Microcirculation and tissue oxygenation in the head and limbs during hyperbaric oxygen treatment

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Abstract
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Introduction: Hyperbaric oxygen (HBO) exposure for 10–15 min has been shown to reduce peripheral blood flow due to vasoconstriction. However, the relationship between decreased peripheral blood flow and the therapeutic effects of HBO treatment on peripheral circulatory disorders remain unknown. Longer exposures have been reported to have vasodilatory effects and increase peripheral blood flow. This study investigated the effect of HBO treatment on blood flow and transcutaneous oxygen pressure ($TcPO_2$).

Methods: Twenty healthy volunteers aged 20–65 years (nine males) participated in this study. All participants breathed oxygen for 60 min at 253.3 kPa. Peripheral blood flow using laser Doppler flowmetry and $TcPO_2$ on the ear, hand, and foot were continuously measured from pre-HBO exposure to 10 min post-exposure.

Results: Peripheral blood flow in each body part decreased by 7–23% at the beginning of the HBO exposure, followed by a slow increase. Post-exposure, peripheral blood flow increased 4–76% in each body part. $TcPO_2$ increased by 840–1,513% during the exposure period, and remained elevated for at least 10 min after the exposure.

Conclusions: The findings of the current study suggest vasoconstriction during HBO treatment is transient, and even when present does not inhibit the development of increased tissue oxygen partial pressure. These findings are relevant to studies investigating changes in peripheral blood flow during HBO treatment in patients with circulatory disorders.

Introduction

Hyperbaric oxygen (HBO) treatment is an effective treatment for diseases such as decompression sickness, radiation tissue injury, and selected non-healing wounds.[1–4] Standard HBO treatment is generally performed for 90–120 min, and involves oxygen (O_2) inhalation at 202.6–253.3 kPa,[5] often with intermittent air breaks. While the therapeutic effect of HBO is thought to be associated with an increase in dissolved O_2 in the blood and changes in blood flow,[1–6] the exact nature of the relationship between oxygen partial pressure (PO_2) and flow remains unknown. Therefore, it is important to clarify the effects of HBO treatment on blood O_2 level and peripheral blood flow.

Peripheral blood flow decreased and transcutaneous partial pressure of oxygen ($TcPO_2$) increased when healthy humans were exposed to HBO for a short duration.[7–10] Increased dissolved O_2 concentrations in the plasma during HBO treatment contributes to the therapeutic effects of HBO treatment.[11] Increased TcO_2 has been reported at the beginning of treatment, followed by an increase in the levels of nitric oxide (NO) and superoxide (O_2^-) that are produced by endothelial cells.[6,10] Subsequently, O_2^- reacts with NO to generate peroxynitrite ($ONOO^-$) between the endothelium and vascular smooth muscle cells, leading to vasoconstriction as the vasodilatory effects of NO were antagonised.[10] This reaction has been considered the reason for decreased peripheral blood flow during single HBO exposures of short duration.

During HBO exposure, extracellular superoxide dismutase (SOD) is gradually activated between the endothelium and vascular smooth muscle cells. This scavenges O_2^- thus ameliorating antagonism of NO.[6,10] Thus, an increase in peripheral blood flow after an initial reduction may occurs due to restoration of the vasodilatory effect of NO during a longer HBO exposure. However, previous reports have only measured peripheral blood flow during short HBO exposures (10–15 min).[8,9] Therefore, it was hypothesised that a longer HBO exposure (e.g., 60 min), as in typical HBO treatments, would increase peripheral blood flow. This

study aimed to investigate the changes in peripheral blood flow and $TcPO_2$ associated with a longer HBO exposure in healthy participants.

Methods

PARTICIPANTS

Ethical approval for this study was granted by the Medical Research Ethics Committee of Tokyo Medical and Dental University (M 2,000–1,814-01). Participants between the ages of 20–65 years were recruited from healthy volunteers at our institution. Informed consent was obtained from all participants who met the inclusion criteria. All participants were lifetime non-smokers and were able to equalise their ears. Exclusion criteria included a history of peripheral circulatory disorders, pneumothorax, convulsions, claustrophobia and current pregnancy. The study was undertaken in accordance with the ethical standards of the Declaration of Helsinki.

HBO PROTOCOL

Each participant received a single HBO exposure session in a multi-place HBO chamber (NHC-412-A, Nakamura Iron Works, Tokyo, Japan). The HBO protocol involved 60 min of O_2 breathing at 253.3 kPa with two 5-min air breaks (Figure 1).

During HBO exposure the participants sat on a chair with their hands and feet on the arm- and foot-rests, respectively. They were instructed to stay relaxed, breathe normally, and notify the staff if they faced any problems during the exposure. Oxygen breathing was via a non-rebreather oxygen mask supplied at 20 $L \cdot min^{-1}$ flow.

MEASUREMENTS

Peripheral blood flow ($mL \cdot min^{-1}$) was measured using laser Doppler flowmetry (LDF) (MBF-11A, Pioneer Corp., Kawasaki, Japan). LDF is a non-invasive method used for real-time assessment of skin perfusion by a fibre optic probe.[12,13] The principle of LDF measurement is that when the tissue is irradiated by a laser, peripheral blood flow can be estimated using the spread of the Doppler-shifted frequency generated by the interference between light backscattered from static tissue and light backscattered from red blood cells flowing in the capillaries.[13–15] The LDF device used in this study was small (105 mm × 62 mm × 25 mm), lightweight (144 g), cordless, and included a wireless transfer function.[14] Additionally, this device is designed to generate minimal artefact in a dynamic environment, including postural changes.[14] The LDF system was confirmed to work normally under HBO exposure by using it with an infusion pump system filled with milk instead of blood.[15]

$TcPO_2$ (mmHg) was measured using a transcutaneous oximeter (TCM400, Radiometer Pacific TCM400, Radiometer Pacific, Copenhagen, Denmark). Transcutaneous oximetry measurement is non-invasive; it is performed through a heated sensor on the skin.[16,17] It is widely used to assess tissue hypoxia and demonstrate responsiveness of the peri-wound tissue to O_2 breathing.[16–18]

Although it is still controversial and not proven, it has been reported that HBO treatment may be effective for diseases such as cerebral infarction as it causes an increase in $TcPO_2$ and cerebral blood flow.[19,20] Several studies have also reported that the measurement of blood flow using LDF in the ear may reflect the values for cerebral blood flow.[13,14] Thus, blood flow and $TcPO_2$ on the ear were measured based on these reports.

Figure 1

HBO protocol; a single HBO exposure for 60 min with oxygen (O_2) inhalation at 253.3 kPa and two air breaks was performed. Pre – pre-phase; UP – under pressure; O_2-1 – first phase of 253.3 kPa O_2 inhalation; Air-1 – first phase of 253.3 kPa air inhalation; O_2-2 – second phase of 253.3 kPa O_2 inhalation; Air-2 – second phase of 253.3 kPa air inhalation; O_2-3 – third phase of 253.3 kPa O_2 inhalation; D – decompression; post – post-phase. * 1–7 – denote points of skin and ambient temperature measurements

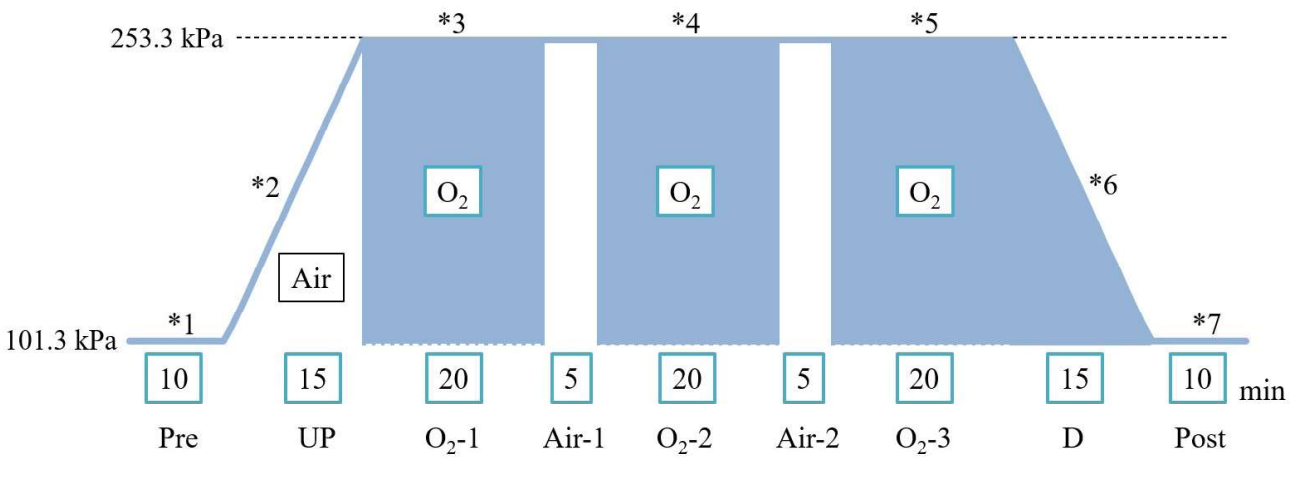


Figure 2
Position of sensors on the earlobe, hand and foot; laser Doppler flowmetry sensor placement: ear sensor – right earlobe; finger sensor – palmar aspect of right index finger; toe sensor – palmar aspect of right first toe. Transcutaneous oximetry sensor placement: ear sensor – front of right ear; hand sensor – dorsum of the right first interdigital space; foot sensor – dorsum of the right foot between the first and second metatarsal heads. Skin temperature sensor placement: ear sensor – front of ear; finger sensor – palmar aspect of right middle finger; toe sensor – palmar aspect of right first toe

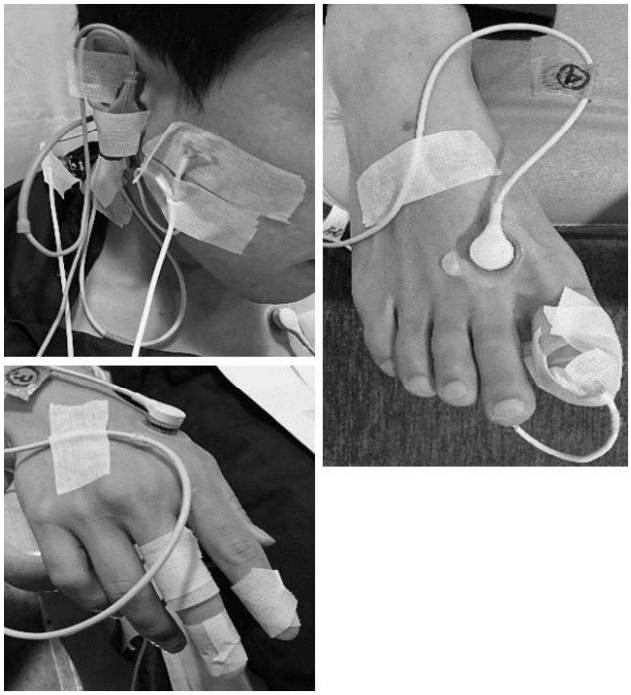
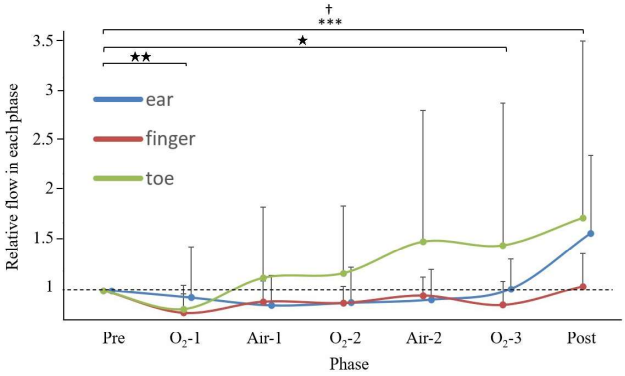


Figure 3
Changes in peripheral blood flow relative to the Pre phase in the ear, finger, and toe (n = 20 subjects); *** difference in the peripheral blood flow in the ear, $P < 0.001$; difference in the peripheral blood flow in the finger, ★★ $P < 0.01$, ★ $P < 0.05$; † difference in the peripheral blood flow in the toe, $P < 0.05$



It was possible that the change in peripheral blood flow and $TcPO_2$ was just a consequence of using the instrument itself rather than an effect of HBO treatment. To assess this, the pulse rate was measured at the palmar aspect of the right index finger simultaneously, and ambient and skin temperatures were measured at the ear, hand, and foot.

The LDF, $TcPO_2$ and temperature sensors were placed on the ear, hand, and feet of the participants (Figure 2). A co-author (TM) attached all the sensors to all participants. Each measurement was continuously recorded between pre-HBO exposure and 10 min post-exposure. Peripheral blood flow, $TcPO_2$, and pulse rate were recorded continuously during each phase (designated in Figure 1) except at one min before and after each phase to exclude the influence of attachment or detachment of participants' masks for air breaks. These measurements were averaged to obtain a single value for each phase. The ambient and skin temperatures were recorded once for each phase (time points indicated in Figure 1). In addition, the changes in peripheral blood flow and $TcPO_2$ were assessed using relative-value-based comparisons (the value of pre-phase was set as the baseline).

ANALYSIS

Sample size was calculated based on an effect size (f) of 0.25, which was calculated as a 25% decrease in peripheral blood flow during HBO exposure compared to baseline, which was statistically significant, and correlation among levels was 0.5 of the repeated one-way analysis of variance (ANOVA) based on the previous reports.[7,8] The power (1-β) was 80%, type I error rate (α) was 5%, and dropout rate was 10%. The results of this calculation indicated that 22 participants were required for this study. All data were analysed using EZR (Saitama Medical Center, Saitama, Japan).[21] Data were analysed for normality using the Shapiro-Wilk test and for homogeneity using the Levene's test. Statistical analyses were performed using repeated one-way ANOVA followed by Dunnett's post-hoc test. The correlation between skin temperature and peripheral blood flow was evaluated using the Spearman's rank correlation coefficient. The significance level for statistical analysis was set at $P = 0.05$.

Table 1
Subject demographic and baseline details; data are mean (SD). BMI – body mass index

Group	Age (year)	Height (cm)	Weight (kg)	BMI (kg·m^{-2})
All subjects	30.7 (5.7)	165.9 (7.2)	60.0 (11.0)	21.7 (2.5)
Male (n = 9)	31.3 (3.5)	170.2 (4.0)	65.5 (9.5)	22.6 (2.4)
Female (n = 11)	29.9 (7.5)	158.6 (2.3)	50.5 (4.4)	20.1 (2.1)

Table 2
Peripheral blood flow (ml·min^{-1}), mean (SD), in the ear, finger, and toe during HBO exposure (n = 20 subjects); * $P < 0.05$, ** $P < 0.01$

Site	Pre	O_2-1	Air-1	O_2-2	Air-2	O_2-3	Post
Ear	23.0 (15.5)	21.0 (10.8)	19.2 (15.9)	18.0 (12.5)	19.0 (12.5)	21.7 (12.5)	32.1 (20.2) *
Finger	67.8 (20.0)	54.5 (19.9) **	61.9 (23.1)	60.3 (19.0)	64.4 (18.0)	59.7 (22.6)	70.3 (22.0)
Toe	48.2 (30.2)	36.6 (19.4)	46.0 (22.8)	45.4 (19.3)	54.0 (25.1)	49.3 (22.6)	56.3 (28.7)

Table 3
$TcPO_2$ (mmHg), mean (SD), in the ear, finger, and toe during HBO exposure (n = 20 subjects); * $P < 0.001$

Site	Pre	O_2-1	Air-1	O_2-2	Air-2	O_2-3	Post
Ear	62.5 (26.2)	814.8 (159.1) *	252.4 (79.4) *	840.8 (157.8) *	293.9 (98.0) *	857.0 (199.1) *	232.1 (182.7) *
Finger	80.0 (12.0)	824.0 (219.1) *	325.1 (64.0) *	852.3 (224.5) *	336.6 (37.2) *	886.5 (202.2) *	164.0 (67.3) *
Toe	82.0 (10.3)	759.3 (147.2) *	306.4 (85.3) *	794.9 (157.9) *	312.9 (45.1) *	813.1 (172.2) *	162.3 (58.0) *

Results

Twenty-two participants (10 males and 12 females) were recruited for the study. Two participants were excluded due to missing data; therefore, 20 sets of data were analysed (nine males and 11 females). The participants' demographic data are shown in Table 1.

Peripheral blood flow measurements are shown in Table 2 and Figure 3. For the ear, the average peripheral blood flow decreased during the O_2-1 and O_2-2 phases relative to pre-phase values, and increased again during the O_2-3 and post-phase. For the finger, the relative value decreased during the initial oxygen exposure, increased during the O_2-2 phase, and returned to the baseline in the post-phase. For the toe, the relative value decreased during the O_2-1 phase and increased during the O_2-2, O_2-3, and post-phase.

$TcPO_2$ measurements are shown in Table 3 and Figure 4. The average value of $TcPO_2$ relative to pre-phase measurements significantly increased in all sites during all oxygen breathing periods ($P < 0.001$).

Measurement of ambient and skin temperatures are shown in Figure 5. Although there were significant differences of skin temperature on the ear at the O_2-1 phase and on the toe at the O_2-2 and O_2-3 phases compared to the pre-phase, there were no significant differences in skin temperature between the pre -and post-phases for each body part. Moreover, there was no significant correlation between skin temperature and peripheral blood flow for each body part (ear: 0.028, $P = 0.741$; hand: 0.077, $P = 0.369$; feet: 0.066, $P = 0.447$).

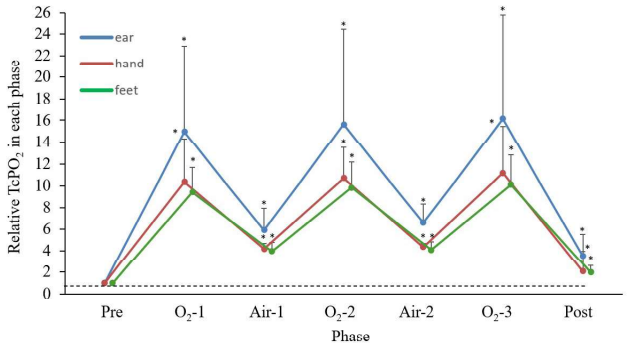
There were minimal and non-significant changes in pulse rate over the exposure phases: pre, mean 68.9 (SD 11.6); O_2-1, 64 (10.8); O_2-2, 63.3 (10.3); O_2-3, 62.5 (11.5); Post, 66.8 (10.6).

Discussion

The increase in dissolved O_2 in blood during HBO treatment contributes to the therapeutic effect of HBO;[1–6] however, any related changes in tissue blood flow have to date been under-researched. Thus, this study was designed to evaluate changes in blood flow and dissolved O_2 during HBO treatment. $TcPO_2$ levels significantly increased at all sites during all oxygen exposure phases. At two of our three sites (ear and finger) tissue perfusion exhibited a sustained reduction followed by a late increase back to baseline, and in the toe there was an early reduction followed by a steady rise to supra-baseline levels (Figure 3).

Previous research has shown that peripheral blood flow using LDF decreased and $TcPO_2$ increased in the hand and foot, respectively, during a period of 10 min HBO exposure at 253.3 kPa.[8] Several studies have reported a decrease in middle cerebral arterial blood flow velocity by transcranial Doppler during a short duration of HBO exposure in healthy volunteers.[7,10] A decreased peripheral blood flow early in the HBO exposure was also seen in this current study; however, as the exposure continued, an increase in the peripheral blood flow was observed. These results are consistent with the proposed hypothesis that following an initial decrease in peripheral blood flow there would be a subsequent increase in flow as a result of a relative increase in the vasodilatory effect of NO compared to the vasoconstrictive effect of

Figure 4
Changes in $TcPO_2$ relative to the Pre phase in the ear, hand, and foot (toe) (n = 20 subjects); *P < 0.001

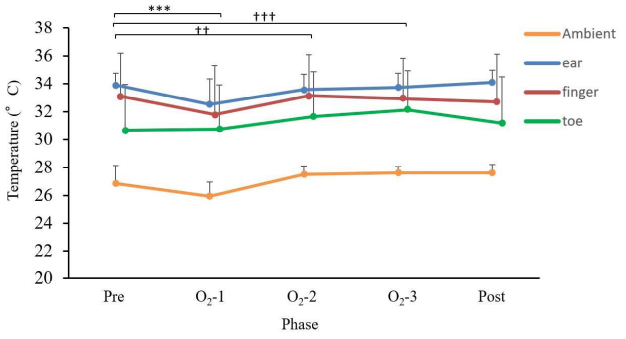


O_2 during a longer HBO exposure. It has been unclear how early effects of HBO treatment on peripheral blood flow would evolve over a longer exposure. Thus, this study is the first to examine peripheral blood flow and $TcPO_2$ during a longer HBO exposure and to show that peripheral blood flow increases.

There have been several reports that the peripheral blood flow in the earlobe might reflect the cerebral blood flow as the branches from the external carotid artery supply the earlobe.[13,14,22,23] Research in mice and rats has revealed an increase in the cerebral blood flow after a certain duration of HBO exposure.[23,24] Clinical research in healthy humans has indicated an increase in cerebral blood flow within one hour following the end of HBO treatment at 253.3 kPa.[19,25] Previous studies had assessed the peripheral blood flow in the limbs rather than in the ear.[8,9,19,20] In this study, it was observed that the changes in the blood flow in the earlobe (an initial decrease followed by an increase) were similar to those in the limbs. Thus, the changes in the blood flow in the earlobe observed in this study were consistent with the changes in the cerebral blood flow reported in other studies.[23–25]

The fluctuation measured in peripheral blood flow in the limbs (the acral dermis) was large and that in the ear (the non-acral dermis) was small. The vasoconstriction and vasodilation in the non-acral dermis are controlled by the sympathetic nervous system, and those in the acral dermis are controlled mainly by the opening and closing of arteriovenous anastomoses.[26] Thus, it has been reported that the vasoconstriction and vasodilation in the acral dermis may be influenced by the surrounding environment, such as temperature and O_2 levels, to a larger extent than those in other regions.[26,27] These findings are congruent with the findings in the current study, as fluctuation measured in the values of the peripheral blood flow was greater in the limbs than in the ear. Further studies should be conducted to provide details on the direct relationship between cerebral blood flow and peripheral blood flow in the earlobe.

Figure 5
Changes in ambient room temperature and skin temperature in the ear, finger, and toe (n = 20 subjects); comparisons are made with the Pre measure. *** difference in the temperature in the ear, P < 0.001; difference in the temperature in the toe, ††† P < 0.001, †† P < 0.01



In this study, there was a sustained increase in peripheral blood flow in the ear and feet after HBO exposure; however, the peripheral blood flow in the hand after HBO exposure returned to the level observed in the pre-phase. Although the exact reason for this difference is unclear, the hand may be more likely to undergo hyperoxia-induced vasoconstriction as it is a highly perfused area with systemic nervous regulation.[8] Thus, the peripheral blood flow in the hand may not increase more than the baseline level after HBO treatment. Further studies should be conducted to explore this issue.

LIMITATIONS

This study has several limitations. First, there is a possibility of errors in the measurement occurring due to differences in the positioning of sensors and body movements. Body movements and changes in sensor positioning may cause measurement errors as the LDF is a sensitive device.[20] However, a new wireless LDF device developed to reduce the influence of artefacts and noise was used in this study.[14] Thus, the results of this study may be considered more accurate than those measured by the conventional LDF devices in previous studies.[20]

Second, changes in skin temperature may have influenced the peripheral blood flow measurements.[8] Although significant differences in skin temperature were observed during several phases, the skin temperature in the post-phase was close to that in the pre-phase for each body part (Figure 5). Moreover, there was no significant correlation between the skin temperature and the peripheral blood flow. Thus, it was inferred that the influence of changes in skin temperature was too small to affect the outcome.

Third, $TcPO_2$ levels have been reported to return to pre-exposure levels gradually after HBO treatment;[28] however, we are unable to comment on the duration of increased peripheral blood flow as it was only measured for 10 min post exposure.

Fourth, only the effects of 60 min of HBO exposure at 253.3 kPa were evaluated in this study. This is a common treatment duration in Japan, although it is acknowledged that 90–120 min durations are standard in many places.[13,14] Thus, similar studies of HBO treatment with 90–120 min of exposure should be conducted in the future.

Fifth, it is still unclear whether the vasculature will respond in a similar manner after several HBO treatments as this study only evaluated a single HBO treatment in healthy volunteers. Changes in the peripheral blood flow following multiple HBO treatments should be investigated in the future.

Sixth, it is unclear why the values of peripheral blood flow measured in the finger and toe were higher than that in the ear lobe (Table 2). Furthermore, it has been reported that the value of peripheral blood flow measured in the ear was lower than those in the limbs in normal room environments.[13] Further studies exploring this issue should be conducted in the future.

Seventh, because of chamber configuration limitations it was necessary to use non-rebreather masks supplied by oxygen at 20 $L \cdot min^{-1}$ for oxygen administration. It is possible that this did not result in a 100% inspired fraction of oxygen. Nevertheless, the method was consistent between patients, and would have resulted in delivery of HBO at close to the ambient pressure of 253 kPa.

Finally, patients with circulation disorders, diabetic wounds, and radiation necrosis may not respond in the same way as the healthy volunteers included in this study. Based on the current study, future studies to investigate changes in the peripheral blood flow during HBO treatment in patients with circulatory disorders should be performed.

Conclusion

This study continuously examined the peripheral blood flow and $TcPO_2$ throughout the entire duration of a 60 min HBO exposure in healthy participants. Peripheral blood flow decreased at the beginning of the exposure, followed by a gradual increase, maintaining this level or increasing for at least 10 min after exposure compared to the baseline. $TcPO_2$ levels also increased throughout the treatment profiles. These findings show that peripheral blood flow increases. Thus, the study findings are meaningful for understanding that a longer HBO exposure causes an increase in peripheral blood flow after a decrease seen at 10–15 min of HBO exposure.

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