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Chapter 3

Adaptations and Disturbances of Physiological Functions in Extreme Hyperbaric Environments

Olga Sergeevna Alekseeva,
Alexander Ivanovich Krivchenko and
Ivan Timofeyevich Demchenko

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Abstract

Academician E.M. Kreps founded the Laboratory of Hyperbaric Physiology in 1960. Heads of the Laboratory were G.L. Zaltsman (1960–1972), A.I. Selivra (1972–1975), I.A. Aleksandrov (1975–1982) and I.T. Demchenko (1983–2009). In 2009, the Laboratory was merged with the Laboratory of Respiratory Physiology (A.I. Krivchenko). For more than five decades, Hyperbaric Laboratory has conducted basic and applied researches dealt with CNS oxygen toxicity, the high pressure nervous syndrome and nitrogen narcosis. Main achievements of basic researches are as follows: identified key mechanisms of adaptive responses of CNS and cardiorespiratory systems to breathing gas mixtures at high pressure, neurophysiological mechanisms of CNS oxygen toxicity and high pressure nervous syndrome, and pathogenesis of nitrogen narcosis. Main achievements of the translation of hyperbaric researches are as follows: new technology for 1000 m dive of animals (monkeys) using the gas mixture (He-N_2-O_2), new compression and decompression profiles for free escape of monkey from a depth of 700 m, use preconditional hypoxia and hyperthermia for the protection of nitrogen narcosis. Currently, main researches are focusing on the evaluation of molecular and cellular mechanisms of biological responses to extreme hyperbaric environments.

Keywords: hyperbaric oxygen, high pressure nervous syndrome, nitrogen narcosis, CNS oxygen toxicity, reactive oxygen and nitrogen species, oxidative stress, hyperoxic vasoconstriction, hyperoxic baroreflex

1. Introduction

Hyperbaric physiology researches have been conducted at the Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences (IEPhB) during last 60 years and

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can be divided into three periods. The initial stage of hyperbaric studies is directly linked to academician Leon A. Orbeli (founder of IEPhB), who had great interest in scientific and practical aspects of the diving. Since 1935, he headed the commission for a coordination of technical projects aimed on the development of new technology for underwater diving in the USSR (former Soviet Union). After the World War II, these works were intensified markedly in order to improve the technology for raising the sunken ships, cleaning rivers, lakes and bays, and building new bridges. At that time, the breathing oxygen-helium mixture was introduced in deep sea diving. It was necessary to examine the biological effects of the helium and to develop the decompression tables for saturation diving. In 1956, academician Leon Orbeli founded the Institute of Evolutionary Physiology and organized a small group to study the biological effects of inert gases under pressure. According to Orbeli's conception, hyperbaric biological research in addition to practical aspects will help to substantiate the role of extreme environmental factors in the evolution of physiological functions. In 1960, new director of the IEPhB academician Evgeny M. Kreps organized the Laboratory for Environmental Physiology and invited Henry L. Saltzman, a former naval doctor, to conduct physiological studies in hyperbaria. For next 8 years, the world standard results were obtained regarding the physiological responses to oxygen, helium, and nitrogen under high pressure [1].

By the mid 1960s, a new trend in the hyperbaric researches has been appeared. George F. Bond (US NAVY officer) offered a new technology that consists of the pressure chamber is installed on the board of ship, and divers living in hyperbaric conditions for several weeks are delivered to the sea bottom by special bell with subsequent return to the pressurized chamber. Academician E.M. Kreps has initiated a discussion of novel diving technology at Russian Academy of Sciences, which resulted in a new building, the installation of hyperbaric facilities and substantially expanded stuff. Since then, the second phase of hyperbaric researches began in the Institute. Animals (guinea pigs, rats and rabbits) were exposed to normoxic helium-oxygen gas up to 41 ATA for 2–3 weeks following physiological and morphological examinations. Many experts were involved in these studies, and the results of 10 years of experimental work were summarized in the book [2]. From 1972 to 1983, experimental studies were focused on the biological effects of indifferent gases, toxic effects of hyperbaric oxygen and morphological changes and functional disorders after prolonged hyperbaric exposures. At the same time, academician E. Kreps initiated the construction of new hyperbaric facilities. In 1983, the Laboratory was headed by Professor Ivan T. Demchenko. One year later, a new hyperbaric complex "KIZH-100" has been put into operation. KIZH-100 was specially designed for hyperbaric studies on animals when breathing gas mixtures are at pressures up to 101 ATA (atmospheres absolute). The number of staff of Hyperbaric Laboratory has been increased to more than 70 specialists in 1985. It has been purchased and installed world-class equipment for physiological and biochemical studies on animals and for the efficient operation of chambers. The main subject for hyperbaric studies were the monkeys (Macaca irus). In the short time, new approaches and methods were developed for experiments on monkeys with chronically implanted electrodes and probes. The continuous exposure of monkeys in helium-nitrogen-oxygen mixtures under high pressure was up to 5 weeks. The focus of the research was to explore the possibility of 1000 m diving with a protection of the high pressure nervous syndrome. The results were published by Russian Physiological Journal [3] and later in the Proceeding of III International Meeting "High Pressure

Biology," Durham, USA, 1993 [4] and in the V International Meeting "High Pressure Biology and Medicine," St. Petersburg, Russia, 1997 [5]. The experimental results obtained in KIZH-100 remain unique in the international research practice. Unfortunately, the economic situation in Russia since the 1990s did not allow continuing saturation diving studies.

The third period of hyperbaric researches in IEPhB started since 1991. Because of limited funding, the chamber saturation diving studies were discontinued. Main efforts have been directed to study cellular and molecular mechanisms of action of helium, nitrogen and oxygen under pressure. Valery B. Kostkin evaluated the molecular effects of hyperbaric environmental factors [6]. Alexander N. Vetosh and Olga S. Alekseeva studied the biological effects of hyperbaric nitrogen at normoxic and hypoxic conditions [7–10]. Hyperbaric studies in the Institute have been supported by the Foreign Members of the Russian Academy of Sciences, Professor Peter B. Bennett and Professor Claude A. Piantadosi (Duke University, Durham, USA). Important support for hyperbaric research was provided by its former employees: D.N. Atochin (Harvard University, Boston, USA) and D.R. Gutsaeva, (Medical College of Georgia, Augusta, USA). Long-time cooperation with American colleagues has been productive in studying molecular mechanisms of hyperbaric oxygen toxicity.

2. CNS O_2 toxicity

Over the past 50 years, Hyperbaric Physiology Lab has carried out basic researches to explore mechanisms by which hyperbaric oxygen (HBO_2) elicits CNS O_2 toxicity. The objectives of these studies were: (1) to determine the temporal and spatial profiles of reactive oxygen and nitrogen species (RONS) in the brain during the development of HBO_2-induced seizures; (2) to evaluate the physiological and pathological responses to HBO_2 related to oxygen seizures development and (3) to identify the crucial large-scale sites for CNS O_2 toxicity. Achievements of these studies were published (see References) and are briefly described here as follows:

(1) Concise accomplishments of studies. We have confirmed and expanded the concept that primary HBO_2-derived originators initiated toxic effects on CNS are reactive oxygen and nitrogen species (RONS). We measured RONS ($^{\bullet}O_2^-$, OH^-, H_2O_2, $NO^{\bullet}$, and $ONOO^-$) in the brain during HBO_2 exposures at 5–6 ATA and found their excessive production and progressive accumulation, as a function of the inspired oxygen partial pressures and the time of exposure [11–13]. We clarified that one root component of RONS is superoxide anion excessively produced in HBO_2 as a by-product of the nonspecific transfer of electrons to O_2 by either mitochondrial electron transport proteins or by non-mitochondrial enzymes. Brain H_2O_2 and OH^- levels increased in HBO_2 as a result of excessive $^{\bullet}O_2^-$ production and superoxide dismutase (SOD) and catalase activity [13]. Nitric oxide ($NO^{\bullet}$) is the other root component of RONS excessively produced in HBO_2 by L-arginine biotransformation involving endothelial and neuronal NOS, as demonstrated on knock-out mice [14]. HBO_2 stimulates the production of $^{\bullet}O_2^-$ and $NO^{\bullet}$ leading to an increase in peroxynitrite ($ONOO^-$) formation prior to seizures. Neuronal NOS-derived $NO^{\bullet}$ generates the bulk of brain $ONOO^-$, which mediates neurotoxic effects of HBO_2 [13]. We also found different rates of $^{\bullet}O_2^-$ - and $NO^{\bullet}$ accumulation in the brain and showed that an emergence of $^{\bullet}O_2^-/NO^{\bullet}$ imbalance is crucial for oxygen seizures development [15]. $NO^{\bullet}$ is exquisitely sensitive to

inactivation by $^{\bullet}O_2^-$, and extracellular superoxide dismutase (SOD3) regulates $NO^{\bullet}$ bioavailability [15]. Thus, excessive formation and accumulation of RONS in the brain are inevitable in HBO_2 and can be considered as a trigger for the development of CNS O_2 toxicity.

(2) Concise accomplishments of studies. Physiological and pathological responses to HBO_2 have been determined as follows. CNS responds to HBO_2 by a progressive disruption of the brain's normal electrical activity finally manifested by generalizing EEG spikes [1, 16, 17]. The appearance of EEG spikes (seizures), as a sign of CNS O_2 toxicity, always followed by excessive RONS accumulation in the brain [11, 13]. Any interventions limiting RONS production or their scavenging prevented EEG seizures. For example, systemic nonselective NOS inhibition with L-NAME prevented O_2 seizures [16, 19], and the source of $NO^{\bullet}$-mediated HBO_2 seizures is neuronal NOS as demonstrated experiments on gene knockout ($nNOS^{-/-}$, $eNOS^{-/-}$ and $iNOS^{-/-}$) mice [13]. Transgenic mice with SOD3 overexpression showed higher susceptibility to HBO_2 than wild type demonstrating important role of $^{\bullet}O_2^-/NO^{\bullet}$ balance for CNS O_2 toxicity [15]. Thus, EEG spiking activity is mediated by RONS accumulation in the brain, and the hypersynchronization of neuronal firing signifies the brain overexcitation and impairment of CNS functions. CNS-derived somatic (motor) responses in dogs, cats, rabbits, rats and mice to HBO_2 are manifested by the progressive behavioral and motor disturbances such as intensive grooming, local jerks, "wet-dog" shakes, fast-running and finally tonic and clonic convulsions with the loss of consciousness. These disturbances correlated with specific EEG patterns and final convulsions always followed EEG spikes with short delay [1, 20]. Rats treated with myorelaxants (tubocurarine or pancuronium bromide) did not exhibit any motor responses in HBO_2 at 5 or 6 ATA but paroxysmal EEG activity has been manifested [16]. We think that any local or generalized motor jerks or convulsions (seizures) in HBO_2 are secondary to CNS dysfunction and not direct effects of hyperbaric oxygen on skeletal muscle. Supporting findings of this point is that systemic nonselective NOS inhibition with L-NAME prevented both EEG seizures and motor convulsions in HBO_2 [16, 19].

The lungs' responses to hyperoxia are O_2 pressure dependent. In $HBO_2 \leq 2.5$ ATA, motor convulsions or EEG seizures have never been observed at least for 16 h exposures [21]. Because the entire surface of the lung is directly exposed to the hyperoxic environment for many hours, the inflammatory responses are developed slowly with destruction of the alveolar-capillary barrier, edema, impaired gas exchange, respiratory failure and death. However, the lungs respond to O_2 at 5 or 6 ATA by acute damage [22]. Pulmonary damage, characterized by transpulmonary leakage of protein and focally distributed intra-alveolar hemorrhage, developed rapidly, and key factors for lung injury were left ventricular function impairment and abruptly elevated pulmonary venous pressure leading to the cardiogenic lung injury [22]. Systemic NOS inhibition protected against HBO_2-induced pulmonary damage in $eNOS^{-/-}$ and $iNOS^{-/-}$ mutants compared to that seen in wild-type (WT) mice, but $nNOS^{-/-}$ mutants were relatively protected [14]. Collectively, these findings demonstrate that neuronal NOS (nNOS) play a prevalent role in the development of HBO_2 pulmonary toxicity [19].

Responses of autonomic nervous system (ANS) to HBO_2 are O_2 partial pressure and time exposure dependent. When HBO_2 does not exceed 2.5 ATA (clinical HBO settings), the parasympathetic (vagal) activity dominates as indicated, a decrease in heart rate, cardiac output and respiration. In this case, ANS controls cardiovascular and pulmonary functions reflexively mainly through baroreflex activation triggered by a rise in arterial pressure due to hyperoxic

vasoconstriction [23]. Resulting afferent discharges from the arterial baroreceptors evoke central responses that suppress efferent sympathetic activity and augment parasympathetic outflow providing short-term adaptation to hyperoxic environments. HBO_2 exposures exceeding 3 ATA also initially exhibit prevalent vagal tone but then autonomic imbalance appears in favor of sympathetic activation and parasympathetic withdrawal. Progressively increased sympathetic outflow affects cardiac function and pulmonary hemodynamic, leading to lung injury [16].

Cardiovascular system responds to HBO_2 by systemic vasoconstriction, bradycardia, cardiac output reduction and redistribution of organ blood flow. Moderate HBO_2 (<2.5 ATA) induces cerebral vasoconstriction that is associated with increased $^{\bullet}O_2^-$ production and a decrease in $NO^{\bullet}$ availability around the vessel's smoth muscle. Hyperoxic vasoconstriction is attenuated in $SOD3^{+/+}$ mutant or eNOS-/- mice demonstrating critical role of $^{\bullet}O_2^-/NO^{\bullet}$ balance in cerebrovascular responses to HBO_2 [15]. Extreme HBO_2 (>3 ATA) induces biphasic CBF response: transient vasoconstriction followed by hyperemia [16–18]. HBO_2-stimulated $NO^{\bullet}$ production increased CBF and oxygen delivery prior to the appearance of EEG spikes. Transgenic $SOD3^{+/+}$ mice are more sensitive, while $eNOS^{-/-}$ mice are more resistant to HBO_2-induced seizures. HBO_2 seizures are associated with an increase in cerebral blood flow (CBF) that hastens the onset of convulsions through delivery of a toxic oxygen dose. Endothelial-derived $NO^{\bullet}$ has a principal contribution to the development of hyperemia preceding O_2 seizures.

(3) Concise accomplishments of studies. Hyperbaric studies have identified neuronal discharges related to HBO_2 seizures both in CNS and periphery. Earlier neurophysiological studies of CNS O_2 toxicity have shown that the development of oxygen EEG seizures is dynamic process that comprises three distinct stages. The first stage characterized by a formation of single unstable foci of neuronal excitation in subcortex centers (reticular formation, thalamus and hypothalamus), following the appearance of stable and multiple foci in mesodiencephalic parts of the brain during the preconvulsive second EEG stage [1]. Finally, in the third convulsive stage, the process terminates in a synchronization of paroxysmal EEG activity in all parts of the brain [1]. Stages in EEG seizures correlate with a balance between excitatory and inhibitory neurotransmission. Our work demonstrated that the brain excitability in HBO_2 is occurred first in subcortical structures after a significant reduction in extracellular GABA content and a minor increase in glutamate [25]. The Glu/GABA imbalance appears to be the critical trigger for the hypersynchronization of neuronal firing manifested as EEG spiking activity. CNS O_2 toxicity is linked also with the autonomic nervous system. Neuronal endings (receptors) stimulated or inhibited by an alteration in arterial PO_2, intravascular pressure and RONS in visceral tissues initiate three types of reflexes such as chemoreflex, baroreflex and cardiac sympathetic afferent reflex, by which ANS modulates brain excitation. We showed that afferent signaling from aortal and carotid baroreceptors normally restrain brain excitability, but in HBO_2 5 or 6 ATA, baroreflex is impaired and seizure latency shortened [24]. Cerebrovascular responses to HBO_2 affected by RONS are also critical contributors to CNS O_2 toxicity. Hyperoxic vasoconstriction decreases CBF and delays seizures, but cerebral hyperemia accelerates seizure development through the alterations of oxygen content delivery.

Thus, our studies outlined here dealt with temporal and spatial RONS accumulation in the brain during extreme hyperoxic exposures, RONS-related physiological and pathological responses in HBO_2 and CNS O_2 toxicity initiation and progression. However, an overall view

of CNS O_2 toxicity should also be comprised primary targets affected by RONS, in particular, their location, molecular structures and mechanisms of RONS-target interactions. All of these issues are remained still obscure and are the object of future studies.

3. High pressure nervous syndrome

High pressure nervous syndrome (HPNS) is a neurological disorder occurs when man dives below 150 m using helium-containing breathing gas. The severity of HPNS depends on the rate of descent, the depth and the percentage of helium. First noted in the 1960s, HPNS was referred as "helium tremor." Helium tremor was reported by G.L. Zaltsman in his human studies since 1961 [26]; however, this experimental fact was not available in English-language publications until 1967 [27]. At the same time, P. Bennett investigated helium tremor and widely described its patterns in 1965 [28]. The term "high pressure nervous syndrome" was introduced by Brauer in 1968 to describe the combined symptoms of tremor, electroencephalography (EEG) changes, and somnolence that appeared during a 362 m chamber dive [29, 30]. Main symptoms of HPNS in humans are dizziness, nausea, vomiting, postural and intention tremors, fatigue and somnolence, myoclonic jerking, stomach cramps, decrements in intellectual and psychomotor performance, poor sleep with nightmares, and increased slow wave and decreased fast wave activity on electroencephalogram [31]. In animal study, HPNS is manifested by tremor, myoclonic jerks, convulsions and specific patterns on EEG including spiking activity [31].

In Hyperbaric Physiology Lab, HPNS was evaluated in experiments on monkeys exposed to heliox at 101 ATA. Polarographic measurements demonstrated physiological levels of brain PO_2 at 101 ATA, when oxygen pressure in inspired gaseous mixture was 0.35 ATA, but decreased in normoxic heliox mixture [4, 5, 32]. Monkeys have shown the signs of HPNS (tremor upper limbs, specific EEG pattern) at 20–25 ATA but these symptoms were delayed by adding nitrogen (7 or 10%) to heliox. Using neuropharmacological approaches, Alexandr Sledkov has shown that HPNS manifestation is a result of an increase in brain excitability and the threshold for excitability, in various brain structures was different [33]. In rabbits, the lowest threshold response to increased helium pressure (about 15 ATA) had the limbic system and especially, the hippocampus [33]. This neuropharmacological study also showed that the adrenergic system does not involve in the HPNS pathogenesis, and its pharmacological activation does not lead to an alteration in functional activity of the subcortex. Activation of dopaminergic system prevents the development of HPNS manifestations. The serotonergic system may play a role in the mechanisms of HPNS manifestations, but the hypothesis of its compliance with the so-called "serotonin syndrome" has not been confirmed. Activation of the cholinergic system in hyperbaric conditions is very dangerous because of the sharp drop in the sensitivity thresholds and seizures. Apparently, HPNS implementation that takes place chiefly through N-cholinergic has confirmed the protective effect of N-cholinolytics, whose mechanism of action is based on reducing the level of hippocampal excitability, when the suppression of muscarinic receptor type comes with potentiation effect of HPNS. Activating the GABAergic system plays a protective role in HPNS. The mechanism of this protective effect of brake amino acids, possibly nonspecific and acts by enhancing inhibitory and excitatory inhibition processes in the CNS [33].

4. Hyperbaric nitrogen narcosis

Nitrogen narcosis is a condition that occurs in divers when breathing compressed air. Behnke et al. were the first to prove that the nitrogen in compressed air is responsible for signs and symptoms of narcosis, characterized as "euphoria, retardation of the higher mental processes and impaired neuromuscular coordination" [31]. When divers go below the depths of approximately 30 m, an increase in the partial pressure of nitrogen alters mental state similar to alcohol intoxication. This discovery stimulated a research of biological effects of hyperbaric nitrogen in Military Medical Academy in Leningrad, Russia [1]. In the Laboratory of Hyperbaric Physiology, nitrogen narcosis studies have been carried out since 1960s on three lines.

The first line of research concerned the electrophysiological analysis of CNS responses to hyperbaric nitrogen breathing. Zaltzman et al. investigated nitrogen, argon and helium narcosis in animals (dogs, rabbits and mice) by multichannel EEG recording. The results of EEG analysis in rabbits have shown that air pressure at 5 ATA suppressed the alpha wave but the beta activity increased. At pressure of 8 ATA, EEG exhibited slow theta activity, and an exposure to 12 ATA led to pronounced suppression of EEG activity [1]. The first EEG changes in the dogs were observed under the pressure of argon-5 atm, nitrogen-10 atm and helium-15 atm. The EEG patterns in hyperbaric argon and nitrogen were similar. The progression of EEG changes had three stages such as the depression of cortex activity, the domination of theta rhythm in the brain subcortex with the transition to delta activity, and the generalization of delta activity. At 35–40 atm of nitrogen, EEG generalization was unstable. A peculiar feature of the hyperbaric helium was that the theta rhythm in the brain stem structures developed and generalized without any preliminary suppression of the activity of cortex against a background of increased activity in the structures of the striatal system [1].

The second line of research concerned the determination of physiological and biochemical correlates of nitrogen narcosis. Alexander Vetosh has found behavior correlates in the progression of nitrogen narcosis [7]. He determined the patterns of motor activity and posture reflexes in mammals exposed to hyperbaric nitrogen and developed quantified scale of nitrogen narcosis levels. It was established experimentally that mammals can maintain vital functions while breathing oxygen-nitrogen mixtures at density up to 151 g/l. This is 117 times greater than the density of air. Continuing this line of research, O. Alekseeva et al. found the biochemical markers of the nitrogen narcosis. They also reported an increase in heat shock proteins of HSP-70 family in nitrogen narcosis stage [8, 9].

The third line of research concerned the mechanisms of nitrogen narcosis. According to the literature, the primary molecular mechanism of nitrogen narcosis is based on the ultrastructural changes in biological membranes of neurons in the brain due to excess dissolved nitrogen in their lipids [31]. A new suggestion about the mechanism of nitrogen narcosis was offered by A. Vetosh [7] and expanded by O. Alekseeva [8]. They showed a correlation between nitric oxide ($NO^{\bullet}$) formation, generation of heat shock proteins and the progression of nitrogen narcosis. They suggested that RONS formed in hyperbaric nitrogen are implicated in narcosis through the alteration in cellular function leading to motor, emotional and cognitive symptoms of nitrogen narcosis. Studies showed that L-NAME, nonselective inhibitor of NOS,

significantly delayed the nitrogen narcosis symptoms [7]. Hypoxic preconditioning before nitrogen diving mobilized HSP-70 family of proteins in blood and brain, and delayed the signs of nitrogen narcosis by 67% [8, 9]. Thus, the problem of biological action of hyperbaric nitrogen has a long history, and we think that the abovementioned experimental data contribute to the understanding of the pathogenesis of nitrogen narcosis as well as the creation of technological and pharmacological methods of its correction.

Extreme hyperbaric environments perturb various cellular processes at the molecular level due to the effects of pressure per se, gas partial pressure alone, through an intensive production of reactive oxygen and nitrogen species (ROS/RNS), which can incorporate in redox signaling pathways stimulating adaptive physiological responses or damaging cellular machinery. Altered pressure environments are routinely encountered in hyperbaric medicine (hyperbaric oxygen therapy) and diving (hyperbaric gases), and next basic research will focus on the obtaining data for better understanding of these potential applications.

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Author details

Olga Sergeevna Alekseeva[1], Alexander Ivanovich Krivchenko[1] and
Ivan Timofeyevich Demchenko[1,2]*

*Address all correspondence to: itdemch@mail.ru

1 Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences, St. Petersburg, Russia

2 Duke University Center for Hyperbaric Medicine and Environmental Physiology, Durham, NC, USA

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