Effect of age and repeated hyperbaric oxygen treatments on vagal tone.

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INTRODUCTION

The reason for increased parasympathetic activity during hyperbaric exposure is increased partial pressure of oxygen (1,2). Hyperbaric oxygen (HBO₂) treatment decreases heart rate and increases peripheral vascular resistance with redistribution of regional blood flow to central circulation (3-5). Arterioles have been found to constrict in the environment of increased dissolved oxygen content in vitro (6). Hyperbaric oxygen has been shown to form peroxynitrite (ONOO⁻) from superoxide (•O₂⁻) and nitric oxide (NO). This reaction decreases bioavailability of NO for vasodilatation (7). However, increased endothelin-1 concentrations have been detected during hyperoxia in healthy volunteers, suggesting that endothelin-induced vasoconstriction may also be involved (8). Increased peripheral vascular resistance increases blood pressure and activates baroreflex, which could be one of the main factors that increase parasympathetic tone during single exposure to hyperbaric hyperoxia. The increase in parasympathetic tone during hyperoxia has been detected by increased high frequency power of heart rate variability (HRV) (1,2).

In hyperbaric medicine, HBO₂ treatments are usually given in series, depending on the indication. Repeated hyperbaric exposures have been found to decrease lung function in man (9,10).
but the influence of repeated exposures on hemodynamic control and autonomic nervous system in man is not known. In rats, repeated hyperbaric oxygen exposures to 5 ATA caused higher blood pressure values at normal ambient pressure compared to rats that were not exposed to hyperbaric conditions (11). In our earlier study, endothelin-1 was found to increase during single hyperbaric exposure (8). The effect of endothelin can be long lasting because the gene coding its production is autoinductive (12). Repetitive hyperbaric exposures can theoretically cause a long-lasting increase in peripheral vasoconstriction, and by changing hemodynamic control feedback mechanisms, can also influence the autonomic nervous system.

High frequency (HF) power decreases linearly with age (13-17). The reason for this decrease is not clear, but it may reflect parasympathetic nervous system dysfunction related to aging. There are many elderly people that are treated by hyperbaric oxygenation for various reasons. It is not clear whether the effect of aging also translates to the vagal response to hyperbaric oxygen treatment.

The aims of this study were, first, to find out if repeated HBO₂ exposures influence the autonomic response to hyperbaric oxygenation and, secondly, to evaluate the influence of age on autonomic response during hyperbaric oxygenation. Furthermore, we wanted to evaluate the time course of changes in vagal activity during HBO₂ treatment in more detail.

### METHODS

We studied 23 patients who were treated for chronic osteomyelitis or radionecrosis of the jaw or reconstructive surgery of the facial region (Table I). Patients with diabetes and atrial fibrillation were excluded from the study. The Joint Ethical Committee of the University of Turku and Turku University Hospital approved the study. The patients gave a written informed consent for participating in the study.

The study was conducted in a multiplace hyperbaric chamber (Rauma Oceanics, Tampere, Finland) at the ICU of Turku University Hospital. HBO₂ treatment was given for 90 min at 2.5 ATA (15 meters seawater, Fig. 1) in 15 sessions during 3 weeks, one session per day from Monday to Friday. All patients had a surgical intervention during the course of the study, usually two weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI</th>
<th>Male/Female</th>
<th>Diagnosis</th>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Osteoradionecrosis</td>
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<tr>
<td>≥ 50 years</td>
<td>62.8 (8.7)</td>
<td>77.1 (11.1)</td>
<td>174 (7)</td>
<td>25.4 (3.7)</td>
<td>9/3</td>
<td>10</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>35.4 (10.5)</td>
<td>63.1 (10.4)</td>
<td>170 (8)</td>
<td>22.0 (4.4)</td>
<td>5/6</td>
<td>4</td>
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<tr>
<td>Statistics</td>
<td>p &lt; 0.001</td>
<td>p = 0.012</td>
<td>p = 0.105</td>
<td>p = 0.050</td>
<td>p = 0.214</td>
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Abbreviations: kg = kilograms, cm = centimeters, BMI = body mass index
after the beginning of the HBO$_2$ treatments, and they were treated with antibiotics. For statistical analysis, the patients were divided into two age groups (under 50 years old, n = 11 and over 50 years old, n = 12).

**Compression Protocol**

The compression was started after 30 min bed rest and 2.5 ATA was reached in 10-15 min. At 2.5 ATA, the patients started breathing 100% oxygen via a mask (Built-in-Breathing-System, BIBS). The pressure was kept at 2.5 ATA for 80 min. The oxygen breathing continued uninterrupted for 90 min. A 5-min stop was taken at 1.6 ATA during decompression of the chamber. The patients stayed in supine position during the whole session.

**Measurements**

The patients were studied during 5 treatments of 15. The sessions for measurements were chosen to be evenly distributed during the whole treatment period. HRV measurements were made before compression and three times at 2.5 ATA (as soon as 2.5 ATA was reached, and after 30 min and 70 min at 2.5 ATA), at 1.6 ATA during decompression and after surfacing (Fig. 1). During the measurements, the patients were advised to breathe 15 breaths per min during sampling, synchronized to inhalation and exhalation by signals of a sound generator.

**Fig. 1.** Treatment protocol. Numbers 1-6 refer to measurement occasions: 1 = before compression, 2 = as soon as 2.5 ATA was reached, 3 = after 30 min at 2.5 ATA, 4 = 70 min at 2.5 ATA, 5 = during decompression at 1.6 ATA and 6 = after surfacing. Decompression stop at 1.6 ATA took 5 min.

**HRV Analysis**

For HRV analysis, a four-min sample of ECG was registered into computer memory, and this was subjected to power spectral analysis of HRV using a commercially available software package (CAFTS, Medikro, Tampere, Finland). This program utilizes a modified algorithm for QRS detection described by Englese and Zeelenberg (18). From the ECG recording, mean heart rate and RR-interval (RRI) in time domain were calculated from a user-defined stationary region, free from ectopic beats. The stationary time series of RRI were then subjected to power spectral density analysis in frequency domain. Modified covariance autoregressive modeling with a model order selection using Akaike Information Criterion (19) was used for spectral analysis. Total power, i.e., variance, of RRI variability was generated after linear detrending of the signals. The powers of RRI signals in the two frequency bands [high frequency, HF (0.15-0.40 Hz) and low frequency, LF (0.07-0.15 Hz)] (20) were calculated by integration over the corresponding frequency bands. The ratio of LF and HF powers (LF/HF) was used as an index of sympatho-vagal balance (21).

**Statistical Analysis**

The demographical data between the age
groups was tested by Student’s t-test (Excel 2000 for Windows) and Fisher’s exact test. Statistical analysis for HRV data (SAS 8.2. for Windows) was made in three steps. First: The influence of repeated hyperbaric oxygen treatments on HRV response to hyperbaric oxygenation was evaluated with 2-way analysis of variance (ANOVA; treatment sessions and measurement occasions as within factors). Second: Because the HRV response did not vary statistically significantly between the repeated exposures, the analysis was continued to measure the effect of age on HRV response during HBO2 treatments. To analyze the effect of age a 2-way ANOVA (measurement occasion as within factor and age as between factor) was done for calculated mean values of measurement occasions. The measurement occasions of all sessions were analyzed together. Finally, consecutive measurement occasions were compared with 1-way ANOVA for the variables that did not differ significantly between the age groups. P-values were corrected using the Bonferroni method. The differences were regarded statistically significant if p<0.05.

RESULTS

The two age groups differed from each other demographically. The older group weighted statistically significantly more (p=0.012, table I). The response to hyperbaric oxygenation of any of the measured variables did not differ significantly between repeated treatments.

Mean heart rate decreased markedly in both age groups (p<0.001) during the treatments (Fig. 2, Table II). Mean heart rate decreased more but stayed at significantly higher level in the younger age group during the treatments (p=0.041). In the older group, mean heart rate returned to baseline level after the treatment but in the younger group it was lower after the exposure than before. The changes in heart rate were significantly different between the groups (p<0.001 for interaction of age and measurement occasion).

**Fig. 2.** Responses in mean heart rate during repeated HBO2 treatments in younger (< 50 years, squares; □) and older (> 50 years, triangles; *) patients. The curves indicate mean heart rate during the chosen treatment sessions as follows: first (black); second (red); third (blue); fourth (yellow) and fifth (grey). Mean heart rate of the younger group was higher during all treatments. Also, the response between the age groups differed.

Mean total power increased up to 5-fold (p<0.001) during the treatments, but returned to baseline levels after the treatments (Table II). Total power stayed at higher level in the younger group compared to the older group during the treatments (p=0.004), but the pattern of increase in total power was similar in the two age groups (p=0.510).
Table 2. The effects of hyperbaric hyperoxia on heart rate and selected heart rate variability indices. Data are presented as means (SD).

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<th>Measurement occasion</th>
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<th>Age by measurement occasion interaction</th>
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<td>Heart rate (&lt;50)</td>
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<td>Heart rate (&gt;50)</td>
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Statistical analysis (ANOVA)

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<td>LF/HF Ratio (&gt;50)</td>
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Abbreviations: HF power = high frequency power, LF power = low frequency power, ATA = atmospheric pressure, ANOVA = analysis of variance for repeated measurements
Mean HF power increased markedly during the treatments (p<0.001), but returned to baseline levels after the treatment (Fig. 3, Table II). HF power was at a higher level in the younger group than in the older group during the treatments (p=0.007), but the pattern of increase did not differ between the age groups (p=0.580).

LF power increased in both age groups significantly during the treatments (p<0.001), but it was at a significantly higher level in the younger group (p=0.001, table II). The response of LF power to hyperbaric oxygenation did not differ between the age groups (p=0.644). Mean LF/HF ratio decreased significantly (p<0.001) during the treatments (Fig. 4, Table II). There was no difference either in the level or response to the treatment between the age groups (p=0.378 and p=0.519, respectively).

**Time Course of Changes**
The differences between the baseline and the first measurement at 2.5 ATA were significant in all variables.

Also, comparisons between the last measurement at 2.5 ATA and the measurement at 1.6 ATA and between the measurement at 1.6 ATA and the measurement occasion after decompression were significant in all variables.

**Fig. 3.** Responses in mean HF power during repeated HBO2 treatments. HF power increased significantly in both age groups during the treatments. However, there was no difference in HF response between the groups. See Fig. 2 for symbols.

**Fig. 4.** Responses in mean mean LF/HF ratio during repeated HBO2 treatments. Graph A refers to the younger group and graph B to the older group. Mean LF/HF ratio and the response to the treatments did not differ significantly between the groups. See Fig. 2 for symbols.
DISCUSSION

The main findings of this study were: 1. Repeated hyperbaric oxygen treatments do not change vagal response to hyperbaric oxygenation, 2. HF power and thus the vagal response to hyperbaric oxygenation appears to be preserved with aging even if the level of HF power is higher in younger persons, and 3. vagal tone increases during compression, stays relatively stable at steady partial pressure of oxygen at 2.5 ATA and decreases gradually towards baseline during decompression.

In our previous studies, we found that a single HBO₂ treatment increased temporarily vagal tone, as measured by different HRV indexes (1,2). For clinical purposes, series of 2-45 HBO₂ treatments are given. Theoretically, there are two different ways how repeated hyperbaric oxygen exposures can affect autonomic nervous system function. First, increased expression of endothelin-coding gene related to increased endothelin-1 secretion caused by repeated HBO₂ treatments (8) can cause long-lasting mild increase in blood pressure and thus increase vagal tone during the treatment period. Second, direct CNS toxicity of hyperbaric oxygen detected in animal models and in vitro (22-23), can cause changes in autonomic function, because autonomic reflexes are under central control (24). However, in this study, vagal response to hyperbaric oxygenation did not change during a series of 15 treatments in the present study.

Aging diminishes heart rate variability and especially high frequency power (13-17). In the present study, subjects who were younger than 50 years had statistically significantly higher mean HF power levels at the baseline and during the exposure at 2.5 ATA than the subjects older than 50 years. There were, however no statistically significant difference between the measurement and age interaction even though the level of the mean values was different. Proportional increase in mean HF power in the older group was 3.5 fold from the mean baseline compared to the increase of approximately 4.5 fold in the younger group (Table II). Analysis of variance evaluates the difference in response for the interaction between the within and between factors. In both groups, the change in HF and total power was a similar increase of almost equal proportional magnitude compared to the baseline.

Preservation of vagal responsiveness to HBO₂ in advanced age is in concordance with findings of Reardon and Malik (25). They found using long-term time domain recordings that short-term heart rate variability measured by RMSSD (square root of the mean squared differences of successive normal-to-normal RR intervals) does not differ between ages. They concluded that responsiveness of autonomic activity to external stimuli decreases with age but fast vagal modulations are preserved. In their study, White and co-workers found that in the elderly, mean decrease in heart rate in response to phenylephrin infusion did not differ from the response of young subjects (26).

In this study, vagal response to HBO₂ treatments did not change during a series of 15 treatments in the present study. Comparisons between consecutive measurements were not done. In the present study, significant increases in vagal activity were detected immediately after the compression to 2.5 ATA. One reason for this could be vasoconstriction induced by increasing partial pressure of oxygen (5,6), causing a reflexory increase in vagal tone. Correspondingly, the LF/HF ratio increased
and HF power decreased significantly during decompression, reflecting decreased vagal activity. These results show that the main stimuli to changes in vagal tone in this study are compression and decompression of the chamber.

There is one confounding factor that could influence vagal activity during the study period. This is the oxygen-breathing system (Built-In-Breathing-System, BIBS) that was used during the treatments. The mask creates some resistance to breathing, which might activate the stretch receptors of the thoracic cage. However, in our previous study with healthy volunteers, the mask did not influence HF power significantly (1).

**CONCLUSIONS**

Repeated hyperbaric oxygen treatments do not influence on the response of autonomic nervous system during hyperbaric oxygen exposures. Basic vagal activity in older persons is lower during hyperbaric oxygen exposure, but vagal response to the exposure seems to be preserved. The changes in vagal activity are directly associated with changes in ambient pressure and partial pressure of oxygen.
REFERENCES
