EFFECT OF INTERMITTENT HYPOXIC TRAINING ON ORTHOSTATIC TOLERANCE IN HUMANS BEFORE AND AFTER SIMULATED MICROGRAVITY

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Reduced orthostatic tolerance (OT) is a serious concern facing space medicine. This work sought to evaluate the effects of intermittent hypoxic training (IHT) on OT in humans before and after 3 days of head-down bed rest (HDBR) used to model microgravity. The study was carried out in 16 male volunteers aged 18 to 40 years and included 2 series of experiments with 11-day and 21-day IHT administered on a daily basis. During the first IHT session, the concentration of oxygen in the inspired gas mixture was 10%; for other sessions it was adjusted to 9%. OT was assessed by a 20-minute-long orthostatic tilt test (OTT) conducted before and after HDBR. Before HDBR, orthostatic intolerance was observed in 3 participants, while after HDBR, it was observed in 9 of 16 volunteers ($p < 0.05$). During OTT conducted after HDBR, the heart rate (HR) exceeded control values by 26.8% ($p < 0.01$). Preexposure to any of the applied IHT regimens led to a reduction in the number of volunteers with orthostatic intolerance. After the 11-day IHT program, there was a less pronounced increase in HR during OTT before HDBR; with the extended IHT regimen, less pronounced changes were observed for HR, systolic, diastolic and mean blood pressure (BP). The increase in HR during OTT after HDBR was significantly lower in the group that had completed the 11-day IHT program, while BP remained stable. The changes in HR and systolic BP were less pronounced in the group that had completed the 21-day IHT program than in the control group ($p < 0.05$). Thus, IHT reduced the risk of orthostatic disorders and mitigated changes in cardiovascular parameters during the orthostatic test.

Keywords: intermittent hypoxic training, orthostatic tolerance, head-down bed rest, blood pressure, heart rate

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ВЛИЯНИЕ ГИПОКСИЧЕСКИХ ТРЕНИРОВОК НА ОРТОСТАТИЧЕСКУЮ УСТОЙЧИВОСТЬ ЧЕЛОВЕКА ДО И ПОСЛЕ МОДЕЛИРОВАННОЙ МИКРОГРАВИТАЦИИ

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Снижение ортостатической устойчивости (ОУ) является актуальной проблемой космической медицины. Целью работы было оценить влияние интервальных гипоксических тренировок (ИГТ) на ОУ человека до и после воздействия трехсуточной антиортостатической гипокинезии (АНОГ) как модели микрогравитации. При участии 16 мужчин-добровольцев в возрасте 18–40 лет проведены две серии исследований с 11- и 21-суточным курсом ежедневных ИГТ. В первой ИГТ концентрация кислорода во вдыхаемой газовой смеси составляла 10%, во всех последующих — 9%. Оценку ОУ выполняли до и после АНОГ проведением 20-минутной ортопробы (ОП). Развитие ортостатической неустойчивости до АНОГ наблюдали у трех, а после АНОГ у девяти из 16 обследуемых ($p < 0{,}05$). Во время ОП после АНОГ среднее значение частоты сердечных сокращений (ЧСС) превышало контрольные значения на 26,8% ($p < 0{,}01$). После 11- и 21-суточных ИГТ отмечена тенденция к снижению числа случаев с развитием ортостатической неустойчивости. По сравнению с контролем при ОП до АНОГ после 11-суточного курса ИГТ наблюдали менее выраженный прирост ЧСС, а при увеличении курса ИГТ до 21 суток — менее выраженные реакции со стороны ЧСС, систолического, диастолического и среднего артериального давления (АД). При ОП после АНОГ в серии с 11-суточным курсом ИГТ имело место достоверно меньшее увеличение ЧСС при стабильном уровне АД. В серии с 21-суточным курсом ИГТ наблюдали меньшие сдвиги ЧСС и систолического АД ($p < 0{,}05$). Таким образом, проведение ИГТ приводило к уменьшению риска ортостатических нарушений и менее выраженным сдвигам показателей сердечно-сосудистой системы во время постуральных воздействий.

Ключевые слова: интервальные гипоксические тренировки, ортостатическая устойчивость, антиортостатическая гипокинезия, артериальное давление, частота сердечных сокращений

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Exposure to a natural or modelled microgravity environment leads to the deconditioning of the physiological systems involved in maintaining the upright posture under Earth's gravity. Diminished orthostatic tolerance (OT) is a serious symptom of deconditioning that was recognized in the early days of manned space missions [1, 2]. After short-duration Space Shuttle flights, about 20% of astronauts were unable to complete a 10-minute orthostatic tilt test (OTT) due to a progressive blood pressure fall and presyncope [3]. Even more American astronauts developed orthostatic intolerance after long-duration missions aboard Mir [3] and the International Space Station (ISS). Besides, ISS astronauts took longer to recover than Space Shuttle crews [4].

Countermeasures against the adverse effects of microgravity on the human body during orbital flights are complex, time-consuming and include daily exercise for about 2.5 hours [5]. However, they cannot completely avert the development of orthostatic intolerance in the early postflight period [4, 6]. The first Russian experimental studies investigating the effects of the modeled lunar gravity field on human physiology [7] underscore the significance of this yet unsolved problem for future space missions [8].

Manned space missions to the Moon and beyond to Mars will require more effective and less time-consuming countermeasures enhanced by cutting-edge technologies against the deconditioning effects of micro- and hypogravity on gravity-dependent body systems. Creating artificial gravity on board of a spacecraft is the most radical solution to counter microgravity [9]; in turn, methods for targeted physiological action [10], including adaptation to hypoxic hypoxia [11], might reinforce the effect.

Today, adaptation to hypoxic hypoxia through normobaric or hypobaric intermittent hypoxic training (IHT) is widely used in clinical, sports, aviation and space medicine as a non-drug therapy for restoring body function, improving physical performance and resisting occupational stress [12, 13]. According to some publications, IHT can reduce the intensity of hemodynamic changes during orthostatic tests [14, 15]. It is reported that a 14-day-long exposure to a hypoxic environment reduces orthostatic hypotension and increases orthostatic tolerance in rats kept in the antiorthostatic position (modeled microgravity) for 2 weeks [16]. The findings of the cited study inspired us to carry out an experiment on human subjects in the attempt to investigate the effects of IHT on OT before and after a 3-day exposure to modeled microgravity.

METHODS

The study was carried out in 16 healthy, non-smoking male subjects aged 18 to 40 years (the mean age was 26.4 ± 1.5 years; the mean body weight, 76.8 ± 2.6 kg; height, 177 ± 1.9 cm) and not involved in professional sports. The following inclusion criteria were applied: approval by the medical board and informed consent to participate. Two days before the experiment, the subjects were accommodated in an inpatient unit for adaptation. During the adaptation period, their condition was closely monitored by the medical personnel. Physical loads were banned. Meals were provided 4 times a day. Sleep time was from 23:00 to 8:00. Microgravity was simulated by 3 days of –6° head-down tilt bed rest (HDBR) [17].

IHT sessions were conducted using a Bio-Nova-204 system for hypoxic therapy (Bio-Nova; Russia). The hypoxic gas mixture was delivered to the seated participants through a mask pressed tightly against the face, in a well-ventilated room for physiological tests involving humans. IHT sessions were held daily and lasted 60 min each. Each session consisted of 6 cycles: 5-minute periods of breathing the hypoxic gas mixture followed by 5 minutes of breathing ambient air. During the first IHT session, the concentration of oxygen in the inspired gas mixture (FIO_2) was 10%. Starting from the 2nd session, FIO_2 was adjusted to 9%. During IHT, the condition of the participants was closely monitored; oxygen saturation (SpO_2), heart rate (HR), systolic and diastolic pressures (BP) were taken every 3 minutes.

OT was assessed a day before HDBR and immediately after 3 days of HDBR on a tilt table by transferring the subjects to a vertical position at an angle of + 70 ° for the maximum of 20 min. Before, during (every 2 minutes) and after the end of OTT, HR, systolic and diastolic BP were measured. Subjective and objective indicators of health status were evaluated. Prior to OTT, baseline physiological parameters were recorded in the supine position (before hypokinesia) and in the HDBR position (after hypokinesia).

Physiological parameters were measured using a PVM-2703 bedside monitor (Nihon Kohden Corporation; Japan) fitted with a pulse oximeter and channels for measuring BP and ECG. Mean BP was computed as the sum of diastolic BP and 1/3 of pulse pressure. OTT was terminated if the tested participant had a progressive BP decrease, bradycardia, nausea, excessive sweating, blurred vision and other signs of imminent syncope. Two different IHT regimens were used. In the first part of the experiment, IHT duration was 11 days; in the second part, IHT was extended to 21 days. The number of the participants involved was 6 and 11, respectively.

Statistical analysis was carried out in Microsoft Excel ver. 2016 (16.0.5071.1000; Microsoft Corporation; USA). Significance of differences was assessed using the nonparametric Wilcoxon signed-rank test, the Mann–Whitney *U* test and Fisher's — criterion. Differences were considered significant at $p < 0.05$. The table and figures below show the mean values of the studied parameters and the mean error (M ± m).

RESULTS

IHT tolerance by subjects

During hypoxic gas breathing, the subjects did not feel any discomfort or had any health complaints. SpO_2 was falling from 97.0 ± 0.5% to 77.6 ± 2.6%; HR was increasing from 71.7 ± 4.0 min^{-1} to 89.0 ± 4.3 min^{-1} ($p < 0.05$). BP did not change significantly. When the participants were breathing ambient air, their SpO_2 and HR were recovering, reaching the initial values by the beginning of the next IHT cycle.

Table. Effects of 3-day HDBR on orthostatic tolerance in subjects

Orthostatic tilt test parameters	Before HDBR	After HDBR
Number of completed OTT/total number of OTT	13/16	7/16*
Average test duration, min	18.6 ± 0.8	13.8 ± 1.6*
Average time to presyncope, min	12.7 ± 1.6	9.0 ± 1.4*

Note: OTT — orthostatic tilt test; * — $p < 0.05$.

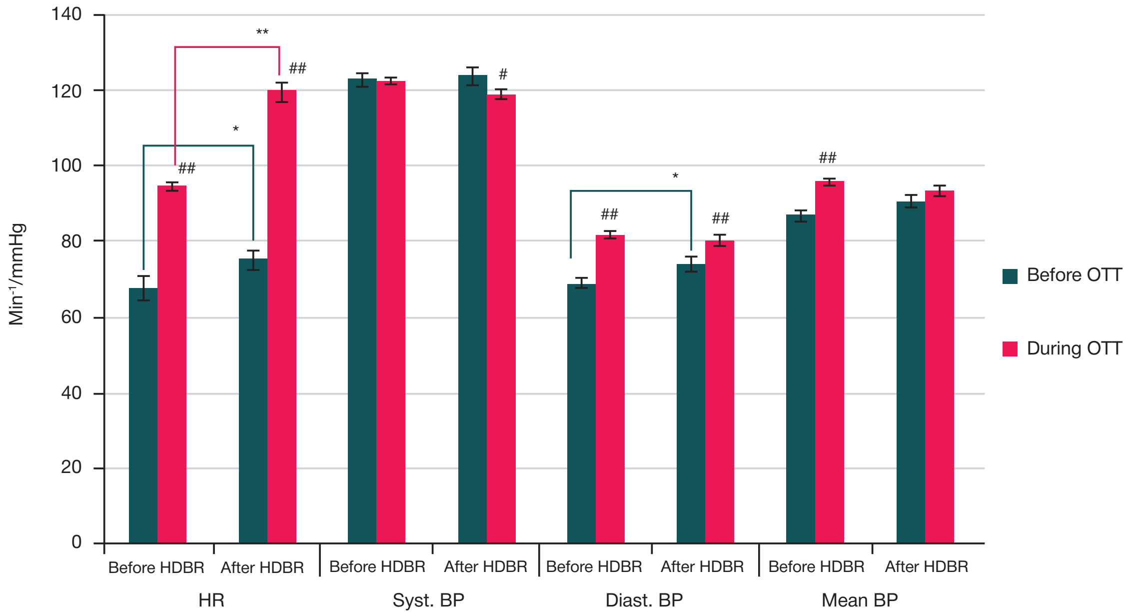

Fig. 1. Effects of 3-day HDBR on cardiovascular responses to the orthostatic test. # ($p < 0.05$) and ## ($p < 0.01$) designate differences between the data obtained during OTT and the data obtained from supine subjects before OTT; * ($p < 0.05$) and ** ($p < 0.01$) designate differences before and after HDBR

Effects of 3-day HDBR on orthostatic tolerance

The Table below shows the results of OTT before and after 3 days of HDBR. After HDBR, the number of successfully completed OTTs dropped from 13 to 7, whereas the number of OTTs terminated due to the symptoms of presyncope increased threefold, from 3 to 9 ($p < 0.05$). For the group, the average time of OTT after HDBR significantly decreased by 4.8 min ($p < 0.05$) in comparison with the control.

In addition to the increased number of presyncopies, time from tilting the subjects upward to the onset of presyncopal symptoms also tended to decrease by 3.7 min.

Following 3 days of HDBR, the mean HR during OTT exceeded the control values by 26.8% and was 119.8 ± 2.6 min^{-1} vs. 94.6 ± 0.9 min^{-1} before HDBR ($p < 0.01$; Fig. 1). Moreover, the post-HBDR HR was significantly higher in the experimental group than in the controls throughout the test (Fig. 2). The significant increase in HR was accompanied by a slight (about 5%) yet reliable mean systolic BP fall from 123.8 ± 2.2 to 118.8 ± 1.3 mmHg and an elevation of diastolic BP, which was less pronounced in the experimental group: 8.9% (from 73.9 ± 1.6 to 80.5 ± 1.2 mmHg) vs. 18.5% in the control group (from 69.2 ± 1.4 to 82 ± 0.6 mmHg). There was no reliable increase in the mean BP (see Fig. 1). Of note, the absolute values of HR and diastolic BP measured in the supine position before the initial OTT were 11% and 6.8% lower, respectively, than the absolute values of HR and diastolic BP measured in the antiorthostatic position before the post-HDBR tilt test ($p < 0.05$).

Effects of 11-day IHT on orthostatic tolerance

In the first part of the experiment, OTTs (before and after HDBR) were carried out on 6 participants. Later, one of them decided to drop out. Consequently, the effects of IHT on orthostatic tolerance before and after HDBR were investigated in a group of 5 individuals, and the data on the dropout was not included in the analysis.

Before HDBR, the tilt test was completed by 4 (80%) of 5 participants; after IHT, 5 of them (100%) were able to pass the test. Initially, of 5 OTTs performed after HDBR, 3 (60%) were

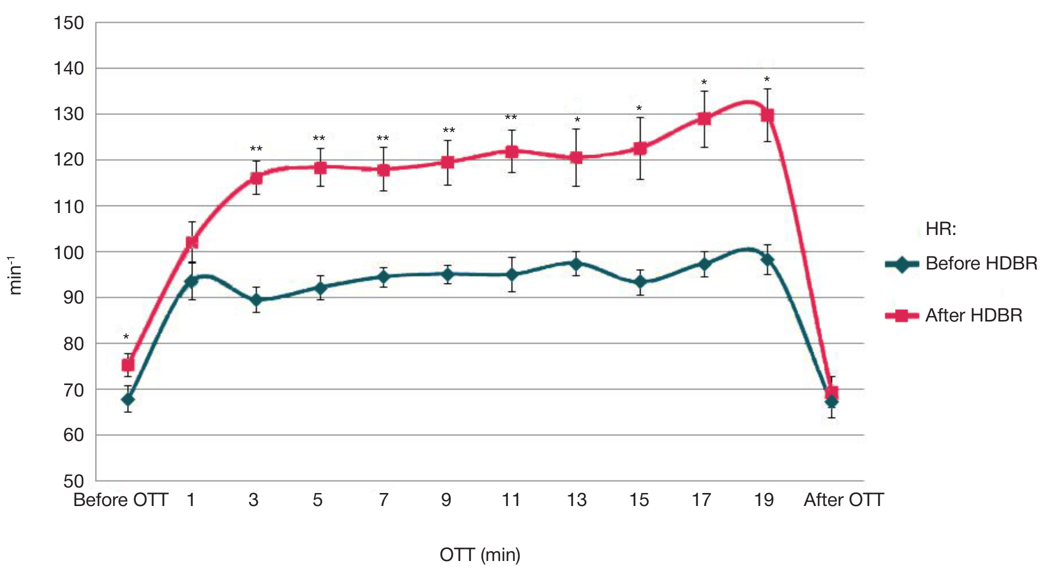

Fig. 2. HR dynamics during the orthostatic test before and after 3 days of HDBR.* ($p < 0.05$) and ** ($p < 0.01$) designate differences before and after HDBR

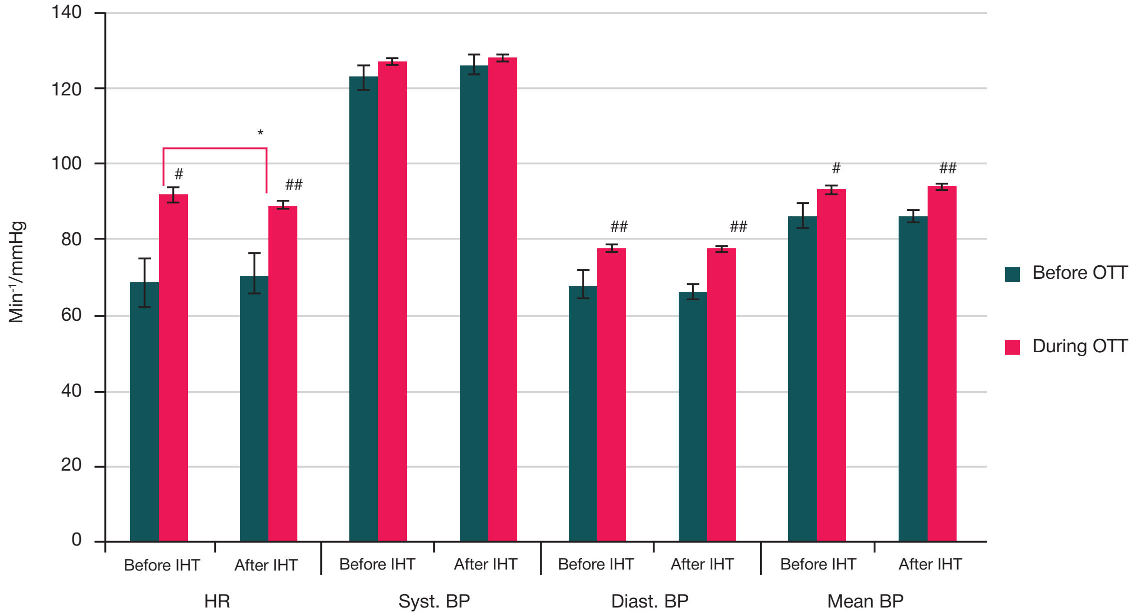

Fig. 3. Effects of 11-day IHT on cardiovascular responses to the orthostatic test before HDBR. # ($p < 0.05$) and ## ($p < 0.01$) designate differences between the data obtained during OTT and the data obtained from supine subjects before OTT; * ($p < 0.05$) marks differences before and after IHT

terminated because the participants became presyncopal. However, IHT presyncopal symptoms were observed in only one (20%) of 5 participants. The mean OTT duration tended to increase from 13.4 ± 3.5 min to 18.6 ±1.6 min.

The effects of 11-day IHT on the cardiovascular system undergoing orthostatic exposure are shown in Fig. 3. IHT before HDBR resulted in a less pronounced (3%) increase in HR ($p < 0.05$) in comparison with no IHT. Interestingly, the increase in HR during OTT after HDBR was much less pronounced (16.1%; $p < 0.05$) in the participants who had completed the IHT program than in the control group (Fig. 4). Other IHT effects included a stable systolic BP and a higher mean BP (7.2%; $p < 0.05$).

Effects of 21-day IHT on orthostatic tolerance

Of 10 participants included in the second part of the experiment, 8 (80%) individuals were able to successfully complete pre-IHT OTT before HDBR, whereas after IHT 9 (90%) subjects were able to pass the test. In 3 cases (2 before IHT and 1 after IHT), OTT was terminated because the participants developed the symptoms of presyncope. A slight (4.9%) increase in mean orthostatic tolerance (18.2 ± 1.2 vs. 19.1 ± 0.9 min) was observed in the participants who had undergone the IHT program, as compared with the control group.

Prior to IHT, 4 (40%) of 10 participants were able to complete OTT after HDBR; their number increased to 6 (60%) after IHT. In 6 cases before IHT and 4 cases after IHT, OTT was terminated because the participants were showing the signs of presyncope. There was a tendency to better tilt test tolerance in the group that had undergone the IHT program: the test duration increased from 13.4 ± 2.1 to 14.7 ± 2.2 min, i.e. by 9.7%, in this group as compared to the control.

The effects of IHT on hemodynamics observed during OTT before HDBR are provided in Fig. 5. In comparison with the control group, HR, diastolic BP and mean BP increased

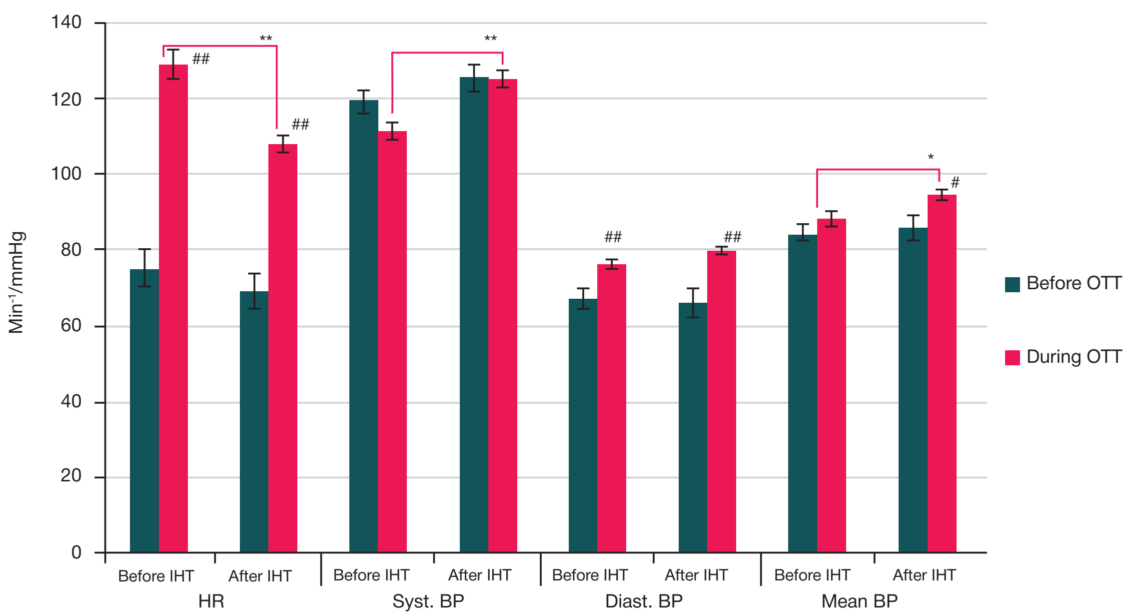

Fig. 4. Effects of 11-day IHT on cardiovascular responses to the orthostatic test after HDBR. # ($p < 0.05$) and ## ($p < 0.01$) designate differences between the data obtained during OTT and the data obtained from supine subjects before OTT; * ($p < 0.05$) and ** ($p < 0.01$) designate differences before and after IHT

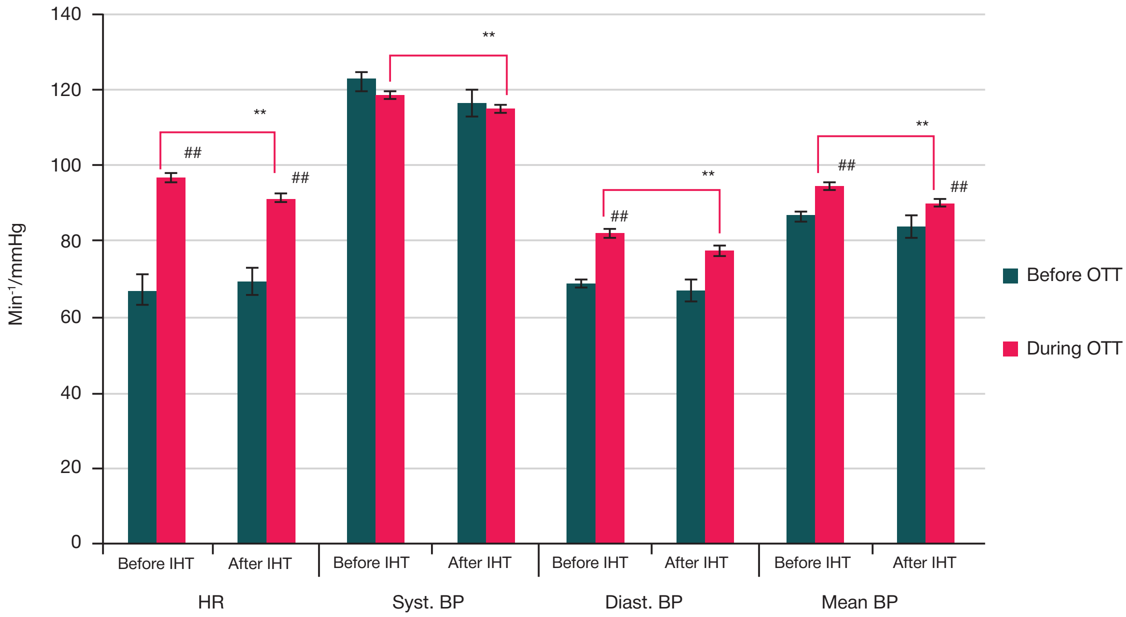

Fig. 5. Effects of 21-day IHT on cardiovascular responses to the orthostatic test before HDBR. # (p < 0.05) and ## (p < 0.01) designate differences between the data obtained during OTT and before OTT; * (p < 0.01) marks differences before and after HDBR

less dramatically during OTT (by 5.4%, 6.3% and 5.1%, respectively; $p < 0.01$) in the participants who had completed the IHT program. Systolic BP did not change significantly during OTT but was 3.3% lower than before IHT ($p < 0.01$).

During the post-HDBR tilt test (Fig. 6) performed after IHT, an increase in HR was less pronounced (4.6%) and BP values were lower (5.8%) ($p < 0.05$). Before OTT, HR, diastolic BP and mean BP were 14.5%, 5.1% and 4.3% lower in the participants who had completed the IHT program than in the control group ($p < 0.05$).

DISCUSSION

The study demonstrates that 3 days of HDBR reduces OT in human subjects. After HDBR, significantly fewer participants could complete the test due to the symptoms of presyncope and the trending early onset of such symptoms in the vertical position. After 3 days of HDBR, orthostatic intolerance was observed in 9 (56.3%) of the total 16 participants. Our findings support the data generated by other studies. It is reported that after 4 days of HDBR, as many as 5 (63%) of 8 subjects were unable to finish the orthostatic test [18, 19]. There is evidence that orthostatic intolerance can develop after shorter exposures to HDBR. For example, 6 (75%) of 8 participants became presyncopal during OTT after only 4 h of HDBR [20].

Differences in the estimated frequency of orthostatic intolerance after HDBR might largely be due to the employment of different methods for OTT, different tilt table angles (60 to 80°), OTT duration (10–20 to 60 min), application of negative pressure to the lower body after OTT, nonuniform criteria for assessing OT (based on test duration or the onset of presyncope), individual physiological response to OTT [21, 22].

The key role in maintaining systemic BP and cerebral circulation during orthostatic exposure is attributed to the cardiovascular system [23]. In our study, the hemodynamic response to orthostatic exposure was characterized by

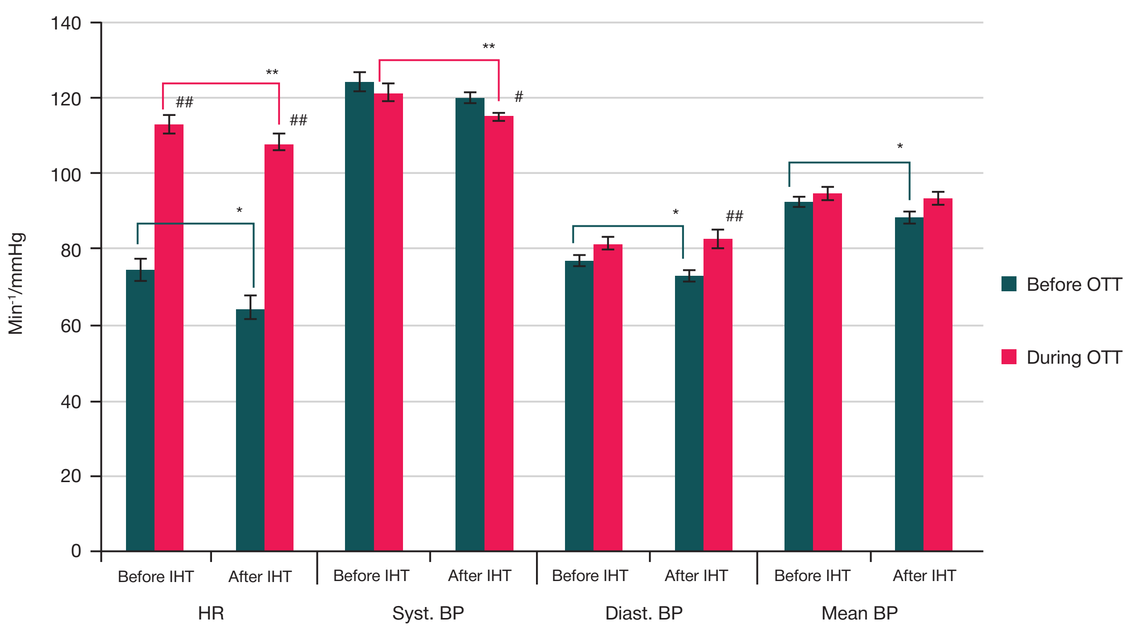

Fig. 6. Effects of 21-day IHT on cardiovascular responses to orthostatic test after HDBR. # (p < 0.05) and ## (p < 0.01) designate differences between the data obtained during OTT and before OTT; * (p < 0.05) and ** (p < 0.01) designate differences before and after IHT

pronounced tachycardia and low systolic BP after HDBR. These findings are consistent with the results of space flight studies [24] and studies of antiorthostatic hypokinesia [25].

Pronounced tachycardia observed during OTT after HDBR should be considered a symptom of cardiovascular deconditioning caused by hypokinesia. It is known that –6° HDBR leads to blood/fluid redistribution toward the skull and increases the blood volume in the thoracic compartment [26]. Increased venous return to the right atrium triggers secretion of the atrial natriuretic peptide [27]. This results in reduced water reabsorption, diuresis, increased natriuresis and, eventually, decreased plasma volume. After 2 days of HDBR, the central blood volume drops by approximately 11% [28], and the plasma volume decreases by 6.1% [29]. It normally takes 2 to 4 days for the cardiovascular and related systems to adapt to HDBR; the adaptive state is characterized by slower HR and slightly lower BP [30]. Higher HR and diastolic BP in the antiorthostatic position before OTT after 3 days of HDBR vs. HR and BP in the horizontal position before the initial OTT observed in our study suggest that the body was still adjusting its water-electrolyte balance to the new environment.

In the setting of moderate hypovolemia that develops after 1 week of a spaceflight/ HDBR, the left ventricular end-diastolic volume, the stroke volume and the cardiac size diminish [31]. Apart from the small stroke volume, increased venous distension in the lower limbs, which often develops during HDBR and spaceflights, is also a precipitating factor for orthostatic disorders: orthostatic exposure increases blood flow to leg veins and makes it difficult for the body to maintain adequate cardiac output in the vertical position [32].

The baroreflex mechanism relying on the receptors of carotid sinuses and the aortic arch is the crucial component of neural circulatory control. The baroreflex regulation of BP is largely implemented through the modulation of HR and the vasomotor activity of the sympathetic nervous system (SNS) [33]. A positive correlation has been established between the level of vasomotor SNS activity and total vascular resistance in young men [34]; unlike changes in the central hemodynamics and HR reported by another study [35], vascular resistance turned out to be critical in maintaining BP in astronauts during OTT after short-duration (9–14 days) space missions. These results are well correlated with the data generated by another study [36]. According to the publication, preexposure prophylaxis with midodrine, which is known to enhance vasoconstriction, prevented syncope due to orthostatic exposure in all of 5 study participants following their return to Earth. It is reported that the baroreflex control of vasomotor SNS activity is weakened during HDBR and the subsequent OTT [21]. Today, it is believed that decreased baroreflex sensitivity is one of the principal causes of poor orthostatic tolerance in the setting of hypokinesia and microgravity [21, 25, 30].

Performing IHT reduces the risk of orthostatic disorders. This can be inferred from the less pronounced changes in cardiovascular parameters during orthostatic exposure and fewer cases of presyncopal symptoms before and after HDBR. The increase in HR during OTT before HDBR was smaller in the group that had completed the 11-day IHT program than in the control group. The extended 21-day IHT program led to less pronounced changes in HR, systolic, diastolic and mean BP. The increase in HR during OTT after HDBR was significantly lower in the participants who had completed the 11-day IHT program; at the same time, systolic BP was stable. Both HR and systolic BP were lower in the group subjected to the extended IHT regimen. HR, systolic and diastolic BP values after IHT preceding the test were lower than before IHT, suggesting faster adaptation to HDBR.

According to the literature, the beneficial effects of IHT observed in our study might be connected to certain changes in the functional state of the autonomic nervous system and the cardiovascular system occurring during adaptation to repeated hypoxic exposure [11]. The mechanisms of immediate adaptation to hypoxia rely on the sympathetic activation of the compensatory cardiorespiratory response, which aims to reduce arterial hypoxemia and improve oxygen transport to tissues [16]. Repeated exposure to moderate hypoxia and reoxygenation create a structural and functional basis for the mechanisms that underlie long-term adaptation to hypoxia and improve oxygen uptake by mitochondria [37]. The long-term effects of IHT include enhanced performance of the parasympathetic components of circulatory control and higher efficacy of baro-and chemoreceptor-based regulation of heart rhythm and vascular tone [38]. Regional blood flow is redistributed toward the brain and the heart. IHT has been shown to exert a beneficial effect on vascularization and myocardial contractility [39]. This leads us to hypothesize that IHT might have had a cardioprotective effect on our subjects by increasing myocardial capacity and negating the main detrimental effects of orthostasis manifested as a dramatic BP decline.

CONCLUSION

Pronounced tachycardia during OTT after HDBR should be considered a sign of cardiovascular deconditioning due to limited physical activity during hypokinetic periods. Preexposure to IHT ameliorates cardiovascular strain during orthostatic tests before and after 3 days of HDBR. IHT reduces the risk of orthostatic syncope. The mechanisms underlying IHT effects on the functional state and ratio of cardiac to vascular components maintaining circulatory homeostasis during orthostatic exposure require further elucidation.

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