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Effect of intermittent normobaric hypoxia exposure on acclimatization to high altitude by air induction

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ABSTRACT

Background: In emergency like condition, defence personnel are deployed to high altitude without proper acclimatization. Maladaptation at high altitude leads to high altitude illness like acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) which hampers the operational capabilities. **Aims and Objectives:** The aim of the present study was to assess the effect of intermittent normobaric hypoxia exposure (IHE) at sea level on different physiological responses during initial days of acclimatization at 3500m and 4000m altitudes in acute induction. **Materials and Methods:** The IHE subjects were exposed to 12% FIO2 (equivalent altitude 14500 ft) for 4 hrs/day for 4 consecutive days at sea level and 5th day they were inducted by air to 3500m altitude. Baseline recording of different physiological parameters like cardiovascular, respiratory, oxygen saturation and AMS score were measured at sea level as well as 3500m altitude on daily basis for 6 days to assess acclimatization status. To confirm acclimatization status at 3500m, on fifth day the IHE group subjects were transported by road to 4000m and again measured different basal physiological parameters (like cardiovascular, oxygen saturation and AMS score) for four consecutive days. **Results:** Different physiological parameters of IHE treated group were stabilized by day 4 of air induction at 3500m altitude. Whereas, at 4000m altitude, these parameters were stabilized by day 2 of induction. **Conclusion:** Acclimatization schedules of four days at 3500m and two days at 4000m are essential to avoid malacclimatization/or high-altitude illness.

Key words: Intermittent; Normobaric; Hypoxia; Exposure; Acclimatization; High Altitude; Air Induction

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INTRODUCTION

High altitude (HA) is defined as 9000 ft (>2400m) and above because at this altitude most of the people develop sign and symptoms which are associated with acute mountain sickness (AMS). Low landlers residents (<1500m) rapidly ascending to high altitude (>2400m) and especially at very high altitude are at risk of developing high altitude illness i.e., acute mountain sickness (AMS), High Altitude Pulmonary Edema (HAPE) or High Altitude Cerebral Edema (HACE). The symptoms of AMS occur within few hours after ascent and become prominent after first night spent at high altitude. In emergencies like conditions, defence personnel also may not get adequate time for staged acclimatization and be inducted to high altitude within a short period of time. As a result some of them are at risk of physical problems related to high altitude disorders, which could be unpleasant and may even lead

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to fatal casualties. The effect of high altitude on common illness,[1] autonomic control of heart rate,[2] cardiovascular system,[3] respiratory system,[4] chemoreceptor sensitivity,[5,6] oxygen saturation response[7] and maximal exercise responses[8] during initial days of acclimatization at different altitudes has already been reported. Immediate response to high altitude is augmented ventilation and considered to be one of the most important indices of altitude acclimatization. Ventilatory acclimatization to altitude is characterized by progressive increase in ventilation that leads to an increase in pulmonary gas exchange and oxygen saturation level. Acetazolamide is the pharmacological drug and in use for prevention of HA illness upon rapid ascent to high altitude.[9-11] However, a promising and an alternative approach to induce acclimatization at sea level is the use of intermittent hypoxic exposure (IHE).

IHE can be administered using either hypobaric hypoxia or normobaric hypoxia. Hypobaric hypoxia is induced by decreasing the barometric pressure, whereas in normobaric hypoxia is induced by lowering the percentage of oxygen in inspired air (FIO_2). Nagasaka and Satake first hypothesized that IHE in hypobaric chamber could induce pre-acclimatization.[12] They exposed the subjects for 3 consecutive days simulating 6000m (354mm Hg) for 5 hrs and 8000m (270mmHg) for next 1 hr observed an increase in V_E and PaO_2 in hypobaric hypoxia, indicating the initiation of ventilatory acclimatization. Previous study from this lab on acclimatization at high altitude at 3500m in gradual (road) and acute induction (air) indicated that it took at least five days for air inductees and three days for road inductees to avoid HA illness.[13] Training in intermittent normobaric hypoxia at sea level and its effect on HA illness like AMS is very limited.[14] Recent study from this laboratory on IHE indicated that normobaric hypoxic exposure at sea level significantly reduces AMS during subsequent exposure to hypobaric hypoxia at 3500 m altitude[15] and also helps in rapid acclimatization process.[16,17] However, no systemic study appears to have been carried out, particularly about the effect of intermittent normobaric hypoxia on basal physiological parameters during acute induction by air to 3500m and 4000m altitudes on initial days of acclimatization. The aim of the present study was to evaluate the effect of intermittent normobaric hypoxia exposure on acclimatization to 3500m and 4000m altitudes.

MATERIALS AND METHODS

The study was conducted on Indian Army Volunteers (n=20) and they were divided into two groups of equal numbers i.e; control and experimental. All the subjects were sea level residents. None of the subjects had been to high altitude within the previous one month. The subjects were in good health with no evidence of cardiovascular or pulmonary disease. The study protocol was approved by the Institute's Ethical Committee and informed consent of all the subjects was taken and also made aware of his right to withdraw without prejudice at any time. At the sea level, base line study was carried out at Delhi (barometric pressure 740 mm Hg) where the laboratory temperature was maintained between 20 and 24°C with a relative humidity range of 40-50%. After recording the base line study at sea level for two days, subjects were exposed to normobaric hypoxia chamber and allowed to breathe 12% FIO_2 (altitude - equivalent 4350m, final SpO_2 in blood was around 86-88%) for four hours per day for four consecutive days.

On the following day (fifth day), the subjects were inducted in the early morning (within 24 hours) to an altitude of 3,500 m at Leh (barometric pressure 483 mmHg) in the Western Himalayas in 55-60 min by pressurized aircraft. The ambient temperature at this altitude (3500m) varied between 02-20°C during the period and relative humidity 40%. At 3500 m altitude all the tests were conducted in the morning for six consecutive days where the temperature was maintained between 20 and 25°C in the recording room. The first recording of the responses was made early next morning (within 24 hours of arrival at HA).After recording different parameters for four consecutive days, the only IHE group of subjects inducted to 4000 m by road in 4-6 hrs. The ambient temperature at this altitude varied between -2 to +12°C. Incidence of AMS in IHE and control group of subjects were scored with the help of the standard Lake Louise questionnaire (LLS). Total LLS scores more than > 3 (range 0 to 15) were considered as AMS.

Heart rate and blood pressure were recorded by battery operated portable BP monitor at both the locations (OMRON). A finger pulse oximeter probe was set on the right index finger to measure resting oxygen saturation (SpO_2) level (Model MU 300). Respiratory parameters like ventilation, oxygen consumption, end tidal PO_2 and PCO_2 was recorded in sitting position at both the locations using breath-by-breath, open-circuit metabolic measurement system (Model K4b^2 mobile breath-by-breath metabolic system, Cosmed, Italy) calibrated with certified gases and volume standard.

Intermittent Hypoxic Exposure (IHE)

Intermittent hypoxic exposure was performed at sea level in the morning after a breakfast using hypoxic air, in which hypoxic air was produced by injecting medical grade nitrogen through solenoid valve into normobaric hypoxia air chamber. The hypoxic air was breathed continuously for four hours per day for four days in experimental group of subjects in a sitting relaxed position. Hypoxic

air consists of 12% oxygen and balance nitrogen (12% FIO_2, altitude - equivalent 4350m, final SpO_2 in blood was 86-88%). Throughout the training period, subjects were carefully monitored. None of the subjects presented any symptoms of physical deterioration during normobaric hypoxia exposure. Control group of subjects were breathing ambient air i.e; 21% oxygen (Sea level, SpO_2 in blood was 98-99%).

STATISTICS

Repeated measure ANOVA has been used to test the significant difference between days (within effect and between control and experimental group) ANOVA is followed by Bonferonini Test to see the pair wise difference between days. Statistica A 6.0 statistical software has been used for analysis of the data. P values considered significant if it was found to be <0.05.

RESULTS

The incidence and severity of the symptoms of AMS was significantly less (P<0.05) in IHE treated group of subjects in comparison to control on initial two days of exposure at altitude. On day 1 at 3500 HA, 4 individuals (40%) of control group suffered from AMS whereas the IHE treated group showed only one volunteer (10%) (P<0.05). On day 2 at HA, there was three incidences (30%) of AMS in control group with only one in experimental group. On day 3 the number of incidence was reduced to one in control group (10%). At 4000 m altitude only two person (20%) of experimental group suffered from AMS on day 1. Subsequently from Day 2 onwards nobody suffered from any symptom of AMS.

The changes in heart rate and SpO_2 at SL and HA is given in Table-1. The mean values of HR and BP (both systolic and diastolic) showed a significant (P <0.05) rise at HA as compared to their initial sea level readings and remained elevated during the period of acclimatization in both the IHT and Control Group. The HR and BP of IHT treated group was comparatively lower than control group. After the initial steeper rise in HR and BP (Sys) of IHT treated, these values were gradually stabilized from day-4.

At SL, there was no difference of SpO_2 between the control and IHE treated groups (experimental: 98.2% + 0.13; control: 98.3% + 0.15). On acute exposure to 3500m high altitude, both the groups showed statistically significant decrement of SpO_2 (P<0.05). However, the experimental group (IHE treated) showed higher value of SpO_2 (around 2%) in comparison to control (P<0.05). SpO_2 value increased gradually (P<0.05) in both the groups (Table-1).

Basal value of pulmonary ventilation (V_E) did not show any statistical significant difference both in IHE and control groups (IHE group: 9.28 ± 0.47; Control: 9.34 + 0.26). On exposure to HA, both the groups showed significant increase in ventilation (P<0.05) on exposure to altitude. At high altitude, V_E of IHE treated group reached its maximum value on second day of induction and remained elevated on subsequent days. Whereas the control group showed a gradual rise at HA and reached its maximum by day four. The V_E values of control group was also significantly (P<0.05) lower on day 1 and 2 in comparison to IHE treated group.

Basal oxygen consumption (VO_2) at sea level for experimental and control groups of subjects was similar (experimental: 277.13 ± 0.01 ml/min; Control: 304 ± 0.01 ml/min). On induction to 3500m altitude, experimental groups showed a significant rise in VO_2 on day 1 of exposure and thereafter it remains almost same level. Whereas, the control group showed a gradual rise of VO_2 at high altitude. However, the VO_2 values of control group was significantly (P<0.05) lower at high altitude in comparison to IHE treated group.

End tidal PO_2 ($PetO_2$) value showed the significant reduction (P<0.001) in both the groups on exposure to high altitude but the drop of PO_2 was less in IHE group in comparison to control. On subsequent days, $PetO_2$ values of IHE treated group remained almost stable with minor fluctuation whereas in control it gradually rises and stability gained around 5 to 6 days. This indicates the better oxygenation capacity in IHE treated group at pulmonary capillary level. End tidal PCO_2 value showed the significant fall (P<0.001) in both the group on day 1 of induction. But the drop of PetCO2 was more in IHE group than that of control indicating relatively higher ventilation than that of control. It stabilizes by day 4 in IHE group whereas in control group it took at least 6 days. At 4000m altitude further fall of PetCO2 values on day 1 and day 2 onwards it attains a relatively steady state level. This indicates further increase in ventilation at second stage. PetO2 value showed further increase at 4000m altitude and attained a stable value from day 2 onwards indicating faster acclimatization processes in IHE subjects.

DISCUSSION

The result of the present study indicated that different physiological variables were stabilized by day four at 3500m altitude and by day two at 4000m altitudes in IHE treated group of subjects. Exposure of sea level residents to high altitude evokes a series of physiological responses in the human system to avoid malacclimatization. The occurrence

of AMS in un-acclimatized persons rapidly increases from 20% to 70% at the altitude between 2000m to 3960m. The results of this study indicated that the incidence of AMS on acute exposure to 3500 m was significantly less in IHE treated group. The immediate response to acute hypoxia is augmented ventilation (hyperventilation), which is mediated through chemoreceptor to compensate the hypoxic stress. Our observation on ventilation at 3500 m indicates a better and fast respiratory adaptation for IHE treated group in comparison to control. This increase in ventilation improves blood oxygenation (SpO_2) and is known to be the most effective mechanism of altitude acclimatization during the initial days at high altitude. Present study also showed the significantly higher level of SpO_2 in IHE group during initial days of exposure at 3500m altitude in comparison to control. The optimum effect of IHE at sea level depends on hypoxia level, exposure duration and number of hypoxic exposure/ sessions. On HA exposure, the level of an unacclimatized individual to a particular altitude depends on percentage of fully acclimatized values of different system(s) obtained (delta) on subjective and objective levels. The person is said to be acclimatized when the different physiological indices attain a hundred percent of fully acclimatized values/ reached a steady condition for subsequent days (delta = 0; where delta is the difference between observed values and fully acclimatized values.). The studies on the effect of IHE at sea level and its possible outcomes on high altitude acclimatization are very limited. Katayama et al (2001)[18] reported that at least an altitude of 4300m m or less than 13% oxygen is required to stimulate ventilatory parameters for acclimatization during short term intermittent hypoxia at sea level. In another study reported the effect of repeated normobaric hypoxia exposure in un-acclimatized sea level residents during sleep for 7.5 hours in each night for seven consecutive days on high altitude illness and sleep during subsequent exposure to hypobaric hypoxia at 4350m high terrestrial altitude.[19] The results indicated that during hypobaric hypoxia, sleep SaO_2 was significantly higher and AMS upon awakening was lower in normobaric hypoxia group than the sham group. In the present study we first to report where subjects breathed normobaric hypoxia air (12% F_IO_2) for four hours per day for four consecutive days at sea level and its effect on acclimatization have been observed at 3500m and 4000m real high altitude conditions in air inductees. Beidleman et al.,[20] observed that the pulmonary gas exchange was improved by 3% increase in SpO_2 in 6 days of stay at 2200m followed by acute ascent to 4300m. However, this staging for 6 days at 2200m induced only half of the ventilatory acclimatization observed following 2 to 3 weeks of altitude residence at 4300m. Muza et al.,[21] showed that IHE exposure altitude greater than 4000m and a daily exposure duration of at least 1.5 h are required to have a high probability of developing altitude acclimatization. Earlier study from this laboratory, we have compared the acclimatization status on gradual ascent by road in four days from sea level to 3500m with air induction in one hour at 3500m altitude.[13] The result showed the acclimatization was completed by day three in road inductees in comparison to air inductees which took minimum 5 to 6 days. Incidence and severity of AMS was less in road inductees in comparison to air inductees. The study also showed higher level of resting ventilation and oxygen saturation in initial days of acclimatization at 3500m altitude in road inductees. Another study by this group on acclimatization on mountaineers showed gradual ascent by trekking coupled with to and fro hikes from 2100m to 4350 m altitude in six days (after 6 days of stay at 2100m altitude) attributes complete acclimatization by stabilizing different basal physiological parameters and improved physical work performance.[3]

In the present study, the stabilization of various physiological variables in IHE treated group is also supported by the low incidence and severity of AMS in comparison to control in both the locations of high altitudes. The low incidence of AMS at 3500m and 4000m altitudes due to hypoxic air breathing at sea level, resulted the increase in ventilatory drive. The limitation of this study that we could not take the control subjects to 4000m altitude on day 5 as the subjects were not fully acclimatized at 3500m altitude.

At 3500m all the physiological parameters attained a relatively steady value by day 4 of acclimatization whereas in control group it took almost 6 days to overcome the initial hypoxic stress. This is the first time, we report that 4 days of IHE exposure at sea level is equivalent to 2 days of stay at 3500m altitude. The stabilization of different physiological parameters reached by day four in experimental group of subjects at 3500m and two days at 4000m altitudes may be due to increase in ventilatory response. Increase in ventilation in IHE at HA is due to stimulation of peripheral chemoreceptor indicating higher ventilatory response/ventilatory drive. This also indicates a better respiratory adaptation and effective oxygen transport system in the tissues of IHE treated group during initial days of acclimatization. On the contrary the control group deprived of rapid acclimatization and suffered from high degree of hypoxic stress in the first few days of exposure at high altitude. It appears that the required magnitude of physiological responses has not been achieved immediately for control group but occurs gradually, during which period they were undergoing a higher level of hypoxic stress. Hence, IHE at sea level at 12 % FiO_2 for four hours per day four days at sea level facilitates the acclimatization process at 3500m altitude and it can be said that minimum acclimatization period of four days are required to avoid malacclimatization/high

Table 1: Basal Physiological Responses of Different Groups and different Locations

Parameters	Groups	SL	3500 m						4000 m			
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 1	Day 2	Day 3	Day 4
HR (bpm)	EXPT	66.40	82.30	78.20	75.80	74.70	-	-	82.50	80.80	79.40	78.80
	SEM	±2.482	±1.422	±1.672	±1.896	±1.789	-	-	±1.565	±1.731	±1.701	±1.638
	CONT	66.60	89.00 *	85.20	82.60	80.40	75.80	75.30				
	SEM	±1.384	±0.494	±0.389	±0.562	±0.400	±0.359	±0.396				
SpO_2 (%)	EXPT	98.20	93.40	94.00	95.40	96.00	-	-	89.10	90.90	91.80	92.00
	SEM	±0.133	±0.499	±0.537	±0.267	±0.211	-	-	±0.233	±0.180	±0.133	±0.000
	CONT	98.30	91.60 *	92.90 *	93.90 *	94.40 *	95.10	95.40				
	SEM	±0.153	±0.267	±0.277	±0.180	±0.221	±0.180	±0.163				
SBP (mmHg)	EXPT	116.80	125.50	123.80	121.20	120.00	-	-	121.40	120.70	119.70	119.10
	SEM	1.549	1.416	1.489	1.806	1.856	-	-	0.427	0.260	0.335	0.314
	CONT	114.00	129.90	126.10	122.80	121.30	119.60	119.50				
	SEM	±2.076	±1.320	±0.781	±0.573	±1.221	±0.542	±0.477				
DBP (mmHg)	EXPT	67.00	78.80	76.00	72.40	72.20	-	-	77.50	77.80	76.80	76.60
	SEM	±2.309	±2.462	±2.251	±2.197	±1.993	-	-	±1.493	±1.497	±1.348	±1.325
	CONT	67.40	85.20 *	79.80	72.70	71.60	70.70	70.50				
	SEM	±2.825	±2.021	±1.245	±0.367	±0.306	±0.396	±0.428				
VE (L/min)	EXPT	9.28	11.00	11.65	11.94	11.97	-	-	13.83	14.01	14.04	14.20
	SEM	±0.476	±0.363	±0.414	±0.408	±0.407	-	-	±0.265	±0.223	±0.211	±0.196
	CONT	9.34	10.20 *	10.45	11.26	11.42	12.00	12.10				
	SEM	±0.267	±0.303	±0.436	±0.329	±0.391	±0.280	±0.287				
VO_2 (L/min)	EXPT	0.277	0.335	0.368	0.392	0.416	-	-	0.395	0.380	0.377	0.375
	SEM	±0.017	±0.012	±0.018	±0.024	±0.040	-	-	±0.035	±0.037	±0.038	±0.038
	CONT	0.304	0.340 *	0.348	0.379	0.392	0.395	0.398				
	SEM	±0.015	±0.029	±0.031	±0.027	±0.026	±0.025	±0.025				
$PeTCO_2$ (mmHg)	EXPT	37.60	31.30	30.40	29.60	28.90	-	-	25.40	24.90	24.70	24.40
	SEM	±0.267	±0.213	±0.221	±0.221	±0.233	-	-	±0.371	±0.314	±0.300	±0.267
	CONT	37.40	32.10 *	31.70*	31.60	30.90	29.80	28.40				
	SEM	±0.163	±0.314	±0.260	±0.221	±0.180	±0.200	±0.267				
$PetO_2$ (mmHg)	EXPT	100.20	58.70	60.00	61.20	62.50	-	-	65.10	66.20	66.90	67.20
	SEM	±0.467	±0.300	±0.258	±0.291	±0.269	-	-	±0.233	±0.200	±0.180	±0.200
	CONT	99.20*	56.00*	56.30*	57.30*	58.80	62.10	62.70				
	SEM	±0.200	±0.211	±0.213	±0.213	±0.249	±0.180	±0.153				

*p<0.05 level of significance

altitude illness. In compliance with this schedule at 3500m, the experimental groups of subjects were transported by road to 4000m and the different physiological responses attained a relatively stable value by day 2 of induction. Therefore, the duration of acclimatization at the second staging can be considered for two days to avoid malacclimatization/high altitude illness.

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REFERENCES

1. Bhaumik G and Upadhyay S. Common ailments at high altitude. Himalayan Mountaineering Journal. 1995; 50: 113-116.
2. Bhaumik G, Dass D, Bhattacharyya D, Sharma YK and Singh SB. Heart rate variability changes during first week of acclimatization to 3500m altitude in Indian military personnel. Ind J Physiol and Pharmacol. 2013; 57:16-22.
3. Purkayastha SS, Bhaumik G, Sharma RP, Arora BS and Selvamurthy W. Effects of mountaineering training at high altitude (4350m) on physical work performance of women. Aviat Space Environ Med. 2000; 71:685-691.
4. Basu C K, Selvamurthy W, Bhaumik G, Gautam RK and Sawhney RC. Respiratory changes during initial days of acclimatization to increasing altitudes. Aviat Space Environ Med. 1996; 71:685-691.
5. Bhaumik G, Sharma RP, Dass DK, Lama H, Chauhan SKS, Verma SS, et al. Hypoxic ventilatory response changes of men and women 6 to 7 days after climbing from 2100m to 4350 m altitude and after descent. High Alti Med Biol. 2003; 4: 341-348. https://doi.org/10.1089/152702903769192296
6. Bhaumik G, Purkayastha SS, Sharma RP, Sharma YK, Selvamurthy W and Banerjee PK. Chemoreceptor sensitivity in women mountaineering trainees of different altitudes inducted by trekking to 4350m. Defence Science Journal. 2005; 55: 427-435. https://doi.org/10.14429/dsj.55.2004
7. Bhaumik G, Purkayastha SS, Selvamrthy W and Banerjee PK. Oxygen saturation responses to exercise VO2 at 2100m and 4350m in women mountaineering trainees. Indian J Physiol Pharmacol. 2003; 47: 43-51.
8. Bhaumik G, Dass D, Lama H and Chauhan SKS. Maximum exercise responses of men and women mountaineering trainees on induction to high altitude by trekking. Wilderness Environ Med. 2008; 19: 151-156. https://doi.org/10.1580/07-WEME-OR-121.1
9. Singh I, Khanna PK, Srivastava MC, Lal M, Roy SB and

Subramnyam CSV. Acute mountain sickness N Engl J Med. 1969; 280(4): 175-184.

https://doi.org/10.1056/NEJM196901232800402

10. Leaf DE and Goldfarb DS. Mechanism of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. J Appl Physiol. 2007; 102:1313-1322.

https://doi.org/10.1152/japplphysiol.01572.2005

11. Basnyat B and Murdoch D. High altitude illness: an update of pathophysiology, prevention and treatment. Lancet. 2003; 361:1967-1974.

https://doi.org/10.1016/S0140-6736(03)13591-X

12. Nagasaka T and Satake T. Changes of pulmonary and cardiovascular functions in subjects confined intermittently in a low-pressure chamber for 3 consecutive days. Fed Proc. 1969; 28:1312-1315.

13. Purkayastha SS, Ray US, Arora BS, Chhabra PC, Thakur L, Bandopadhyay P and Selvamurthy W. Acclimatization at high altitude in gradual and acute induction. J Appl Physiol. 1995; 79: 487 -492. https://doi.org/10.1152/jappl.1995.79.2.487

14. Beidleman BA, Muza SR, Fulco CS, Cymerman A, Ditzler D, Stulz D, et al. Intermittent altitude exposure reduce acute mountain sickness at 4300 m. Cli Sci (Lond). 2004; 106:321-328. https://doi.org/10.1042/CS20030161

15. Bhaumik G, Dass D, Ghosh D, Kumar B and Singh SB. Effect of Intermittent normobaric Hypoxia Exposures on Acute Mountain Sickness during Acute Ascent to 3500 m in Indian Army Personnel. Defence Life Science Journal. 2018;3:209-215.

https://doi.org/10.14429/dlsj.3.12906

16. Geetha S, Ghosh D, Rathore R, Bhaumik G, Singh SN and Kumar B. Rapid acclimatization to high altitude by Intermittent Hypoxia Training at Sea Level: Role of Bio-chemical markers. Defence Life Science Journal. 2021; 6(2):138-145.

https://doi.org/10.14429/dlsj.6.16265

17. Gangwar A, Paul S, Ahmed Y and Bhargava K. Intermittent hypoxia modulates redox homeostasis, lipid metabolism associated inflammatory processes and redox post-translational modifications: Benefits at high altitude. Sci Rep. 2020; 10(1):7899.

https://doi.org/10.1038/s41598-020-64848-x

18. Katayama K, Shima N, Sato Y, Qiu JC, Ishida K, Mori S and Miyamura M. Effect of intermittent hypoxia on cardiovascular adaptations and response to progressive hypoxia in humans. High Alt Med Biol. 2001; 2(4):501-508.

https://doi.org/10.1089/152702901753397063

19. Schommer K, Wiesegart N, Menold E, Haas U, Lahr K, Burl H, et al. Training in normobaric hypoxia and its effect on acute mountain sickness after rapid ascent to 4559m. High Alti Med Biol. 2010; 11:19-25.

https://doi.org/10.1089/ham.2009.1019

20. Beidleman BA, Fulco CS, Muza SR, Rock PB, Staab JE, Forte VA, et al. Effect of six days of staging on physiologic adjustments and acute mountain sickness during ascent to 4300 metres. High Alt Med Biol. 2009; 3:253-260.

https://doi.org/10.1089/ham.2009.1004

21. Muza SR. Military application of hypoxic training for high altitude operations. Med Sc Spor Exerc. 2007; 39:1625-1631.

https://doi.org/10.1249/mss.0b013e3180de49fe

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