1*), while there was a significant increase in SO_2 and $P_{tc}O_2$ (*Table 2*).

Compared to BL1, HBO induced a mild decrease in BF and FV (*Table 1*), while there was a significant increase in SO_2 and $P_{tc}O_2$ (*Table 2*).

Compared to BL1, DC resulted in a significant decrease in BF and FV (*Table 1*), while SO_2 and $P_{tc}O_2$ remained significantly elevated (*Table 2*).

Even compared to HBO, DC resulted in a significant decrease in FV (2mm: -35%, p=0.016; 4mm: -43%, p=0.007) and a non-significant decrease in BF (2mm: -54%, p=0.15; 4mm: -53%, p=0.14).

Compared to BL1, during BL3, $P_{tc}O_2$ (+89%, p=0.009) and SO_2 remained elevated (+9%, p=0.023), while BF and FV returned to baseline (*Figures 1 A, B, C*). Relative hemoglobin concentration was 54.9±9.2 AU at BL1, and values did not change during any treatment phase.

The foot level

Compared to BL1, NBO induced a modest vasoconstriction reflected by a decrease in BF and FV (*Table 1*), which was significant only in 4 mm. Again, these changes were accompanied by a significant increase in $P_{tc}O_2$ (*Table 2*).

During the compression phase, BF and FV (*Table 1*) increased compared to BL1 only in 4 mm (borderline significant), accompanied by a significant increase in $P_{tc}O_2$ (*Table 2*).

HBO induced a nonsignificant decrease in BF and FV (*Table 1*) compared to BL1, while there was a significant increase in $P_{tc}O_2$ (*Table 2*).

The decompression resulted in a nonsignificant decrease in BF and no change in FV (*Table 1*), compared to BL1, while $P_{tc}O_2$ remained significantly elevated (*Table 2*). Microvascular changes in BF and FV were comparable to those during HBO. During BL3, BF and FV returned to baseline.

TABLE 1

		Hand		*Foot*	
		2mm	***4mm***	***2mm***	***4mm***
NBO	***BF***	-37%, p=0.06	-32%, p=0.09	-22%, p=0.11	-21%, p=0.03
	FV	-24%, p=0.07	-27%, p=0.07	-14%, p=0.08	-16%, p=0.02
CP	***BF***	+14%, p=0.51	+9.75, p=0.63	+17%, p=0.31	+21%, p=0.08
	FV	+15%, p=0.07	+8.4%, p=0.26	+5%, p=0.41	+11%, p=0.08
HBO	***BF***	-45%, p=0.08	-40%, p=0.10	-34%, p=0.27	-34%, p=0.18
	FV	-28%, p=0.08	-32%, p=0.08	-17%, p=0.28	-18%, p=0.14
DC	***BF***	-75%, p=0.018	-70%, p=0.02	-44%, p=0.20	-10%, p=0.82
	FV	-53%, p<0.01	-62%, p<0.01	-1%, p=0.96	-12%, p=0.55

TABLE 2

		Hand	*Foot*
NBO	SO_2	+7%, p=0.23	
	$P_{tc}O_2$	+380%, p<0.01	+393%, p<0.01
CP	SO_2	+14%, p<0.01	
	$P_{tc}O_2$	+70%, p<0.01	+55%, p<0.01
HBO	SO_2	+15%, p<0.01	
	$P_{tc}O_2$	+1430%, p<0.01	+1600%, p<0.01
DC	SO_2	+15%, p<0.01	
	$P_{tc}O_2$	+1037%, p<0.01	+970%, p<0.01

TABLES 1 and 2.

Percent decrease in BF and FV (Table 1) respectively SO_2 and $P_{tc}O_2$ (Table 2) relative to BL1 with p-values (two-sided, paired Student's t tests).

Abbreviations: BF=blood flow; FV= flow velocity; SO_2= oxygen saturation of hemoglobin; $P_{tc}O_2$=transcutaneous oxygen pressure; BL1=baseline 1; HBO=hyperbaric oxygen; NBO=normobaric oxygen; CP=compression phase; DC= decompression phase.

Figure 1

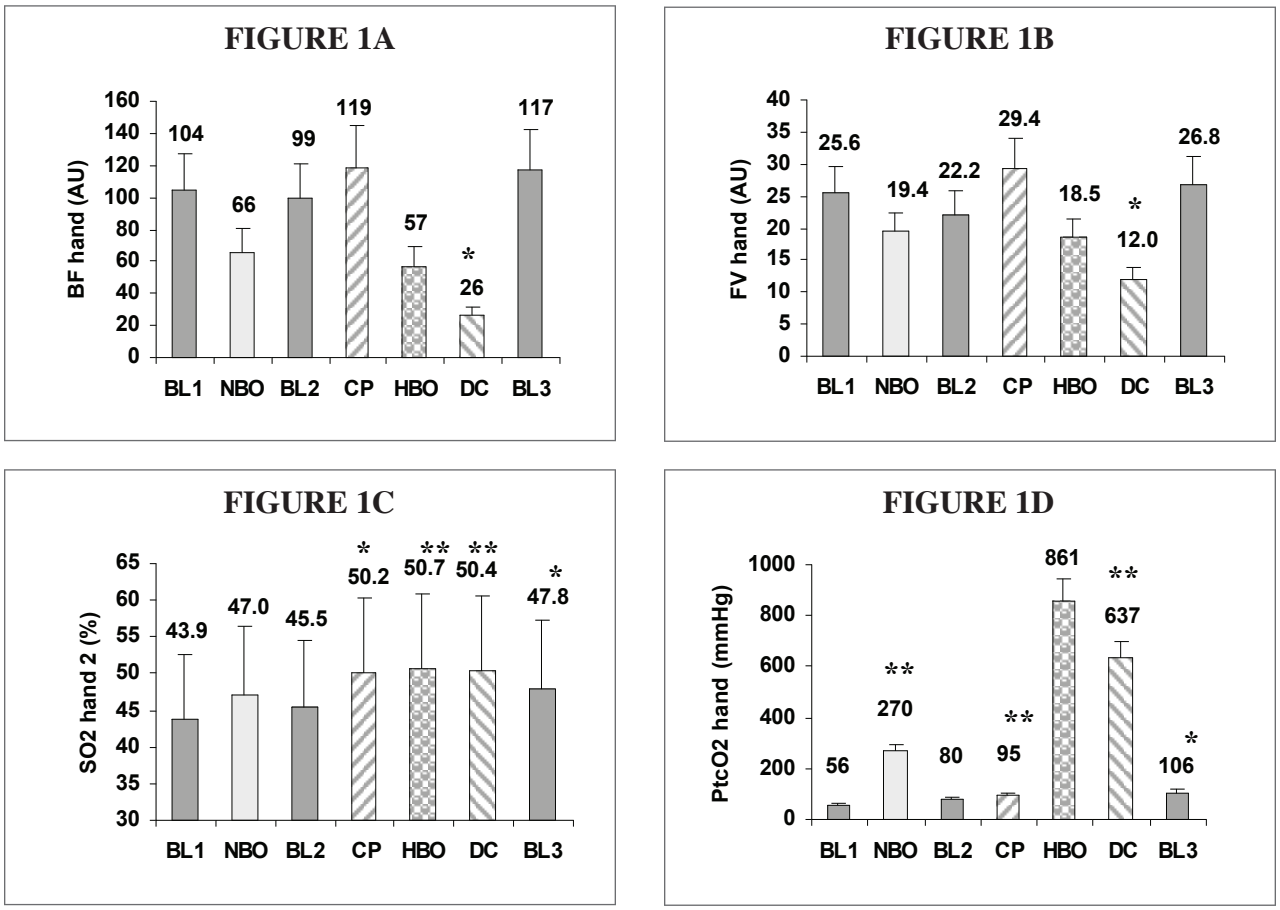

FIGURE 1. Parameters at the hand during NBO and HBO in 2 mm.

(A) Blood flow (BF)

(B) flow velocity (FV)

(C) oxygen saturation (SO2)

(D) transcutaneous oxygen pressure (PtcO2) measured at the hand during baseline (BL), normobaric (NBO) and hyperbaric (HBO) oxygen therapy, compression (CP) and decompression (DC).

(*p<0.05, **p<0.001 vs. BL1; AU = arbitrary units).

Subclavicular measurements of PtcO2 showed, compared to BL1, a significant increase under NBO (+570%, p<0.001), compression (+122%, p<0.001), HBO (+1840%, p<0.001) and decompression (+1025%, p<0.001).

Ambient air temperature inside the hyperbaric chamber was 25.9 ± 0.1 °C during BL1, increased to 27.0 ± 0.1 °C during compression, remained stable at 27.1 ± 0.1 °C during HBO and decreased to 24.4 ± 0.2 °C during decompression.

DISCUSSION

Our study shows that in healthy subjects, NBO and HBO induce to a comparable extent a vasoconstriction of the skin microcirculation, while oxygenation is significantly improved, especially by HBO. We found no signs of tissue hypoxia at any time point of the study. The novelty of our study consists in the assessment of skin microcirculation at 2 and 4 mm depths, as well as the parallel measurement at hand and foot during NBO and HBO.

The regulation of microcirculation went parallel at hand and foot level, but tended to be less marked at the latter site, especially during decompression. This can be explained by a more pronounced vascularization of the hand (39) where changes can be more easily followed (30). Interestingly, foot vasoreactivity was more pronounced in 4 mm than in 2 mm during NBO, showing vasoconstriction during NBO and vasodilatation during the compression phase. Our study confirms previous data (29) reporting a nonsignificant vasoconstriction induced by NBO in superficial foot skin of healthy subjects, but suggests that subcutaneous vasculature shows a significant vasoconstriction at this site. This points out to a different vasoconstrictive effect of oxygen on vascular beds of the skin and subcutaneous foot tissue.

During the compression phase, the temperature in the pressure chamber increased by 1.1 °C and decreased by 2.8 °C during decompression. We cannot exclude that the small external temperature fluctuations influenced skin microcirculation. During compression, BF did not change and FV tended to increase. These data are consistent with an unchanged skin vascularization capacity, despite an increase in external pressure, suggesting that increases in ambient pressure alone (2.5 ATA), do not induce vasoconstriction. Even though subjects inhaled normal air during compression, there was an increase in both SO_2 and $P_{tc}O_2$. This finding is most probably due to the increase in oxygen solubility with ambient pressure raising plasma oxygen.

In contrast to the compression phase, HBO induced a modest, nonsignificant reduction in BF. This effect is mostly due to the addition of oxygen and not to the external pressure. Overall, oxygenation was clearly improved by HBO at all sites — central, hand and foot, as suggested by the increases in SO_2 and $P_{tc}O_2$.

However, increases in $P_{tc}O_2$ were more pronounced than increases in SO_2. This can be explained by the fact that SO_2 measures oxygen saturation of hemoglobin and does not assess soluble oxygen. The effects of NBO and especially HBO are mainly due to an increase in soluble oxygen in plasma. Moreover, SO_2 assesses mostly oxygen saturation in the postcapillar part of the microcirculatory system (after extraction) (34), while $P_{tc}O_2$ measures the oxygen provided by the arterial part of the microcirculation (16). Thus, methods cannot be superimposed.

The $P_{tc}O_2$ value reflects the physically solved oxygen, which is important for the delivery of oxygen by diffusion. In contrast, the post-capillary SO_2 value depends on both precapillary blood oxygen concentration and extracted oxygen. The marked increase in blood oxygen content during HBO led, in spite of vasoconstriction and an increased oxygen delivery (increased $P_{tc}O_2$), to a moderate increase in post-capillary SO_2 values, which did not override the range of physiological values for the hand. From this, two important conclusions can be drawn:

1. The oxygen supply during HBO overweighs the vasoconstriction; and
2) The vasoconstrictive response triggered by the increase in oxygen concentration reduces the risk of tissue hyperoxygenation.

It remains to be elucidated whether these responses jeopardize oxygenation in subjects with ischemic artery disease, since inward remodeling of microvessels (coronary) distal to a stenosis is accompanied by an exaggerated vasoconstrictor response (40, 41) that might be exaggerated by oxygen. In these patients, sympathicolysis or usage of vasodilatory drugs such as alprostadil and other prostaglandin derivatives have been suggested to improve tissue oxygenation (25).

Interestingly, during the decompression phase, a significant decrease in BF was measured at the hand but not at the foot. Moreover, this was the phase when maximal vasoconstriction occurred, even more pronounced than during HBO. It is noteworthy that during this phase, in spite of breathing air, there was a persistent effect of oxygen on vascular tone, since both SO_2 and $P_{tc}O_2$ remained significantly elevated. It is possible, that the influence of temperature drop (2.8 °C) during the decompression might have contributed to the vasoconstriction seen, but further mechanisms cannot be excluded.

During the recovery phase (BL3), $P_{tc}O_2$ remained slightly (but significantly) elevated, suggesting that the oxygen overload persists for at least 30 minutes after the termination of decompression and strengthening previous observations (42). Meanwhile, SO_2 also remained elevated, showing a positive balance of blood oxygen pool and tissue extraction.

In conclusion, in a population of individuals without peripheral artery disease, our study gives insights into the microvascular regulation during NBO

and HBO and excludes the possibility of tissue hypoxia episodes in healthy subjects at the hand and foot level in spite of vasoconstriction. How this vasoconstrictive effect of oxygen might influence tissue oxygenation in a patient with vasoactive drugs and/or obstructive arterial disease remains to be elucidated.

LIMITATIONS OF THE STUDY

Our study group was small (n=7); therefore some borderline significant results might have gained more importance in a larger group. We did not record the skin temperature in the areas under investigation, because we consider skin temperature to be partly an epiphenomenon resulting from external influences and local hemodynamic processes. We have chosen to measure only ambient temperature in order to quantify the potential effect of external factors on vascularization.

We did not assess blood pressure and heart rate, since their regulation under NBO and HBO has already been conclusively described (18, 43, 44). We did not randomize the sequence of NBO and HBO investigations, since a recovery following HBO would have increased the duration of the study sequence too much. Following NBO and before HBO, all parameters returned to baseline during the 15-minute recovery.

■

ACKNOWLEDGEMENT

Alin Stirban and Stefan Lentrodt have contributed equally to this work. We thank Hartmut Strelow (Heinrich-Heine University Duesseldorf) for his excellent work, Dr. Alfons Krug (LEA Medizintechnik Giessen) and Dr. Andreas Christaras (Heinrich-Heine University Duesseldorf) for their valuable assistance, as well as LEA Medizintechnik, Giessen for providing the laser-Doppler for the measurements inside the hyperbaric chamber.

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