Normobaric Hyperoxia Does Not Induce Significant Electroencephalogram Changes in Healthy Male Subjects

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Citation

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Abstract

ObjectiveHyperoxia can cause slowing and epileptic seizures in the electroencephalogram (EEG) when administered under hyperbaric conditions. Also hyperventilation and ensuing hypocapnia induce EEG slowing and may provoke epileptiform acitivity in patients with epilepsy. We aimed to study whether prolonged normobaric hyperoxia without hyperventilation has any effects on EEG. Methods Ten healthy, non-smoking men, aged 21-30 years, were recruited. Nineteen-channel-EEG was recorded continuously during breathing of 100 % oxygen through a tight 5 cmH₂O continuous positive airway pressure –mask for one hour resulting in a mean end-tidal oxygen concentration of 91.1% (SD 1.8%). EEG-signal was analysed both visually and quantitatively after Fast Fourier Transformation. Total power and main frequency band powers (beta, alpha, theta, and delta) were calculated from the power spectrum, and compared between the baseline (before starting 100% oxygen) and after one hour breathing of pure oxygen. ResultsA slight reduction in posterior alpha band power and a simultaneous increase in anterior and lateral slow EEG activity occurred during oxygenation, but none of the changes remained significant after adjustment for multiple statistical comparisons. No epileptiform or other adverse activity occurred in the EEG. ConclusionsIn healthy subjects, normobaric oxygen, even when administered in high concentrations, does not cause significant EEG slowing or produce any other, possibly harmful changes in the EEG.

INTRODUCTION

Hyperoxic ventilation (>21 % O_2) is a widely used method in medical practice, for example in intensive care units and emergency departments. Despite the objective to improve tissue oxygen delivery, hyperoxia can paradoxically hinder oxygen supply to the brain. The mechanism is thought to be mediated via so called Haldane effect, i.e. reduced CO₂carrying capacity of oxyhemoglobin in association with high concentrations of physically dissolved O₂. This leads to an increase in arterial CO₂ which induces hyperventilation, followed by a decrease in CO₂, and the ensuing hypocapnia causes vasoconstriction. Subsequent reduction in cerebral blood flow (CBF) is not, however, normalized by eliminating the hypocapnia (1).

It is well known that normoxic hyperventilation induces slowing of electroenecphalographic (EEG) activity, although the general mechanisms behind this slowing have not yet been settled (1,2,3,4). The prevailing hypoxia theory suggests that the general slowing of the EEG during normoxic hyperventilation results from hypocapnia which initiates vasoconstriction and consequently decreases CBF causing cerebral hypoxia. However, a slight physiological decrease in CBF, such as that occurring during hyperventilation, does not alone cause slowing in EEG (5).

On the other hand, it is known that hyperbaric oxygen (HBO) can cause EEG slowing and seizures (6). It has been demonstrated that EEG power in beta, delta and theta frequency bands increases during HBO, and before seizures there is an increase in theta activity and slowing in alpha rhythm (6). In an experimental study, Sato et al. showed (7) that HBO increases CBF and nitric oxide production before epileptiform EEG discharges occur.

As a part of an anaesthesia research project using xenon gas for single-agent anaesthesia we had a unique opportunity to investigate the isolated effect of excessive hyperoxygenation in normobaric conditions and with normal breathing on EEG in healthy subjects. The oxygenation with 100% oxygen was performed for denitrogenation before anesthesia induction with xenon. The aim of the present study was to investigate the central nervous system (CNS) effects of pure normobaric hyperoxia by means of analysing the classical EEG power spectral variables.

METHODS

The Ethical Committee of the Hospital District of Southwest Finland (Turku, Finland) approved the study protocol and after giving written informed consent, 10 healthy (American Society of Anaesthesiologists physical status I), righthanded, non-smoking male volunteers aged 21-30 years were enrolled. The range of their body mass index was 21-28 kg/m². None of the subjects had history of psychiatric disorder, somatic illness, substance abuse, drug allergies, or ongoing medications. All subjects underwent a detailed health-examination including an interview, physical examination, laboratory testing, urine drug screen and a 12lead ECG. Subjects refrained from using alcohol or any medication for 48 hours before the study and fasted overnight.

One large vein of the right forearm was cannulated and physiological saline was administrated to keep the intravenous line open. Monitoring included non-invasive blood pressure, pulse-oximetry, and 3-lead electrocardiogram , (Datex-Ohmeda S/5 anesthesia monitor, GE Healthcare, Helsinki, Finland). S/5 Collect software (GE Healthcare, Helsinki, Finland) was used to automatically record the vital parameters every 10 seconds throughout the study. The vital signs remained stable throughout the study.

Oxygenation of the subjects was carried out by having them breathe spontaneously 100 % oxygen through a tight 5 cmH_2O continuous positive airway pressure –mask for one hour. Mean end-tidal oxygen concentration was 91.1% (SD 1.8; range 88-94) at the end of oxygenation/denitrogenation.

All EEG studies were performed in a dimly lit room with no sudden loud noises and the subjects kept their eyes shut during the EEG-recording. Baseline EEG was collected before oxygenation started and EEG was then continuously recorded with 28-channel digital EEG equipment and stored in a portable computer and server. (BE-Light peripheral recording unit, Galileo_NT Systems recording, reviewing and database software, EBNeuro, Florence Italy). EEG signal sampling rate was 256 Hz and filter settings 0.1 – 70 Hz. Nineteen-channel EEG was recorded with standard

International 10/20 Electrode Placement System locations using Electrocap (Electro-Cap International, inc Eaton, Ohio 45320 USA) with Ag- AgCl electrodes. EEG derivations used in the quantitative analyses were F3, F4, T3, T4, C3, C4, P3 and P4 referenced to linked-ears. Electrode impedances were kept below 5 kl. A specialist in clinical neurophysiology visually analyzed the raw EEG data off line in order to detect qualitative abnormalities such as epileptiform activity and in addition, to mark artifact-contaminated EEG segments to be excluded from the quantitative analyses. The EEG signal was further processed using commercial software (Insight II, Prism, Spectrum, Averaged developed by Persyst Development corporation Prescott, AZ 86305 USA) to estimate the Power Spectral Density of a discrete-time EEG-signal using Welch's averaged, modified periodogram method.

All quantitative EEG variables were calculated for the following conditions: BASELINE: 1 min period of EEG at the baseline before 100% oxygen was started. OXYGENATION: 1 min period of EEG after approximately 1 hour of oxygenation with 100% oxygen. For these 1 min periods, only epochs without high-amplitude artifacts, such as eye movements and muscle activity, and with stable baseline were accepted for power spectral analysis. Epoch length was 4 sec.

Estimates of power spectra ($\mathbb{I}V^2/Hz$) of each 4 sec epoch were obtained with the Prism, Spectrum function of the Insight II program utilizing Welch's averaged, modified periodogram method. Power spectra from individual epochs were averaged to obtain the final power spectrum for both analysis periods. Absolute EEG power ($\mathbb{I}V^2$) was calculated from the total power spectrum (0-30.0 Hz), and separate band-powers for the following frequency bands: delta (0-3 Hz), theta (3.25-7.75 Hz), alpha (8-13 Hz), beta (13.25-25 Hz), and gamma (25.25-30).

Quantitative EEG variables were analysed with repeated measures analysis of variance with side (left, right), (F3, F4, C3, C4, P3, P4, T3, T4) and time (before and after oxygenation) as a within-factors. All factors were treated as fixed effects in the statistical models. Variables were logtransformed before analyses to meet the assumption of normality. A two-sided value of P<0.05 was considered statistically significant. To avoid multiplicity, Bonferroni correction was applied. Data are presented as mean ± SD unless otherwise stated. Statistical analyses were made with SAS EG (version 4.1; SAS Institute Inc., Cary, NC, USA).

RESULTS

Summary of all EEG variables and statistical analyses are presented in Table 1. When comparing the baseline values to those after oxygenation, there were no significant changes. Delta power increased in the frontal and temporal derivations similarly on both sides as did the total power, but these changes were not statistically significant after Bonferroni correction. Similarly, alpha band power tended to decrease in the posterior derivations during oxygen breathing, but this alteration was not statistically significant. No epileptiform acitivity or other focal or generalized paroxysmal abnormalities occurred in the EEG during normobaric oxygenation with normal breathing. All subjects reported having been alert throughout the one-hour study period because of the rather uncomfortable, tight-fitting mask.

Figure 1

oxygenation (O ₂). Statistical significance (RM ANOVA) between the two conditions was reached only in F3, T3 and T4 derivations where delta band power increased.					
Channel	Condition				
F3	Baseline	22.32 (10.45)	8.91 (5.04)	10.82 (9.10)	4.80 (2.90)
	O2	34.81 (22.44)*	8.84 (3.87)	11.49 (10.07)	5.49 (4.44)
F4	Baseline	21.95 (10.89)	9.27 (4.95)	10.90 (9.11)	4.84 (2.60)
	O2	31.16 (19.12)	8.88 (3.67)	11.87 (10.59)	5.50 (4.31)
C3	Baseline	13.46 (6.05)	7.39 (4.29)	13.75 (12.14)	4.67 (2.85)
	O2	17.41 (7.93)	6.58 (3.03)	11.71 (9.98)	5.30 (4.33)
C4	Baseline	14.03 (7.04)	7.41 (3.96)	13.15 (11.31)	4.87 (2.73)
	O2	16.60 (6.00)	6.49 (2.69)	11.79 (10.43)	5.26 (4.18)
T3	Baseline	10.20 (7.32)	3.42 (2.28)	5.37 (4.55)	8.73 (14.16)
	O2	14.76 (6.68)*	3.33 (1.89)	5.52 (4.47)	8.76 (15.92)
T4	Baseline	10.75 (7.21)	3.51 (1.69)	5.18 (4.35)	3.79 (3.62)
	O2	15.60 (6.61)*	3.42 (1.53)	5.25 (4.38)	5.77 (6.32)
P3	Baseline	13.55 (6.15)	7.63 (5.88)	23.81 (25.20)	4.54 (2.64)
	O2	13.82 (5.35)	6.14 (3.58)	15.95 (14.79)	5.05 (14.79)
P4	Baseline	13.12 (4.73)	7.51 (4.66)	26.22 (29.84)	4.71 (2.73)
	O2	13.83 (3.67)	6.12 (3.17)	18.46 (18.24)	5.10 (4.13)

*p-value less than 0.05 were not significant after Bonferroni correction.

DISCUSSION

This is the first report on the effects of normobaric hyperoxia without hyperventilation on human EEG activity demonstrating that mere oxygenation has no clinically significant electrophysiological CNS effects when assessed using EEG techniques. The effects of hyperventilation induced hyperoxia-hypocapnia and experimental hyperbaric oxygenation on the EEG have been studied, but there are no previous data on whether normobaric hyperoxia with normal ventilation induces significant changes in the neuronal activity of the human brain. The question has clinical importance as adjunct oxygen is regularly used during emergency, intensive care and stroke unit treatments. While pulmonary toxicity may occur during normobaric breathing of oxygen-enriched gas mixture, clinical signs of CNS level oxygen intoxication have been considered to appear only under hyperbaric conditions (6,8). Our results are in line with these previous observations as we did not find any EEG signs of epileptiform or other adverse activity during onehour oxygenation under normobaric conditions.

The most serious sign of CNS toxicity of oxygen is generalized epileptic seizure. In rats, hyperbaric hyperoxia induces a gradual EEG spectral amplitude decrease after beginning of oxygenation and sporadic spikes after prolonged exposure to hyperbaric oxygen before the onset of seizure activity. This activity invariably occurs after 19-106 min depending on simultaneous CO_2 levels, faster with higher arterial CO_2 concentrations (7). However, in human subjects, epileptic seizures seem to appear without any clear predictive EEG alterations preceding the epileptiform discharge (6). This is in line with our data that did not show any signs of amplitude or power decrement neither epileptiform spikes during one-hour exposure to normobaric 100% oxygen and apparent normocapnia.

Visser et al. (6) described the effects of hyperbaric hyperoxia (2.8 bar pure oxygen for 30 min) on quantitative EEG noticing an increase in the total power due to equal increases in the four main frequency band spectra. Similar trends were found in the present data with normobaric oxygenation as the quantitative analyses suggested an increase in total power due to enhancement of slow delta and theta band activity, but these slight alterations remained statistically insignificant. Previously, the effects of normobaric hyperoxia on human brain have been studied with perfusion-MRI technique. CBF decreased independently of arterial PCO₂, indicating an independent cerebral vasoconstrictive effect of hyperoxia, in addition to the effects due to hypocapnia secondary to hyperoxia (1). According to the present results, it seems that the vasoconstrictive effects of prolonged hyperoxia at normobaric conditions without hyperventilation are subtle and do not induce significant changes in the cortical neuronal activity assessed by EEG. Supporting our observations, Kennealy et al. (3) previously showed that hyperventilation-induced EEG changes are

independent of the concentration of inspired oxygen by assessing the effects of different gas mixtures ($16\% O_2$, $21\% O_2$ and $100\% O_2$) on EEG. On the other hand, the rather small group size in the present study may have rendered less robust changes insignificant in the statistical analyses.

The slight increase of delta power and simultaneous decrease of posterior alpha activity found in this and previous studies might also have been caused by decreased vigilance. However, the tight face mask was reported rather uncomfortable by the subjects keeping them alert during the one hour oxygenation. Similarly, the vigilance levels have been controlled in previous studies (1,6,9). On the other hand, the discomfort caused by the mask may have induced slight hyperventilation in the present study. Our study setup can be criticized for not controlling this by measuring arterial and/or end-tidal CO_2 levels before and after the denitrogenation period.

To conclude, our results confirm that oxygen administered at high concentrations under normal atmospheric pressure and with normal ventilation, does not cause significant EEG slowing or produce any epileptiform activity in the EEG in healthy subjects. The importance of this finding is that mere hyperoxia does not seem to alter cortical neuronal activity in a harmful way, which validates its clinical use during emergency and intensive care unit treatments. Further studies in larger, clinical patient groups are, however, warranted.

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