Hydroxina 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 (O2) 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 O2 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% O2 or air. During single oxygen bouts, the half-life of transcutaneously measured partial pressure of O2 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 O2. 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

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INTRODUCTION

Hyperoxia occurs when organs or cells are exposed to an excess supply of oxygen (O2) 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 leukocytes5 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 (pO2), 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...
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 breaks). At that treatment pressure, pO₂ within the chamber was 0.5 bar (= 50 kPa).

**Transcutaneous pO₂**

The transcutaneous pO₂ (tcpO₂) was assessed continuously using oximetry (TCM4, Radiometer, Copenhagen, Germany). The tcpO₂ 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 pO₂. The electrodes were heated throughout to 44°C as hyperthermia creates underlying capillary vasodilatation allowing more oxygen diffusion. The minimum pO₂ value at the onset of 100% O₂ administration was subtracted from the maximum O₂ value before an air break. The result was divided by two and that value was added to the value at the onset (ΔpO₂). The time between the onset of O₂ administration and the time of ΔpO₂ was termed Δt. The ratio between ΔpO₂ and Δt represents the pO₂ 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 tcpO₂ and the HR are presented in the individual tracings, respectively (Figures 3 and 4), and the tcpO₂ 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).
Respiration
To account for respiratory effects, the respiration rate during both air and O₂ 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 O₂-induced changes in the HR. If the expected HR decreases were moderate (Cohen’s δ = 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 ≤ 0.05 level. Results are presented as mean ± standard deviation (SD). To assess the effect size, Cohen’s δ was calculated.

RESULTS
Transcutaneous pO₂
During single oxygen bouts, tcpO₂ increased from 101 ± 46 to 1089 ± 178 mmHg, and ΔtcpO₂ 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 δ = 0.58), and AHR was equal to –0.45 ± 0.19 beat/min², i.e., the decrease in HR was drastically slower than the increase in the tcpO₂.

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 tcpO₂ 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 tcpO₂ 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 tcpO₂ increased 600 times faster than HR decreased. Due to this huge difference, hyperoxia will not directly activate the parasympathetic system as previously reported.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.³⁵

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.²⁷ 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 wall²⁹ and rapidly react with nitric oxide³⁰,³¹ 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 pO₂ levels increase with the diving depth. As a result of the hyperoxic condition, the vasodilator capacity was reduced by about 95% after a dive.³³ 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 dysfunction⁴¹ 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,³³,³⁴ 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.³⁵ 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 pO₂ 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, systolic and diastolic pressures increased after the onset of O₂ 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.

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 tcPO₂ and HR responses, hyperoxia will unlikely directly activate the parasympathetic system.

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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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REFERENCES
1. Winkleswki PJ, Kot J, Frydrychowski AF, Nuckowska MK, Tkachenko Y. Effects of diving and oxygen on autonomic nervous system and cerebral blood flow. *Diving Hyperb Med.* 2013;43:148-156.
2. Brugiaux JV, Coombs GB, Barak OF, Dujic Z, Sekhon MS, Ainslie PN. Highs and lows of hyperoxia: physiological, performance, and clinical aspects. *Am J Physiol Regul Integr Comp Physiol.* 2018;315:R1-r27.
3. Williams DL. Oxidative stress and the eye. *Vet Clin North Am Small Anim Pract.* 2008;38:179-192, vii.
4. Gröger M, Oter S, Simkova V, et al. DNA damage after long-term repetitive hyperbaric oxygen exposure. *J Appl Physiol* (1985). 2009;106:311-315.
5. Dernog C, Hartmann A, Frey G, Speit G. Detection of DNA damage after hyperbaric oxygen (HBO) therapy. *Mutagenesis.* 1996;11:605-609.
6. Lund V, Kentala E, Scheinin H, Klossner J, Sariola-Heinonen K, Jalonen J. Hyperbaric oxygen increases parasympathetic activity in professional divers. *Acta Physiol Scand.* 2000;170:39-44.
7. Shibata S, Iwasaki K, Ogawa Y, Kato J, Ogawa S. Cardiovascular neuroregulation during acute exposure to 40, 70, and 100% oxygen at sea level. *Aviat Space Environ Med.* 2005;76:1105-1110.
8. Stirban A, Lentroti S, Nandrea S, Pop A, Tsoeoe D, Scherbaum WA. Functional changes in microcirculation during hyperbaric and normobaric oxygen therapy. *Undersea Hyperb Med.* 2009;36:381-390.
9. Bak Z, Sjöberg F, Rousseau A, Steinvall J, Janerot-Sjöberg B. Human cardiovascular dose-response to supplemental oxygen. *Acta Physiol (Oxf).* 2007;191:15-24.
10. Smit B, Smulders YM, van der Wouden JC, Oudemans-van Straaten HM, Spoelstra-de Man AME. Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis. *Crit Care.* 2018;22:45.
11. Heyboer M, Byrne J, Pons P, Wolner E, Seargent S, Wojcik SM. Use of in-chamber transcutaneous oxygen measurement to determine optimal treatment pressure in patients undergoing hyperbaric oxygen therapy. *Undersea Hyperb Med.* 2018;45:389-394.
12. Clark LC, Jr. Continuous measurement of circulating glucose using the transcutaneous PO₂ electrode. *Birth Defects Orig Artic Ser.* 1979;15:39-42.
13. Huch R, Huch A, Lübbers DW. Transcutaneous measurement of blood PO₂ (tcPO₂) -- Method and application in perinatal medicine. *J Perinat Med.* 1973;1:183-191.
14. Leenstra B, Wijnand J, Verhoeven B, et al. Applicability of Transcutaneous Oxygen Tension Measurement in the Assessment of Chronic Limb-Threatening Ischemia. *Angiology.* 2020;71:208-216.
15. Sheffield PJ. Measuring tissue oxygen tension: a review. *Undersea Hyperb Med.* 1998;25:179-188.
16. Hemmerich W. Effektstärkere. https://matheguru.com/stochastik/effektstarke.html. Accessed by September 4, 2021.
17. Bainbridge FA. The relation between respiration and the pulse-rate. *J Physiol.* 1920;54;192-202.
18. Schäfer C, Rosenblum MG, Kurths J, Abel HH. Heartbeat synchronization with ventilation. *Nature.* 1998;392:239-240.
19. Daly WJ, Bondurant S. Effects of oxygen breathing on the heart rate, blood pressure, and cardiac index of normal men--resting, with reactive hyperemia, and after atropine. *J Clin Invest.* 1962;41:126-132.
20. Kot J, Síčko Z, Wozniak M. Oxidative stress during oxygen tolerance test. *Int Marit Health.* 2003;54:117-126.
21. Lund VE, Kentala E, Scheinin H, et al. Heart rate variability in healthy volunteers during normobaric and hyperbaric hyperoxia. *Acta Physiol Scand.* 1999;167:29-35.
22. Tsuji H, Venditti FJ, Jr., Manders ES, et al. Determinants of heart rate variability. *J Am Coll Cardiol.* 1996;28:1539-1546.
23. Gole Y, Gargne O, Coulange J, et al. Hyperoxia-induced alterations in cardiovascular function and autonomic control during return to normoxic breathing. *Eur J Appl Physiol.* 2011;111:937-946.
24. Jackson WF. Arteriolar oxygen reactivity: where is the sensor and what is the mechanism of action? *J Physiol.* 2016;594:5055-5077.
25. Kislevsky M, Mardimae A, Slessarev M, Han J, Fisher J, Hudson C. Retinal arteriolar and middle cerebral artery responses to combined hyperoxic/hyperoxic stimuli. *Invest Ophthalmol Vis Sci.* 2008;49:5503-5509.
