Hyperoxia and the cardiovascular system: experiences with hyperbaric oxygen therapy

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Abstract

Hyperoxia has been described to induce bradycardia by direct stimulation of the parasympathetic nervous system. Also, hyperoxia has been found to increase blood pressure by an elevation of vascular resistance. However, the latter effect itself would induce bradycardia by baroreceptor stimulation. This single-arm monocentric retrospective study aims to evaluate the correlation between these effects by investigating the relation between oxygen (O_2) administration and heart rate over time. Data were collected from 23 patients without cardiovascular problems undergoing hyperbaric oxygen therapy (2.4 bar) retrospectively. During single oxygen bouts, transcutaneously measured partial pressure of O_2 was increased. During this surge of oxygen pressure, the arterial blood pressure was increased while the heart rate was decreased. Respiration rate was maintained independently from breathing 100% O_2 or air. During single oxygen bouts, the half-life of transcutaneously measured partial pressure of O_2 was 5.4 ± 2.1 mmHg/s, and the half-life of heart rate was 0.45 ± 0.19 beats/min. It has been shown that hyperbaric oxygen therapy increases the transcutaneously measured partial pressure of O_2. This increase was rather fast, followed by a rather slow decrease in HR. This finding does not support direct vagal activation. Heart rate is not decreased due to a direct vagal activation during hyperbaric oxygen therapy. Our single-arm, retrospective study has additionally confirmed that oxidative stress injures the endothelium, and the reduced endothelial-derived vasodilators cause vasoconstriction. As a consequence, blood pressure increases, and heart rate is then further decreased via the baroreceptor reflex.

Key words: autonomic nervous system; blood pressure; endothelium; heart rate; hyperbaric oxygen therapy; oxidative stress; vascular resistance; wound healing

doi: 10.4103/2045-9912.337997
How to cite this article: Schipke JD, Muth T, Pepper C, Schneppendahl J, Hoffmanns M, Dreyer S. Hyperoxia and the cardiovascular system: experiences with hyperbaric oxygen therapy. Med Gas Res. 2022;12(4):153-157.

Introduction

Hyperoxia occurs when organs or cells are exposed to an excess supply of oxygen (O_2) or higher than the normal partial pressure of oxygen. It is unlikely that hyperoxia had much impact during the evolution of vertebrates, and the effects of hyperoxia on the human body remain relatively unclear.[1]

Over the last 50 years or so, hyperoxia has been employed in a wide range of clinical interventions and pathologies.[2] In addition, hyperoxic conditions develop in the context of diving and hyperbaric oxygen (HBO) therapy.

Adverse effects of oxidative stress on the central nervous system and the lungs are well described. Also, adverse effects to the eyes,[3] to the DNA of isolated lymphocytes,[4] and to *in vivo* DNA of leucocytes[5] were described.

While the results of the studies mentioned above are consistently accepted, the effect of hyperoxia on the autonomous nervous system is discussed controversially. On the one hand, hyperoxia is described to induce bradycardia by direct stimulation of the parasympathetic nervous system.[6,7] On the other hand, hyperoxia is described to increase vascular resistance,[8] thereby increasing blood pressure. With an intact baroreceptor reflex, bradycardia will be induced.[9,10]

The purpose of this retrospective study was to help answer the question, whether hyperoxia affects the heart rate (HR) directly or indirectly. This was done by investigating the scheduled course between partial oxygen pressure (pO_2), HR, and blood pressure.

Subjects and Methods

Patients

Data from 23 patients (13 females) were collected during HBO treatment. The age of the patients ranged from 22 to 79 years. Included in this study were routine patients that did not suffer from cardiovascular problems as hypertension but underwent HBO treatment for other reasons, predominantly for wound healing problems and tinnitus. Excluded from the study were patients having major problems with pressure equalization. The trial flow chart is shown in **Figure 1**.

This single-arm, retrospective study was registered in the former study register of the University Hospital Düsseldorf (ID 2020-05-5532) and approved by the Ethical Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (Study No. 2020-998) on August 18, 2020.

HBO treatment scheme

In line with the diagnoses of our patient group, the problem wounds scheme was employed. Thus, all patients followed the protocol outlined in **Figure 2**, i.e., they all spent 135 minutes

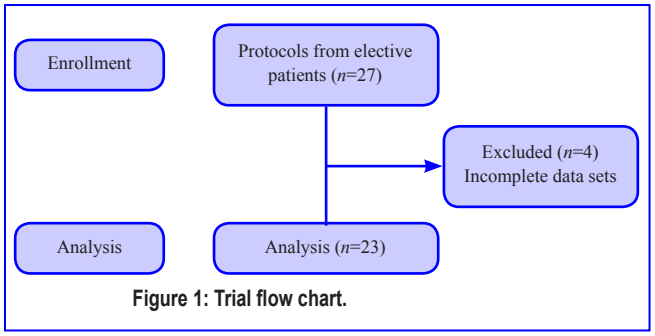

Figure 1: Trial flow chart.

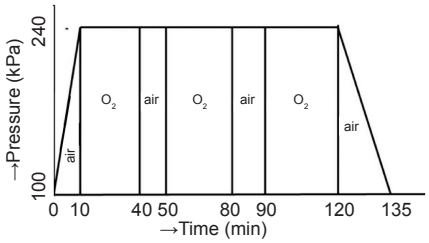

Figure 2: Hyperbaric oxygen therapy scheme.

in the HBO chamber. Using breathing masks, 100% oxygen was administered at a pressure of 2.4 bar (= 240 kPa) (three times 30 minutes with 10-minute air breakes). At that treatment pressure, pO_2 within the chamber was 0.5 bar (= 50 kPa).

Transcutaneous pO_2

The transcutaneous pO_2 ($tcpO_2$) was assessed continuously using oximetry (TCM4, Radiometer, Copenhagen, Germany).[11] The $tcpO_2$ electrode was attached to the supraclavicular area. If needed, a second electrode was attached close to the healthy margin of a wound. The electrodes are sensitive to only oxygen that generates a current proportional to the pO_2.[12] The electrodes were heated throughout to 44°C as hyperthermia creates underlying capillary vasodilatation allowing more oxygen diffusion.[13] $TcpO_2$ measurement is widely applied for the evaluation of chronic limb-threatening ischemia[14] but also to predict responders to hyperoxia.[15] The minimum pO_2 value at the onset of 100% O_2 administration was subtracted from the maximum O_2 value before an air break. The result was divided by two and that value was added to the value at the onset (= ΔpO_2). The time between the onset of O_2 administration and the time of ΔpO_2 was termed Δt. The ratio between ΔpO_2 and Δt represents the pO_2 half-life. The half-life of the HR was determined analogously.

Electrocardiogram and arterial blood pressure

An electrocardiogram (Haux-Life-Support, Karlsbad, Germany) was assessed using three leads that were attached to the chest. The best signal was used to calculate HR. The $tcpO_2$ and the HR are presented in the individual tracings, respectively (**Figures 3** and **4**), and the $tcpO_2$ half-life and the HR were assessed from these tracings. Finally, the arterial blood pressure was measured in 5-minute intervals using an inflatable cuff connected to a blood pressure monitor (Haux-Life-Support) (**Figure 5**).

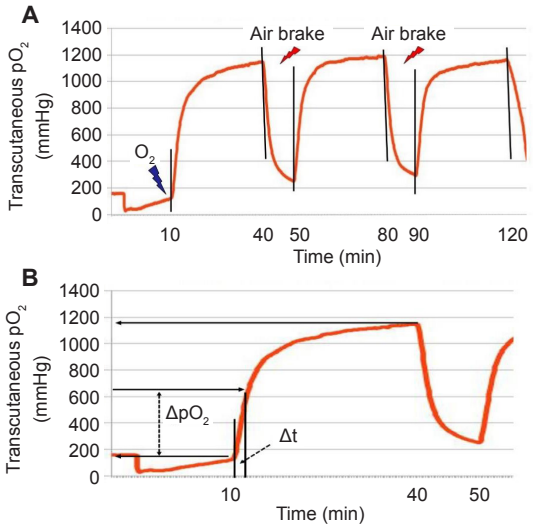

Figure 3: Time course of the transcutaneous partial oxygen pressure (pO_2). Note: (A) Time course of the transcutaneous pO_2 during an entire problem wound scheme session in one patient. (B) Determination of the slope of the pO_2 signal by calculating the pO_2 half-life. Horizontal arrows, Bottom: minimal pO_2 at the onset of 100% O_2-breathing. Middle: mean pO_2 between maximal and minimal values. Top: Maximum pO_2 before the first air break. Δt: Time from minimal pO_2 at the onset of 100% O_2 and mean increase. This variable rapidly increases after patients start breathing 100% oxygen via their masks.

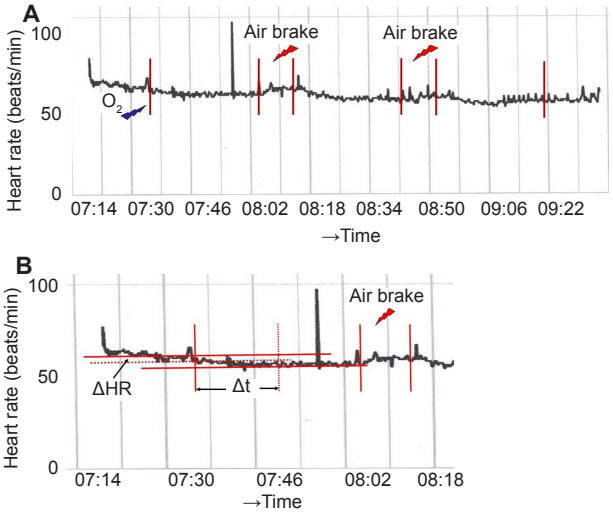

Figure 4: Original tracing of the time course of the heart rate (HR). Note: (A) Time course of the HR during an entire problem wound scheme session in one patient. (B) Determination of the slope of the HR signal by calculating the HR half-life. This variable slowly decreases after patients start breathing 100% oxygen via their masks.

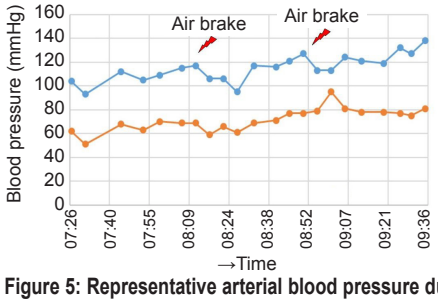

Figure 5: Representative arterial blood pressure during the wound scheme protocol

Respiration

To account for respiratory effects, the respiration rate during both air and O_2 intervals was assessed in a blinded manner on three patients that kept their masks on during an air break.

Sample size

The sample size was calculated based on expected O_2-induced changes in the HR. If the expected HR decreases were moderate (Cohen's $\delta = 0.6$), a power of 0.8, and a significance level of 0.05 were chosen, then the sample size of $n = 19$ resulted.[16]

Statistical analysis

MicroSoft Excel 2007 (MicroSoft, Redmond, WA, USA) was used for calculations and creating tables and graphs. HR between the onset and the end of the HBO treatment was compared using the one-side *t*-test for paired samples and continuous variables (SPSS Statistics 24, IBM, Armonk, NY, USA). Differences were considered significant at the $P \leq 0.05$ level. Results are presented as mean ± standard deviation (SD). To assess the effect size, Cohen's δ was calculated.

RESULTS

Transcutaneous pO_2

During single oxygen bouts, $tcpO_2$ increased from 101 ± 46 to 1089 ± 178 mmHg, and $\Delta tcpO_2$ was equal to 5.4 ± 2.1 mmHg/s.

Heart rate

Within a single bout of oxygen, HR decreased from 71.7 ± 15.2 to 63.6 ± 13.5 beats/min ($P < 0.05$; Cohen's d = 0.58), and ΔHR was equal to –0.45 ± 0.19 beat/min^2, i.e., the decrease in HR was drastically slower than the increase in the $tcpO_2$.

Blood pressure

Both systolic and diastolic arterial blood pressure increased from 115 ± 15 to 148 ± 21 mmHg (31%) and from 62 ± 8 to 81 ± 11 mmHg (31%), respectively during the entire HBO session. This entire pressure increase was not linear, but the pressure decreased shortly during both air breaks ($n = 8$).

DISCUSSION

It is the main finding of this retrospective study that $tcpO_2$ rapidly increases following exposure to HBO while the HR decreases rather slowly.

It is well established that respiration rate and HR are synchronized: cardiorespiratory synchronization.[17,18] It is also established that breathing oxygen exerts bradycardia.[6,19] To evaluate whether or not breathing oxygen would affect the respiration rate and thereby the HR in this study, the breathing gas (air/oxygen) was exchanged in a blinded manner in one of the 30-minute cycles. This maneuver was done in only three patients to not endanger the effects of HBO therapy. No obvious HR differences were found between the breathing of normal air compared to oxygen.

While the half-life of the increase in the $tcpO_2$ was roughly 5 mmHg/s rather short, the half-life of the decrease in HR was roughly 0.5 beats/min rather long. This means that $tcpO_2$ increased 600 times faster than HR decreased. Due to this huge difference, hyperoxia will not directly activate the parasympathetic system as previously reported.[19,20] It could, however, well be that those findings came about, after steady state conditions had established, i.e., sometime had elapsed after the onset of oxygen breathing. In case the increased vagal activity had been determined via indices of the HR variability,[21] it is remembered that indices of vagal activity can increase while HR decreases.[22]

It is well known that hypoxia is associated with vascular dilatation to secure sufficient oxygen supply. In turn, hyperoxia is associated with systemic vasoconstriction.[23,24] More precisely, arterioles in the peripheral microcirculation constrict with higher oxygen concentrations, e.g. during normobaric or hyperbaric oxygenation therapy.[25]

As a result, perfusion is reduced in most tissues.[26] This oxygen-induced vasoconstriction is thought to serve as a protective mechanism to reduce oxidative stress.[24,27] Although that topic is beyond the aim of this study, a minor excursion may be permitted: The mechanisms underlying the effect of hyperoxia are not fully understood.[28] Yet, increases in the contracting potential, decreases in the dilatating potential, or both have been suggested. One study favors the hypothesis that hyperoxic vasoconstriction is mediated by inhibition of prostaglandin synthesis.[28] Others suggest that reactive oxidative species are generated in the vessel wall[29] and rapidly react with nitric oxide[30,31] thereby reducing/inactivating the vasodilating potential.[32,33]

The hypothesis that the vasodilating nitric oxide potential is reduced is supported by data derived from scuba diving. Here, the pO_2 levels increase with the diving depth. As a result of the hyperoxic condition, the vasodilator capacity was reduced by about 95% after a dive.[34] For comparison: this value is comparable to patients having significant atherosclerosis.[35] Other studies,[36,37] as well as this study describe a decrease in the flow-mediated dilatation as well,[38] and yet another study reports significantly impaired vasodilation after diving that does not recover until the next dive.[39] Likewise, single air dives were also shown to reduce arterial endothelial function.[34,40] Seemingly, hyperoxia-associated formation of reactive oxygen species induces endothelial dysfunction[41] that can be attenuated using antioxidants.[42]

Although the hyperbaric chamber was used as an experimental model to investigate a physiological issue, the results might also have clinical importance. Since oxidative stress does contribute to the development of atherosclerosis,[43,44] patients that suffer from atherosclerosis should be monitored carefully when undergoing HBO therapy. This is of particular importance since atherosclerosis is a common comorbidity in diabetes.[45] Diabetic patients frequently undergo HBO therapy for the treatment of diabetic foot syndrome. It is also conceivable that the fitness of professional divers could be screened in a hyperbaric chamber to assess responses of hyperoxia toward blood pressure and electrocardiograms, because these divers will be confronted with elevated pO_2 levels both using open or closed-circuit breathing apparatuses.

Assessment of the blood pressure is not well tolerated by the patients inside the chamber. Thus, measurements were made only randomly in some patients. We are presenting pressure data from eight patients with typical reactions of the blood pressure towards hyperoxia. In line with the previous

literature,[46,47] systolic and diastolic pressures increased after the onset of O_2 breathing

Assessment of the arterial blood pressure via the inflatable cuff provides a limited temporal resolution, as the pressure was measured at five-minute intervals. Still, as the curve shape was of no importance, blood pressure values at all permitted a sound analysis.

One might consider that our results originated from a synergistic effect of hyperbaric and hyperoxic conditions. However, we exclude effects owing to increased pressure as it does not affect arterial blood pressure.[48-50]

We conclude that after administration of HBO, increases in the vascular tone lead to increases in blood pressure. In our patient group, blood pressure increases stimulated the baroreceptor reflex thereby decreasing the HR. Thus, because of the large differences in the temporal course between $tcpO_2$ and HR responses, hyperoxia will unlikely directly activate the parasympathetic system.

Acknowledgements
We greatly appreciate the comprehensive cooperation with our patients.

Author contributions
JDS and MH: developed the concept and design of this study; TM: performed the statistical analyses; CP: did multiple proofreading and correct usage of the English language; JS: covered the medical portion of the study: patient care, information on the current approach; MH: took care of providing the tools for measurements, collected the data; SD: secured the correct execution of the HBO treatment prerequisites.

Conflicts of interest
There is no conflict of interest to declare for any of the authors.

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Date of submission: December 12, 2020
Date of decision: January 20, 2021
Date of acceptance: February 15, 2021
Date of web publication:April 17, 2022