Autonomic Mechanisms of Bradycardia During Nitrox Exposure at 3 Atmospheres Absolute in Humans

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Background: This experiment was designed to examine the involvement of the autonomic nervous systems and intrinsic component in the occurrence of hyperbaric bradycardia. ***Methods:*** Eight male divers were exposed to a N_2-O_2 (Nitrox) environment at 3 atmospheres absolute (ATA) for 7 d. The heart rate (HR), plasma norepinephrine (NE), and a spectral power of the variability of cardiac interval were measured during a 4-d predive control period, a 7-d saturation period at 3 ATA, and a 4-d postdive period. In each dive period, atropine and propranolol were administered intravenously for cholinergic blockade and β-adrenergic blockade, respectively. ***Results:*** Basal HR decreased by ~10% ($p < 0.05$) during the saturation period compared with that of the predive control. The HR after an administration of atropine was attenuated by 5.5 ± 2.4% ($p < 0.05$) during hyperbaric exposure. The HR after a simultaneous administration of atropine and propranolol, the intrinsic HR, was similar throughout the dive periods. Plasma NE decreased at 3 ATA ($p < 0.05$). The basal level of high-frequency power of cardiac interval variability, an index of cardiac parasympathetic modulation, remained unchanged throughout the dive period, whereas this power was eliminated by atropine administration. ***Conclusions:*** These results suggest that reduced sympathetic activity plays a primary role in the reduction of HR in the present hyperbaric environment.

Keywords: autonomic nerve activity, autonomic blockade, intrinsic heart rate, spectral analysis.

IT IS WELL DOCUMENTED that exposure to a high-pressure environment induces bradycardia (hyperbaric bradycardia) in humans and animals (4,14,16,22,24,28,31). It is thought that both oxygen-dependent and oxygen-independent factors operate to cause this bradycardia (14). Observations that hyperoxia causes bradycardia at both sea level and hyperbaria (7,12,25,26), indicate that an increased arterial O_2 partial pressure (P_{O_2}) is an important factor for the response. Respiratory inert gases, high environmental pressure, and high gas density also have been proposed as oxygen-independent factors (14). These factors may induce the bradycardia through the effect of autonomic nervous activity on the pacemaker cells in the sinus nodes. The bradycardia is attributable to either a decrease of sympathetic activity, an increase of parasympathetic activity, or a combination of these factors during exposure to hyperbaria.

In previous studies (28,31) investigating the neural mechanism of the hyperbaric bradycardia, we used a spectral analysis of cardiac variability as a tool for estimating cardiac autonomic nervous activity. We found that high-frequency (0.15–0.5 Hz) power of cardiac variability, an index of cardiac parasympathetic modulation (1,6,20,21), increased during He-O_2 (heliox) saturation dives at 16 and 24 atmospheres absolute (ATA) (28,31). Daly and Bondurant (3) showed that intramuscular administration of atropine diminished the bradycardia induced by oxygen breathing under normal atmospheric pressure. Above findings postulate that the hyperbaric bradycardia occurs in accordance with an increased parasympathetic activity. Recently, a decreased sympathetic nerve activity measured as muscle sympathetic nerve activity (MSNA) at 3 ATA has been reported in humans (30). The reduced MSNA together with reduced norepinephrine (NE) concentration in plasma strongly suggests diminished sympathetic nerve activity in hyperbaric environment in humans (30).

The present study was designed to examine the involvement of autonomic nerve activity and an intrinsic component in hyperbaric bradycardia in humans. We measured the heart rate (HR) before and after cholin-

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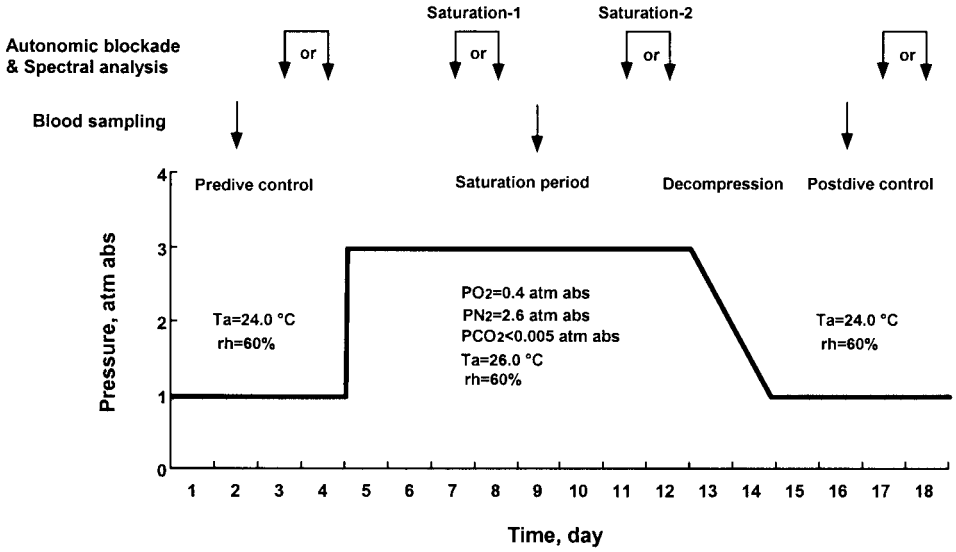

Fig. 1. Dive profile and chamber gas composition. Arrows indicate where experiments were conducted. Ta: ambient temperature, rh: relative humidity.

ergic and β-adrenergic blockade in an 18-d experimental period, including a 4-d pre-exposure period, a 7-d saturation at 3 ATA, and a 4-d post-exposure period.

METHODS

Subjects

Eight healthy males, 31 ± 4 yr old (mean ± SE), 69.0 ± 2.2 kg in weight, 170 ± 1 cm in height, and 17.0 ± 0.9% in body fat served as subjects. All subjects were accustomed to a saturation dive and had participated 2–3 times in earlier saturation dive experiments in the past 5 yr at the Japan Marine Science Technology Center (JAMSTEC), Yokosuka, Japan. Comprehensive physical examinations, including chest X-ray, electrocardiograph (ECG), and chemical analysis of blood and urine confirmed that all subjects were in good health. The Institutional Committee on Human Experimentation of the JAMSTEC approved the study protocol, and all subjects gave their written consent to participate after being fully informed of the procedures and possible risks.

Dive Protocol and Environmental Variables

The experiment was carried out in a hyperbaric chamber (7.5 m long, 2.3 m in diameter) at JAMSTEC. **Fig. 1** depicts the dive profile. The dive protocol consisted of a total period of 18 d, including a predive control period (4 d), a compression period (1 d), a saturation period (7 d), a decompression period (2 d), and a postdive control period (4 d). During the predive and postdive periods, the subjects breathed normal air in the chamber. The chamber temperature was kept constant at 24 ± 0.5°C and the relative humidity at 60 ± 10% during the predive and postdive periods. The chamber pressure was raised to 3 ATA at 0.1 atm · min^{-1} from 1 to 1.9 ATA and at 2 atm · h^{-1} from 1.9 to 3 ATA. The total pressure of 3 ATA consisted of 0.4 ATA oxygen and less than 0.005 ATA carbon dioxide and was balanced with nitrogen. During the 3-ATA saturation dive, the chamber temperature and relative humidity were kept constant at 26 ± 0.5°C and at 60 ± 10%, respectively. The decompression procedure was carried out according to the standard U. S. Navy schedule (27). Subjects retired at 2300 h and got up at 0700 h and had meals at scheduled hours (0800 h, 1200 h, 1500 h, 1800 h, and 2100 h) through the experiment.

Measurements and Analyses

Autonomic blockade and HR: Basal HR was determined in supine position at 0700 h throughout the experimental period by palpation on the radial artery. The ECG records in four of eight subjects were commenced at 1000 h on the third day of the predive period, the second and sixth days at 3 ATA, and on the third day of the postdive period; the ECG records for the remainder of the subjects began on the fourth day of the predive period, the third and seventh days at 3 ATA, and on the fourth day of the postdive period (Fig. 1). Daily activity of the subjects was scheduled identical for 1 and 3 ATA; the subjects were ambulatory for 30 min before the experiment. After resting supine for 15 min (control period), atropine sulfate (0.04 mg · kg^{-1}) was injected through a 21-gauge Teflon catheter inserted in the antecubital vein. Propranolol hydrochloride (0.2 mg · kg^{-1}) was injected 10 min after atropine. The administration of atropine and propranolol took 3 min. Measurement was continued for 15 min after the intravenous injection of propranolol. The ECG was recorded on a data recorder (RD-111T, TEAC, Tokyo) for HR and for analyses of spectral power of R-R intervals. Arterial BP was measured at a 5-min interval throughout the experimental period with an automated oscillometric BP device (UA-751, Takeda Medical, Tokyo).

Blood sampling and plasma NE: Blood sampling was made at basal condition at 0700 h on the second day in the predive period, the fourth day at 3 ATA, and the second day in the postdive period (Fig. 1). Blood samples were taken through a 21-gauge Teflon catheter inserted in an antecubital vein. For measurement of NE, 2.5 ml of blood was placed in a chilled tube containing heparin. The plasma was separated by centrifugation

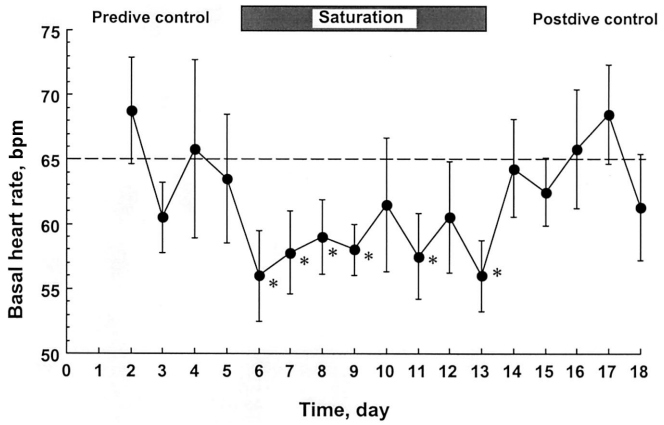

Fig. 2. Daily changes of basal heart rate throughout the 18-d experimental period. The heart rate was measured in a supine position when subjects got up at 0700 h. Broken line shows the average level of predive heart rate (65.0 ± 4.4 bpm). Values are means ± SE. * $p < 0.05$ from predive value.

(3000 rpm, 15 min) at 5°C and stored frozen at –70°C until assayed. Plasma NE was partially purified with adsorption on activated alumina, eluted with 2% acetic acid, separated with a high-performance liquid chromatography (Nanospace SI-1, Shiseido, Tokyo), and quantified with an electrochemical detector (Nanospace SI-1/2005, Shiseido). The detection limit of the assay was 8 pg.

Spectral analysis: The steady-state data of R-R intervals before and after autonomic blockade were used for the power spectral density analysis (Vital Rhythm 98III, NEC Medical Systems, Tokyo). A fast Fourier transform was used to calculate the power spectral density. The time series of R-R intervals were interpolated at 2 Hz by a Lagrange interpolation method. Consecutive data over 256 s were used for analysis. All analyses were performed between 0.03 Hz and 0.5 Hz. A frequency range between 0.05 and 0.15 Hz was defined as the low-frequency band, and between 0.15 and 0.5 Hz as the high-frequency band. The high-frequency power of cardiac variability was used as an index of cardiac parasympathetic modulation (1,6,20,21).

Statistics: We gave the autonomic blockade test twice during 3 ATA exposure, and the two results were statistically similar. Accordingly, we averaged the two values for the statistical analysis. A one-way analysis of variance with repeated measures was used to test the effect of pressure. When significant F ratios were obtained, least significant differences were calculated for comparisons between means. Effect of autonomic blockade was determined by using Student's paired *t*-tests. The null hypothesis was rejected when $p < 0.05$. Data are expressed as mean ± SE.

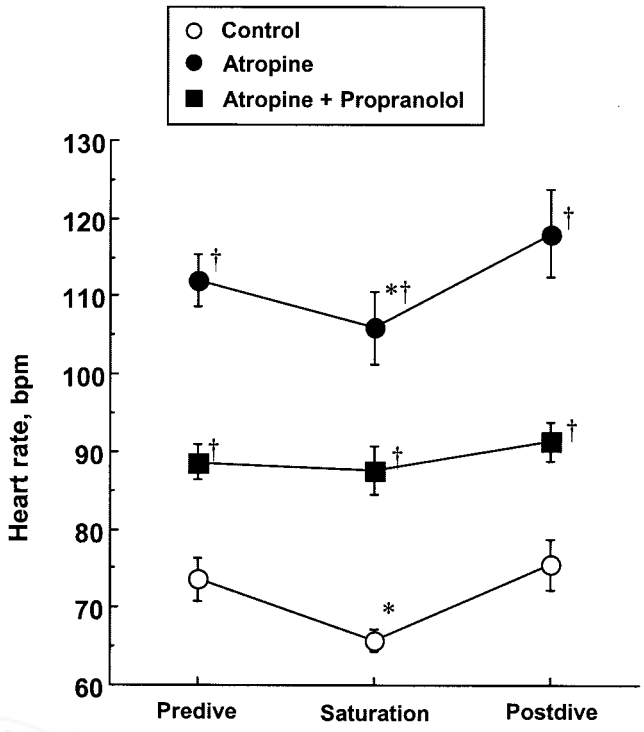

Fig. 3. Heart rate changes induced by intravenous atropine and propranolol during each dive period. Values are means ± SE. * $p < 0.05$ from predive value. † $p < 0.05$ from the control in each dive period.

RESULTS

Fig. 2 shows the basal HR in the morning (0700 h) throughout the experimental period. A reduction of HR was observed during hyperbaric exposure at 3 ATA and it returned to control level at postdive period. **Fig. 3** summarizes the average response of HR to the blockades over the experimental period. The control HR during the exposure to 3 ATA decreased by 10.1 ± 2.5% ($p < 0.05$) from the predive control level (Fig. 3 and **Table I**). **Fig. 4** shows an example of HR responses to atropine and propranolol injections at 1 and 3 ATA. In the predive period, the intravenous administration of atropine increased ($p < 0.05$) HR by 53 ± 6% from the control level, whereas the intravenous injection of propranolol decreased HR ($p < 0.05$) by 20 ± 3% from the level after atropine injection (Fig. 3 and Table I). The level of HR after atropine injection decreased significantly at the first measurement during the saturation dive compared with the predive control (Fig. 3). As a result, the magnitude of HR response to atropine was not changed during the saturation period compared with the predive control (Fig. 3 and Table I). After administration of both atropine and propranolol, intrinsic HR did not differ significantly among the dive

TABLE I. EFFECT OF AUTONOMIC BLOCKADE ON HEART RATE CHANGES DURING HYPERBARIC EXPOSURE.

	Predive control	Saturation	Postdive control
HRc	73.6 ± 2.8	65.8 ± 2.0*	75.5 ± 3.3
HRa – HRa+p (sympathetic influence)	23.5 ± 3.1	18.4 ± 3.6	26.8 ± 7.1
HRa – HRc (parasympathetic influence)	38.5 ± 3.4	40.2 ± 3.8	42.6 ± 5.1

Values are presented as means ± SE. *$p < 0.05$ compared with the predive control. HRc, control heart rate; HRa, heart rate after administration of atropine; HRa+p, heart rate after administration of atropine and propranolol. Heart rate is given in bpm.

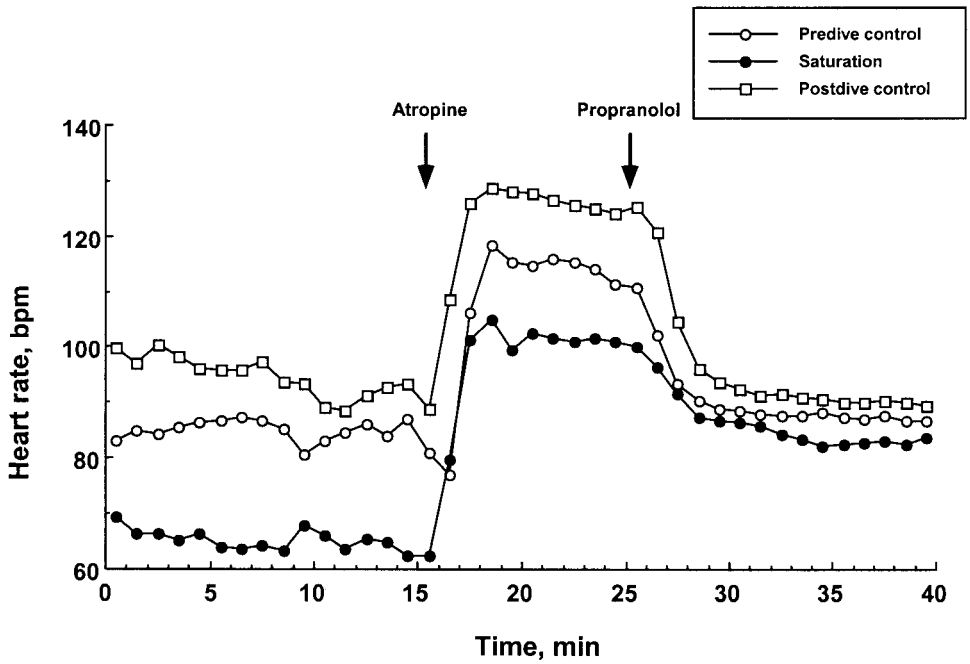

Fig. 4. An example in the time course of heart rate changes due to intravenous atropine and propranolol during each dive period. Arrows indicate where atropine or propranolol was injected.

periods (Fig. 3). Arterial BP was not significantly affected by either hyperbaric exposure or autonomic blockade (data not shown).

Plasma NE decreased significantly during the saturation period at 3 ATA (276 ± 33 pg · ml^{-1}) compared with the predive control (412 ± 24 pg · ml^{-1}). The decreased level of plasma NE persisted until the postdive control period (242 ± 18 pg · ml^{-1}).

The changes in the spectral power of cardiac variability over the experimental periods are presented in **Table II**. High-frequency power was blunted by the intravenous injection of atropine in all experimental situations. The control level of the high-frequency power remained unchanged throughout the experimental period. The control level of the low-frequency power was similarly not influenced by hyperbaric exposure.

DISCUSSION

The salient findings of the present study were as follows. First, HR response to atropine did not differ between predive control and saturation periods. This finding indicates that factor(s) other than parasympathetic efferent activity to the sinus node plays a role in the bradycardia during the hyperbaric exposure. Second, HR response to a simultaneous blockade for sympathetic and parasympathetic nerves was similar at 1 and 3 ATA. Accordingly, we may exclude a reduction of the intrinsic HR as a causative factor of hyperbaric bradycardia.

We used an approach of pharmacological blockade to examine the autonomic mechanisms underlying the hyperbaric bradycardia. Intravenous administration of atropine completely abolished the high-frequency power of the variability of R-R intervals, an index of cardiac parasympathetic modulation. The level of HR induced after administration of atropine and propranolol in the present study was within the range observed in normal individuals in normal situations (8,9). Thus, we may assume that the activities of cholinergic and β-adrenergic receptors in the heart were blocked successfully in the present study at 1 and 3 ATA. Therefore, the pharmacological approach in the present study suggests that an attenuated sympathetic nerve activity plays an important role in the bradycardic response to hyperbaric exposure.

A reduced NE concentration in plasma is consistent with a recent finding of a reduced sympathetic nerve activity. Yamauchi et al. (30) found a reduction of

TABLE II. EFFECT OF AUTONOMIC BLOCKADE ON SPECTRAL POWER OF THE VARIABILITY OF R-R INTERVALS DURING HYPERBARIC EXPOSURE.

	Predive control	Saturation	Postdive control
		High-frequency power, ms^2	
Control	279 ± 79	323 ± 92	237 ± 45
Atropine	4 ± 2†	5 ± 2†	4 ± 2†
Atropine + Propranolol	11 ± 3†	13 ± 4†	14 ± 5†
		Low-frequency power, ms^2	
Control	889 ± 189	1106 ± 232	826 ± 192
Atropine	35 ± 10†	48 ± 19†	24 ± 8†
Atropine + Propranolol	10 ± 5†	8 ± 3†	8 ± 1†

Values are presented as means ± SE. †$p < 0.05$ compared with the control.

MSNA and plasma NE by 30% during acute exposure at 3 ATA air in the presence of significant reduction of HR. This observation strongly suggests an attenuation of sympathetic nerve activity in the hyperbaric environment. The reduced level of plasma NE persisted until the postdive period, although the postdive HR recovered to the level of the predive control. Although plasma NE was measured only once during each dive period, the blood sampling was made at the basal condition of each period, so we considered the NE levels of the present measurements to be representative of the NE levels throughout the respective pressure conditions. This notion may be reasonable because we observed a consistent reduction of plasma NE concentration after nitrox exposure at 3 ATA for 6 d in a previous experiment (5). However, it is unknown why a reduced NE concentration in the plasma persisted during the postdive period in the presence of a chronological recovery of the heart. A decreased spillover of NE in regions other than the heart may be one of contributing factors. A future study of NE in connection to the time course of the NE recovery during postdive period is warranted.

As to the mechanism responsible for the sympathoinhibitory influence of hyperbaria, there are several candidates. Increase of arterial P_{O_2} may play a role in attenuating sympathetic nerve activity during hyperbaria, because hyperoxia has been reported to lower HR and MSNA at rest in normal atmospheric pressure (7,25). However, intramuscular administration of atropine abolishes bradycardiac response to 100% O_2 breathing in humans in a normal atmosphere (3); the hyperoxia-induced bradycardia in conscious dogs was unaffected by β-adrenergic blockade but it was completely prevented by cholinergic blockade (17). Thus, these reports suggest that parasympathetic nerve activity has an intimate relation with a hyperoxia-induced bradycardia. It is surmised, therefore, that hyperoxia produces decreased sympathetic activity and increase of vagal activity in the heart. Another possibility of inhibition of sympathetic activity is hyperbaria per se. Linnarson et al. (16) have found that HR control is sensitive to relatively small increases in ambient pressure. An elevated gas density is also a potential responsible factor, because a reduction of HR has been observed in a high gas density environment (14). In the present study, gas density increased from 1.2 $g \cdot L^{-1}$ at 1 ATA to 3.4 $g \cdot L^{-1}$ at 3 ATA.

We failed to observe a pressure-related increase in the high-frequency power of cardiac interval variability under the control condition. This result is in disagreement with the previous reports where an increased high-frequency power was observed during heliox saturation dives at 16 and 24 ATA (28,31). The disagreement may be due to a difference in the experimental conditions (e.g., different ambient pressure and composition of inert gases). As regards the effect of He gas, Lin and Kato (13) have reported that He-O_2 gas breathing decreased HR via increased vagal activity and decreased sympathetic activity in rats. The density of inspired gas may not be a major factor, because the present study (gas density, 3.4 $g \cdot L^{-1}$) did not result in an increase in the high-frequency power, whereas He-O_2 environment at 16 ATA (gas density, 3.0 $g \cdot L^{-1}$) (28) and at 24 ATA (gas density, 5.6 $g \cdot L^{-1}$) (31) resulted in an increased high-frequency power of cardiac interval variability.

The autonomic control of HR has been assumed to be additive (11,29) or multiplicative (2,23). An approximation of autonomic control of HR change during hyperbaric exposure may be presented by the following equation (29):

$$HRc = HRi + S - P$$

where, HRc is HR in the normal control condition; HRi is intrinsic HR (obtained during combined cholinergic and β-adrenergic receptor blockade); S is the change of HR which is augmented as a result of sympathetic activation (HR after cholinergic receptor blockade minus HRi); and P is the change of HR by parasympathetic influence (Table I). Although sympathetic-vagal interaction is not considered in this model (10), one can determine experimentally the factors that influence the model. When data from this study have been applied to the above additive model, 65% of the bradycardiac responses during the saturation dive is explained by the sympathetic withdrawal. Although no significant change in HRi was observed during the saturation period, we cannot exclude the possibility that direct effect of hyperbaria at the sinus node decreased HR, because it has been reported that the compression from 6 to 150 ATA decreased the beating frequency in the sinus node preparation by approximately 30% (19).

Cardiovascular deconditioning, including a greater reduction of BP during a head-up tilt has been observed under a 31 ATA environment (15). It was suspected that the occurrence of cardiovascular deconditioning in the hyperbaric environment may be related to an insufficient compensatory action of the autonomic nervous system, and the hypovolemia resulted from a persisting diuresis (12,15). In the present experiment we observed a sustained lowering of basal HR by ~10% during the hyperbaric exposure at 3 ATA, however there exists a controversy if the bradycardia is sustained throughout the hyperbaric exposure (18). It is not certain whether cardiovascular deconditioning occurred during the saturation period as during exposure to a very high pressure environment, because no tachycardia was observed during the postdive period. For safety and efficiency of diving work, the changes in autonomic nerve activity should be also studied during postural change and physical exercise in high-pressure environments.

In conclusion, the decrease of HR during nitrox exposure at 3 ATA is caused mainly by a decreased sympathetic nerve activity in humans. However, we do not entirely rule out a possibility that an increased parasympathetic activity and a reduced intrinsic HR are related partly to the bradycardiac response in the hyperbaric environments.

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