Institut für Anästhesiologie, Technische Universität München, Klinikum rechts der Isar
(Univ.-Prof. Dr. E. Kochs)

Cerebral blood flow and cerebrovascular response to intermittent hypercapnia during hyperbaric oxygenation treatment

Marcella Josephine Lanzinger

Vollständiger Abdruck der von der Fakultät für Medizin
der Technischen Universität München zur Erlangung des akademischen Grades eines
Doktors der Medizin
genehmigten Dissertation.

Vorsitzender: Univ.-Prof. Dr. D. Neumeier
Prüfer der Dissertation:
1. apl. Prof. Dr. R. Hipp
2. Univ.-Prof. Dr. G. Tempel

Die Dissertation wurde am 08.01.2002 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 12.11.2003 angenommen.

Table of contents

Introduction **3**

Materials and Methods **5**

Hyperbaric Exposure 5
Transcranial Doppler Sonography 7
Hypercapnia 7
Statistical analysis 8

Results **8**

Biometric data 8
Cardiovascular data 9
Cerebral blood flow velocity 10
Cerebrovascular reactivity 11
Complications 12

Discussion **13**

TCD and CBF during HBO 13
Changes in CBF during HBO 13
Relationship of CBF and hyperoxia 13
Influence of intermittent hypercapnia on time course of CBF 14
Time course of CBF during HBO 14
Reversibility of CBF decrease after HBO 15
Influence of intermittent hypercapnia on CBF 15
Oxygen and carbon dioxide gas tensions during HBO 17

Conclusion **18**

Summary **19**

References **20**

Tables and figures **24**

Abbreviations **25**

Dedication **26**

Cerebral blood flow and cerebrovascular response to intermittent hypercapnia during hyperbaric oxygenation treatment

Marcella J Lanzinger

Introduction

Hyperbaric oxygenation (HBO) increases tissue oxygen delivery and has several physiological and pharmacological effects, which include a reduction in cardiac output, peripheral vasoconstriction, inhibition of β_2 – integrin mediated leucocyte adhesion and lipid peroxidation [14]. Experimental data suggest a potential benefit of HBO in conjunction with head injury and cerebrovascular ischemia and stroke [1,18,22,23, 25,28].

Extremely high blood oxygen tensions (> 1500 mmHg) can be attained during HBO. The effects of extreme hyperoxia on cerebral blood flow (CBF) have been studied in animals and to a limited extent in humans [12,19,20,24,26,29]. HBO reduces CBF through arteriolar vasoconstriction, which is caused in part by a decrease in basal arteriolar vasorelaxation as a result of a decrease in nitric oxide (NO) availability [9,24]. However, the decrease may not be sustained over time. Prolonged HBO exposure at 5 ATA reveals a cyclic response of CBF in rats with an increase in CBF of up to 50 % above baseline by 75 min [2,3,8]. In head injured patients, the decrease in CBF is also not consistently sustained over 30 min at pressures up to 2.5 ATA [11,23].

Prolonged hypercapnia significantly shortens the period to onset of cerebral convulsions with HBO. Potential mechanisms include an increase in tissue oxygenation to toxic levels as a result of cerebral hypercapnic vasodilation, or a worsening of tissue acidosis, which can develop during HBO as a result of CO_2 retention in combination with a lack of free hemoglobin for venous CO_2 transport. However, brief periods of limited hypercapnia might be able to improve tissue oxygenation as well as CO_2 elimination through intermittent increases in CBF. For the full expression of vasodilation with hypercapnia under hyperbaric conditions in rats basal NO production is required [7]. Since basal NO is reduced during exposure to HBO cerebral hypercapnic vasodilation might be impaired and physiological responses of the vasculature to hypercapnia could differ from those under normobaric, normoxic conditions. Under normal conditions hypercapnia induced cerebral vasodilation is fully reversible. This may not be the case during HBO, thereby hastening the onset of central nervous system toxicity through sustained increases in CBF and oxygenation. In baboons insufflation of 2 % CO_2 at 2 ATA caused a normalization of CBF measured by electro-magnetic flowmeter; Lambertsen proposed a linear relationship between the degree of hypercapnia and increases in CBF in man, but observations of CBF were abandoned with onset of symptoms of oxygen toxicity [15,26]. In humans during HBO the effect of brief intermittent CO_2 exposure on the cerebral vasculature has not been investigated, and conclusions based on animal studies are of limited value since effects of HBO may be species dependent [22].

We designed our study to evaluate CBF under the conditions of a routinely used HBO treatment profile, with healthy volunteers breathing 100% O_2 at 2.5 ATA for 70 min, to determine:

1) if there is a continuous decrease in CBF with increasing oxygen tension,

2) if the decrease in CBF at maximum pressure is sustained, and

3) if the cerebral vasculature maintains a dynamic response to hypercapnia.

Materials and Methods

After institutional review board approval and informed consent, 29 adult volunteers (8 female, 21 male, ages 20 – 53) were included in the study. Procedures followed were in accordance with institutional guidelines. Individuals with the following criteria were excluded: medication affecting vascular reactivity including nitrates, beta-blockers and calcium channel antagonists, a history of cardiac disease, a history of cerebral events including seizure and stroke, pulmonary disease, pregnancy, claustrophobia, or inability to autoinflate the middle ear. Subjects were assigned to one of two groups, group HBAir or group HBOx. Each subject was studied one time only. Throughout the study heart rate and non-invasive blood pressure were monitored and recorded (Sirecust 630, Siemens, Germany). A physician was immediately present to monitor for complications during hyperbaric exposure.

Hyperbaric Exposure

All studies were performed in a multiplace hyperbaric chamber (Medstar 2000, Fa. HAUX, Germany). Subjects were exposed to this HBO protocol: Compression over 15 min to a maximum pressure of 2.5 ATA (equals 15 meters of sea water) for 70 min followed by decompression at a rate of 0.1 ATA/min. Subjects were comfortably seated breathing room air (group HBAir) or 100% oxygen via a tightly fitting Scott mask (group HBOx). Room air oxygen content was monitored to detect incomplete mask seal indicating less than 100% oxygen inhalation. During decompression all subjects breathed oxygen to minimize risk for decompression illness. After decompression all subjects breathed room air. The exposure pattern for the two groups is displayed in figure 1.

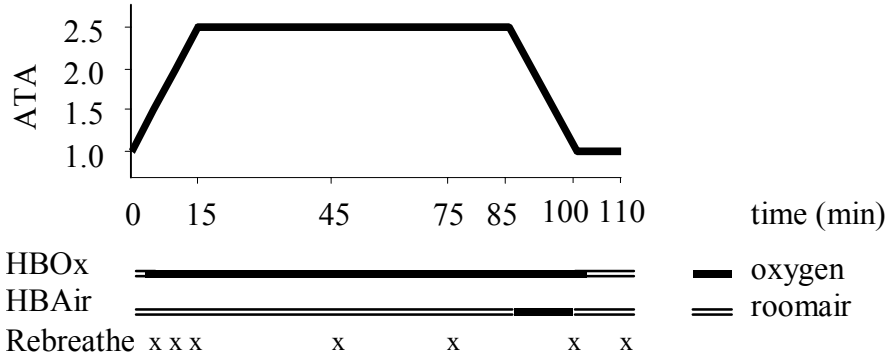

Figure 1. Exposure pattern for group HBOx and group HBAir.

Baseline measurements at 1.0 ATA room air followed by compression at 0.1 ATA per minute to 2.5 ATA, 70 min at 2.5 ATA, decompression at 0.1 ATA per minute, follow-up for 10 min. Group HBOx breathing 100% oxygen until end of hyperbaric exposure, group HBAir breathing room air throughout, except during decompression. Cerebrovascular reactivity testing at seven timepoints by closed circuit rebreathing over

10 respirations: 1.5 ATA, 2.0 ATA, 2.5 ATA/0 min, 2.5 ATA/30min, 2.5 ATA/60 min, 1.0 ATA/0 min, 1.0 ATA/10 min.

Transcranial Doppler Sonography

TCD was performed continuously throughout the study. Mean arterial blood flow velocity (V_{mean}) was measured in the proximal M1 segment of the middle cerebral artery (MCA) [31]. After manual localization of the optimal signal a 2 MHz TCD probe (MultiDop, DWL, Esslingen, Germany) was securely attached using a headband. Visual and acoustic signals were monitored continuously for optimal signal transduction by an investigator inside the chamber. Data were digitized and recorded on a hard drive for analysis.

Hypercapnia

Cerebrovascular response to hypercapnia was evaluated in five subjects in group HBAir and 15 subjects in group HBOx at seven time points during hyperbaric exposure: 1.5 ATA, 2.0 ATA, 2.5 ATA at 0 min, 2.5 ATA at 30 min, 2.5 ATA at 60 min, 1.0 ATA at 0 min (group HBOx only), 1.0 ATA at 10 min (group HBOx only). Hypercapnia was induced at each time point by rebreathing for 10 respirations into a closed circuit with an approximate volume of 3.4 l.

Experiments at 1.0 ATA had demonstrated a 15 mmHg rise in end-tidal CO_2 after 10 respirations via the closed circuit. The factors that determine the rise in CO_2 are the

volume of deadspace and the amount of CO_2 in the expired gas. The same closed circuit set-up was used for all subjects who rebreathed for 10 respirations without consciously changing their respiratory rate. The amount of CO_2 in the expired gas is determined by the CO_2 production of the subject. Resting CO_2 production rate has been shown to be independent of ambient pressure or inspired PO_2 up to 3.06 ATA [5,30]. Therefore, the rise in CO_2 with rebreathing can be expected to be similar under hyperbaric conditions.

Statistical analysis

Data were analyzed in a mixed model. Evaluation for normality was by Shapiro-Wilk test. Two-sided Wilcoxon two-sample rank-sum test was used for differences between groups at each time point; paired t-test with Bonferroni correction for comparison against baseline values. $P < 0.05$ was considered statistically significant for single comparisons.

Results

Biometric data

Biometric data with baseline blood pressures and heart rate are displayed in table 1. There were no differences between groups except for baseline heart rate, which was higher in group HBOx, $P = 0.03$. V_{mean} at any time point was determined by analysis of digitized data as the mean blood flow velocity over five heart beats.

Table 1. Baseline biometric and physiological data

group		HBAir	HBOx
age	years	38.0 ± 6.5	39.3 ± 9.9
height	cm	178.0 ± 7.9	176.3 ± 8.8
weight	kg	79.0 ± 11.3	73.2 ± 12.3
heart rate	min^{-1}	71.2 ± 7.9	78.8 ± 8.9*
SBP	mmHg	139.6 ± 21.1	137.8 ± 23.5
DBP	mmHg	86.2 ± 16.4	81.6 ± 15.4
MAP	mmHg	103.3 ± 17.3	100.3 ± 17.3
V_{mean}	mm s^{-1}	514 ± 121	584 ± 101
male/female		12/2	9/6

DBP = diastolic blood pressure, MAP = mean arterial blood pressure, SBP = systolic blood pressure, V_{mean} = mean cerebral blood flow velocity in the middle cerebral artery
Data are given as mean ± standard deviation. * P = 0.03 HBOx vs HBAir

Cardiovascular data

Heart rate decreased significantly during hyperbaric exposure reaching a minimum at 2.5 ATA / 30 min, 63.3 ± 7.2 min^{-1} in group HBAir, $P < 0.001$, and 62.0 ± 8.3 min^{-1} in group HBOx, $P < 0.001$ vs baseline. There were no differences between groups over time (table 2). Blood pressures did not differ significantly between groups. Mean arterial and diastolic blood pressure increased over time in group HBOx, P = 0.016 and

P = 0.006. Systolic blood pressure did not change over time. There was no gender influence on heart rate or blood pressures.

Table 2. Heart rate and mean arterial blood pressure over time

	group	1.5 ATA	2.0 ATA	2.5 ATA 0 min	2.5 ATA 30 min	2.5 ATA 60 min	1 ATA
HR	HBAir	68.6 ± 7	66.7 ± 7	63.8 ± 7	63.3 ± 7*	64.1 ± 10	66.7 ± 10
	HBOx	73.3 ± 10	69.1 ± 9	65.3 ± 10	62.0 ± 8	63.8 ± 8	65.9 ± 10
MAP	HBAir	102.8 ± 17	102.4 ± 14	99.5 ± 16	106.1 ± 17	104.5 ± 22	101.9 ± 19
	HBOx	98.1 ± 19	96.0 ± 16	99.1 ± 18	99.2 ± 16	97.4 ± 12	102.8 ± 18

HR = heart rate in beats per minute, MAP is mean arterial blood pressure in mmHg

Data are shown as mean ± standard deviation. *P = 0.03 group HBOx vs group HBAir

Cerebral blood flow velocity

Data for V_{mean} are shown in figure 2. To eliminate inter-individual differences of absolute blood flow velocities as a result of differences in vessel diameter and insonating angle, V_{mean} is presented as percent of baseline values. The maximal decrease in V_{mean} occurred in group HBOx on compression to 2.5 ATA with a mean reduction of 19%, P < 0.001 vs baseline.

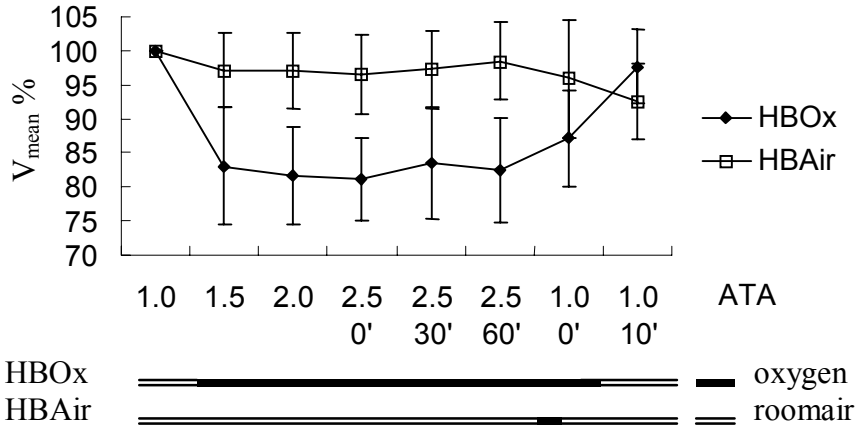

Figure 2. Continuous V_{mean} during HBO over time.

expressed as a percentage of baseline V_{mean} (mean±SD). Eight time points are displayed by pressure, with three time points at 2.5 ATA, representing 0 min, 30 min, and 60 min exposure, and three time points at 1 ATA representing baseline, end of exposure, and 10 min after end of exposure. Mean change in V_{mean} was significantly different between groups at pressure, $P < 0.0002$. In group HBAir V_{mean} decreased at 2.5 ATA / 0 min by 4 %, $P = 0.05$ vs baseline; the decrease seen after decompression is a result of breathing 100 % during this period. In group HBOx V_{mean} decreased significantly by 17 % at 1.5 ATA, $P < 0.0001$ vs baseline, with a maximal decrease of 19 % at 2.5 ATA / 0 min, $P = 0.15$ vs 1.5 ATA. V_{mean} at 2.5 ATA / 30 min was slightly less decreased with 16 %, $P = 0.05$ vs 2.5 ATA / 0 min. V_{mean} in group HBOx returned to baseline 10 min after end of treatment.

Cerebrovascular reactivity

Cerebrovascular reactivity to hypercapnia, calculated as maximal increase in V_{mean} after rebreathing as a fraction of V_{mean} before the test, was unchanged over time in both groups while at pressure, with a trend towards a less pronounced response in group HBOx, $P = 0.02$ at 2.5 ATA/30 min vs group HBAir (figure 3). After decompression

cerebrovascular reactivity to hypercapnia was significantly reduced in group HBOx, P = 0.002. In group HBAir evaluation of the hypercapnic response was limited to five subjects with 24 measurements performed satisfactorily. In group HBOx 15 subjects were studied with 88 satisfactory measurements. There was no influence of gender. There was no significant difference in V_{mean} before and after hypercapnia at each time point.

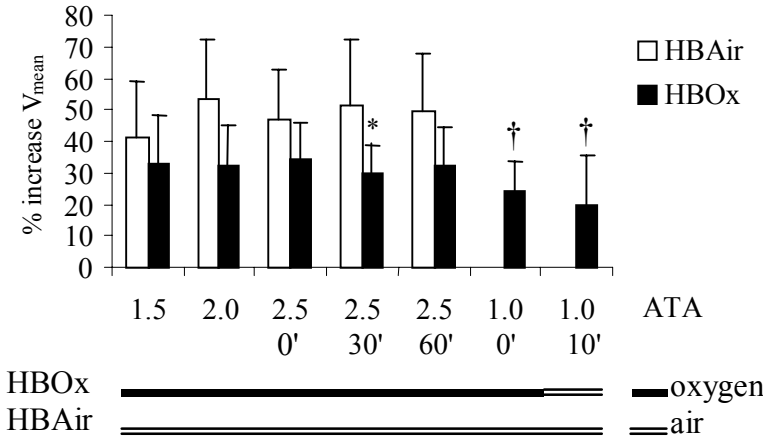

Figure 3. Cerebrovascular reactivity with hypercapnia

Data are shown as mean + SD for each time point. *P = 0.02 group HBOx vs. group HBAir at 2.5 ATA / 30 min; †P = 0.002 group HBOx at pressure vs. 1 ATA after decompression.

Complications

There were no complications in any of our subjects due to hyperbaric exposure, hyperbaric oxygenation, or hypercapnia.

Discussion

TCD and CBF during HBO

V_{mean} is decreased by 19% during an HBO protocol of 70 min at 2.5 ATA. This represents an equivalent decrease in CBF if the assumption is correct that the diameter of the blood vessel in which flow velocities were measured did not change [4]. Angiographic studies at 2.4 ATA demonstrated no appreciable change in the diameter of large or medium sized cerebral vessels in dogs breathing 100% oxygen [10]. This included the MCA, which we targeted in our measurements. We therefore suggest that even under the influence of extreme hyperoxia changes in V_{mean} of the MCA reflect changes in CBF.

Changes in CBF during HBO

The magnitude of decrease in CBF demonstrated in our study is consistent with the results of previous studies. Kety and Schmidt in 1948 first demonstrated a 13% decrease in CBF in response to breathing 100% oxygen at 1 ATA, Lambertsen measured a 25% decrease at 3.5 ATA, and Ohta an 18% decrease at 3 ATA [13,16,19]. Demchenko studied regional CBF in rats and after 30 min of HBO found a maximal decrease of 26 – 39 % at 3 ATA [8].

Relationship of CBF and hyperoxia

We measured a continuous decrease in CBF up to our maximum pressure (2.5 ATA). This does not support findings in human volunteers which suggested the trend of a lesser decrease in CBF when breathing 100% oxygen at pressures higher than 2 ATA [19]. However, our results are consistent with findings by Demchenko who in rats demonstrated a continuous decrease in regional CBF during HBO with increasing barometric pressure which was maximal at 3 ATA [8]. In our study, beyond 1.5 ATA with a 17% decrease in CBF, additional decreases were observed though not statistically significant, but this may have been due to insufficient numbers in our study to reach statistical significance. We did not see an increase in CBF during compression to 2.5 ATA.

Influence of intermittent hypercapnia on time course of CBF

Intermittent hypercapnia might have influenced the changes in CBF. However, there was no significant difference in V_{mean} values before and immediately after rebreathing, and we conclude the influence of intermittent hypercapnia on the overall time course of CBF to be negligible.

Time course of CBF during HBO

Experimental data on rats have demonstrated that the decrease in CBF during HBO at high pressures is not sustained over time [3,8]. After 30 min of HBO at 5 ATA CBF increased and reached pre-exposure levels within 60 min increasing up to 50 % in addition within 75 min; at pressures less than 5 ATA the decrease in CBF was sustained

over 75 min [8]. During our HBO exposures we demonstrated only a slight relative increase in CBF after 30 min at 2.5 ATA which resolved within the next 30 min resulting in no overall change for the exposure period of 70 min at 2.5 ATA. We exposed our subjects to HBO over a time period within which a secondary increase in CBF has been shown to occur, but we did not expose them to the same maximum pressure. Therefore the degree of hyperoxia in our study was less pronounced, which might explain why we did not observe the increase in CBF that has been reported at higher pressures. The slight increase which we noted could be interesting, however, given the inherent limitations of TCD measurements and estimation of CBF, we do not believe that any conclusions should be based on this observation.

Reversibility of CBF decrease after HBO

All of our subjects experienced a full recovery of CBF to pre-exposure values within 10 min of return to breathing room air at 1 ATA. There was no rebound phenomenon as seen in rats at 5 ATA HBO with reversal of cerebral vasoconstriction or as suggested in a study on severely brain injured patients after 1 hour at 1.5 ATA [8,23]. Our results suggest that the decrease in CBF as measured by TCD is reversible within a short time after cessation of HBO after 70 min at 2.5 ATA and appears to be limited to this period.

Influence of intermittent hypercapnia on CBF

The increase in CBF during HBO following inhalation of CO_2 is a recognized phenomenon [14]. However, in humans direct measurements on the extent and course of

the response are limited. Lambertsen performed measurements of the cerebral arterio-venous oxygen difference in four male patients during inhalation of 2 % CO_2 in oxygen at 3.5 ATA. He measured a 58 % decrease in the arterio-venous oxygen difference compared to 100 % oxygen inhalation at 3.5 ATA, which he deducted to be the result of increased oxygen delivery through increased cerebral blood flow [15]. We observed a mean CBF increase by more than 30% in response to hypercapnia during HBO at 2.5 ATA for 70 min, which was consistent within each individual subject over time. The response was less pronounced compared to room air breathing at 2.5 ATA (group HBAir vs group HBOx, P = 0.02 at 2.5 ATA / 30 min); this is similar to the findings in rats at 4 ATA and is possibly related to lack of available NO during HBO for full expression of the hypercapnic vasodilatory response in the brain [6]. However, the increase in CBF with hypercapnia was not prolonged and CBF returned to pre-test values briefly after termination of closed circuit rebreathing. No adverse effects were noted in any of our subjects due to temporary increases in CBF with hypercapnia. Our results indicate that during HBO the cerebral circulation remains dynamic and is able to respond to a CO_2 challenge with vasodilation during the hypercapnic period and that this effect is reversible with reestablishment of normocapnia.

After HBO increases in CBF in response to hypercapnia were still reduced. Following reversal of cerebral vasoconstriction this seems to indicate a limited ability for vasodilatory response in the cerebral vasculature after HBO. A similar situation has recently been demonstrated in conjunction with cerebral vasodilation secondary to hemodilution [27]. These observations are consistent with the mechanism of vasorelaxation mediated by NO, and a limited availability of NO as a result of HBO [9,24].

Normal values for CO_2-reactivity testing under normobaric conditions are variable depending on the technique, ranging from 10 to 24 % change in V_{mean} per 1 vol% change in CO_2 [31]. We measured a 30 % increase in V_{mean} for a 15 mmHg rise in $P_{et}CO_2$. Despite the obvious limitations of this comparison it indicates that cerebrovascular reactivity to hypercapnia during HBO at 2.5 ATA demonstrates the same order of magnitude as under normobaric, normoxic conditions.

Oxygen and carbon dioxide gas tensions during HBO

We did not ascertain changes in arterial O_2 or CO_2 (P_aO_2 or $PaCO_2$) by direct measurement. However, the effects of HBO on blood gases are well known [17]. At 2.5 ATA breathing 100% oxygen the alveolar oxygen tension (P_AO_2) is calculated to 1813 mmHg [21]. P_aO_2 would be slightly lower than predicted due to physiologic shunting and the dilution of P_AO_2 with nitrogen diffusing out of tissues [5,21]. P_aCO_2 during HBO under resting conditions is not significantly different from 1 ATA [5,30]. By using a standardized rebreathing technique a very similar degree of hypercapnia was produced in all subjects allowing a comparison of subjects within our study. Variations between subjects could occur due to a difference in lung volumes since the volume of the closed circuit was fixed. Smaller tidal volume would be associated with a lesser degree of rebreathing. Basing tidal volume on body weight (HBAir 79, 62 – 99 kg; HBOx 73, 53 – 98 kg, mean, min-max) shows a similar distribution in both groups so that we believe the influence of inter-individual differences in deadspace volume on the degree of hypercapnia to be minimal. Therefore, the degree of hypercapnia induced using the

rebreathing technique described earlier should be consistent under the conditions in this study (1.0 -2.5 ATA).

Conclusion

We evaluated the effects of a routinely used HBO treatment protocol and intermittent hypercapnia on the cerebral vasculature using TCD. HBO with 100% oxygen causes a sustained decrease in CBF at 2.5 ATA over 70 min, which is reversed within 10 min after end of exposure. Cerebral vasodilation in response to intermittent hypercapnia is slightly less pronounced compared to room air breathing and the effects reversible with reestablishment of normocapnia.

Summary

Background and purpose: The decrease in cerebral blood flow (CBF) through cerebral vasoconstriction caused by extreme hyperoxia could promote the onset of central nervous system oxygen toxicity during hyperbaric oxygenation (HBO). CBF increases with hypercapnia, but the effects of intermittent hypercapnia during HBO exposure on CBF have not been determined. The aim of the study is to evaluate CBF and cerebrovascular reactivity to hypercapnia during HBO at 2.5 atmospheres absolute (ATA) for 70 min using transcranial doppler sonography (TCD) in healthy volunteers.

Methods: 29 adult subjects were studied during a routine compression profile: 2.5 ATA for 70 min. Fifteen subjects received 100% oxygen simulating a HBO treatment, 14 subjects breathed room air. TCD with a 2 MHz probe was used to continuously measure mean blood flow velocities (V_{mean}) in the middle cerebral artery. Cerebrovascular reactivity was assessed by response to hypercapnia induced by standardized rebreathing.

Results: V_{mean} decreased by 19% during HBO at 2.5 ATA for 70 min, $P<0.0001$, and returned to baseline within 10 min after end of exposure. Hyperbaric exposure alone did not change V_{mean}. Heart rate and blood pressure did not differ between groups over time. Hypercapnic cerebral vasodilation tended to be less pronounced in the HBO group, $P=0.02$ after 30 min at 2.5 ATA, but reversible with termination of hypercapnia.

Conclusions: HBO at 2.5 ATA for 70 minutes causes a sustained decrease in CBF, which is reversible within 10 min after end of exposure. Cerebral hypercapnic vasodilation is slightly reduced during HBO and reversible with normocapnia.

References

1. Badr AE, Yin W, Mychaskiw G, Zhang JH. Dual effect of HBO on cerebral infarction in MCAO rats. Am J Physiol - Regulatory Integrative & Comparative Physiology 2001;280:R766-70.
2. Bean JW. Cerebral O2 in exposures to O2 at atmospheric and higher pressure, and influence of CO2. Am J Physiol 1961;201:1192-1198.
3. Bean JW, Lignell J, Coulson J. Regional cerebral blood flow, O2, and EEG in exposures to O2 at high pressure. J Appl Physiol 1971;31:235-42.
4. Bishop CCR, Powell S, Rutt D, Browse NL. Transcranial doppler measurement of middle cerebral artery blood flow velocity: A validation study. Stroke 1986;17:913-915.
5. Clark JM, Lambertsen CJ, Gelfand R, Flores ND, Pisarello JB, Rossman MD, Elias JA. Effects of prolonged exposure at 1.5, 2.0, or 2.5 ATA on pulmonary function in men (predictive studies V). J Appl Physiol 1999;86:243-259.
6. Demchenko IT, Boso AE, Bennett PB, Piantadosi CA. Role of nitric oxide in cerebrovascular responses to hypercapnia under hyperbaric oxygen exposure. Undersea Hyperb Med 2001:A 21. Abstract
7. Demchenko IT, Boso AE, Natoli MJ, Doar PO, O'Neill TJ, Bennett PB, Piantadosi CA. Measurement of cerebral blood flow in rats and mice by hydrogen clearance during hyperbaric oxygen exposure. Undersea Hyperb Med 1998;25:147-52.

8. Demchenko IT, Boso AE, O'Neill TJ, Bennett PB, Piantadosi CA. Nitric oxide and cerebral blood flow responses to hyperbaric oxygen. J Appl Physiol 2000;88:1381-9.

9. Demchenko IT, Boso AE, Bennett PB, Whorton AR, Piantadosi CA. Hyperbaric oxygen reduces cerebral blood flow by inactivating nitric oxide. Nitric Oxide 2000;4:597-608.

10. Harel D, Saltzman HA. Cerebral angiographic response to hyperbaric oxygen in anesthetized dogs: Proc Fifth Hyperb Cong 1974:341-349.

11. Holbach KH, Wassmann H, Caroli A. Continuous rCBF measurements during hyperbaric oxygenation. Proc 6th Int Cong Hyperb Med 1977:104-111.

12. Jacobson L, Harper AM, McDowall DG. The effects of oxygen at 1 and 2 atmospheres on the blood flow and oxygen uptake of the cerebral cortex. Surgery, Gynecology&Obstetrics 1964;119:737-742.

13. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest 1948:484-492.

14. Kindwall EP, Whelan HT. Hyperbaric medicine practice. Best Publishing Company, 1999.

15. Lambertsen CJ, Ewing JH, Kough RH, Gould R, Stroud MW. Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100% O2 and 2% CO2 in O2 at 3.5 atmospheres ambient pressure. Am J Physiol 1955;8:255-263.

16. Lambertsen CJ, Kough RH, Cooper DY, Emmel GL, Loeschcke HH, Schmidt CF. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5

atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J Appl Physiol 1953;5:471-486.

17. Lanphier EH, Camporesi EM. Respiration and exertion. In: Bennett PB, Elliott DH, eds. Physiology and Medicine of Diving. 4th ed. London: WB Saunders Company, 1993:613.

18. Nighoghossian N, Trouillas P, Adeleine P, Salord F. Hyperbaric oxygen in the treatment of acute ischemic stroke. A double-blind pilot study. Stroke 1995;26:1369-72.

19. Ohta H, Yasui N, Tsuchida H, Hinuma Y, Suzuki E, Kikuchi K. Measurement of cerebral blood flow during hyperbaric oxygenation in man the relationship between PaO2 and cerebral blood flow. Proc 8th Int Cong Hyperb Med 1987:62-67.

20. Omae T, Ibayashi S, Kusuda K, Nakamura H, Yagi H, Fujishima M. Effects of high atmospheric pressure and oxygen on middle cerebral blood flow velocity in humans measured by transcranial Doppler. Stroke 1998;29:94-7.

21. Piantadosi CA. Physiology of hyperbaric hyperoxia. In: Moon RE, Camporesi EM, eds. Hyperbaric Medicine, Part I. Philadelphia: WB Saunders Company, 1999

22. Prass K, Wiegand F, Schumann P, Ahrens M, Kapinya K, Harms C, Liao W, Trendelenburg G, Gertz K, Moskowitz MA, Knapp F, Victorov IV, Megow D, Dirnagl U. Hyperbaric oxygenation induced tolerance against focal cerebral ischemia in mice is strain dependent. Brain Res 2000;871:146-50.

23. Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH. Effects of hyperbaric oxygenation therapy on cerebral

metabolism and intracranial pressure in severely brain injured patients. J Neurosurg 2001;94:403-411.

24. Stamler JS, Jia L, Eu JP, McMahon TJ, Demchenko IT, Bonaventura J, Gernert K, Piantadosi CA. Blood flow regulation by S-nitrosohemoglobin in the physiological oxygen gradient. Science 1997;276:2034-7.

25. Sunami K, Takeda Y, Hashimoto M, Hirakawa M. Hyperbaric oxygen reduces infarct volume in rats by increasing oxygen supply to the ischemic periphery. Crit Care Med 2000;28:2831-6.

26. Tindall GT, Wilkins RH, Odom GL. Effect of hyperbaric oxygenation on cerebral blood flow. Neurol Surg - Surgical Forum 1965;16:414-6.

27. Tomiyama Y, Jansen K, Brian JE, Jr., Todd MM. Hemodilution, cerebral O2 delivery, and cerebral blood flow: a study using hyperbaric oxygenation. Am J Physiol 1999;276:H1190-6.

28. Veltkamp R, Warner DS, Domoki F, Brinkhous AD, Toole JF, Busija DW. Hyperbaric oxygen decreases infarct size and behavioral deficit after transient focal cerebral ischemia in rats. Brain Res 2000;853:68-73.

29. Visser GH, Van Hulst RA, Wieneke GH, Van Huffelen AC. Transcranial Doppler sonographic measurements of middle cerebral artery flow velocity during hyperbaric oxygen exposures. Undersea Hyperb Med 1996;23:157-65.

30. Whalen RE, Saltzman HA, Holloway DH, McIntosh HD, Sieker HO, Brown IW. Cardiovascular and blood gas responses to hyperbaric oxygenation. Am J Cardiol 1965;15:638-646.

31. Widder B. Doppler- und Duplexsonographie der hirnversorgenden Arterien. Springer, 1985.

Tables and figures

Figure 1. Exposure pattern for group HBOx and group HBAir. 6
Table 1. Baseline biometric and physiological data 9
Table 2. Heart rate and mean arterial blood pressure over time 10
Figure 2. Continuous V_{mean} during HBO over time. 11
Figure 3. Cerebrovascular reactivity with hypercapnia 12

Abbreviations

ATA	atmospheres absolute
CBF	cerebral blood flow
CO_2	carbon dioxide
DBP	diastolic blood pressure
HBO	hyperbaric oxygenation
HR	heart rate
MAP	mean arterial pressure
MCA	middle cerebral artery
NO	nitric oxide
O_2	oxygen
P_aCO_2	arterial carbon dioxide gas tension
P_ACO_2	alveolar carbon dioxide gas tension
P_aO_2	arterial oxygen gas tension
P_AO_2	alveolar oxygen gas tension
SBP	systolic blood pressure
TCD	transcranial doppler sonography
V_{mean}	mean arterial blood flow velocity in the middle cerebral artery

Dedication

This thesis is dedicated to my parents in gratitude and acknowledgement of their continued unfailing love and support. Thank you.