PRE-ACCLIMATIZATION FOR HIGH ALTITUDE SOJOURNS IN HYPOXIC CHAMBERS

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Abstract

More and more people go to high altitude without enough time for proper acclimatization. If there is a lack of time for any reason hypoxic chambers may be used for pre-acclimatization to avoid altitude diseases. Since there are different protocols and the data differ, there is no general consensus about the standard how to perform pre-acclimatization by simulated altitude. We review different types of exposure and focus target groups which may get benefit from pre-acclimatization. We suggest to perform pre-acclimatization by sleeping some nights at a simulated altitude which follows the altitude profile of the "Gold Standard" for high altitude acclimatization. Until there are more detailed data about intermittent hypoxia this method should provide the best effect.

Key words: *acclimatization, hypoxia, simulated altitude, acute mountain sickness*

Introduction

High altitude sojourns are more and more common for many people, but many of them go too fast too high, mainly because of a subjective or (sometimes) objective lack of time. Such sojourns include mountaineers or skiers, businessmen travelling to Colorado, South America and other regions, tourists visit historic sites in the Andes, scientists work at telescopes in the Andes or at Hawaii, or workers in the world's highest mines are located at 5,300 m in Chile. Several 10,000 trekkers hike the Annapurna Trek or to the Solo Khumbu region every year (Fig. 1). The highest points of these treks are at about 5,400 m (Thorong La 5,416 m, Everest Base Camp 5,364 m, Kalar Pattar 5,545 m). Time pressure is the reason why Mt. Kilimanjaro (5,860 m) is considered as the most dangerous mountain in the world. More and more people try to climb it within 3-4 days and only the minority reaches the summit healthy, although there would be beautiful alternatives to the most common used so-called "Coca cola route" (Fig. 2) [1]. This group pressure is the argument of the tour operators to offer treks where the participants climb far too high without adequate acclimatization (Fig. 3). Businessmen are another group with limited time or unforeseen trips to high altitude [2]. Principally correct acclimatization was, is, and will ever be the "Gold Standard" for any altitude sojourn [3]. But if immediate ascent cannot be avoided or work in isobaric hypoxia >4,000 m (rsp. 12.5-13% O₂ at 1 bar) must be done for a whole day, pre-acclimatization

avoids altitude-related diseases and stabilizes the performance of the persons.

The main problem for the body is the management of the decreased oxygen pressure. Without such mechanisms an altitude of about 1,500 m could not be survived without accidental oxygen [4]. Fortunately there are multiple systems to manage the problem, some of them reacting within seconds or minutes (e.g. pulse rate, breathing frequency, breathing volume, shift of the oxygen binding curve), some others in days or weeks (e.g. circulation, haemoconcentration, ventilatory acclimatization) or even years or generations (e.g. vascular growth) (Fig.4) [5]. The effect of some of these acute adaptations is enormous: the shift of pH by respiratory alkalosis at high altitude from 7.2 to 7.6 at a partial oxygen pressure (pO₂) of 30 mmHg increases O₂-saturation (SaO₂) from 28 to 57% [4]. A central role for the regulation of many of these mechanisms has a substance called hypoxia inducible factor 1 α (HIF1 α) [6]. HIF1 α is produced permanently and metabolised via hydroxylation and proteosomal lysis. If hypoxia occurs, the system switches to another pathway within seconds: by a massive phosphorylation HIF1 α becomes the active metabolite which joins the hypoxic binding sites and induces the increased transcription of the HIF1 α -dependent genes [7-8].

The vulnerability of a person by AMS, high altitude pulmonary oedema (HAPE), and high altitude cerebral oedema (HACE) is influenced by the hypoxic pulmonary ventilatory drive (HVD), although this correlation is not strong enough to use HVD as a predictor

MONTHLY TOURIST RECORD G.N.P. JORSALE SINCE VISIT NEPAL 98.																										
MONTH	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016							
JAN.	553	594	474	579	235	427	592	426	486	566	643	576	721	619												
FEB.	708	781	876	682	496	518	751	524	455	592	852	659	923	923												
MAR.	1863	2255	2883	2540	1995	1802	2636	2343	1977	3029	3688	3041	3676	3318												
APR.	2734	3440	4238	3834	2313	2759	3914	2458	3439	4246	4661	4513	5112	6651												
MAY.	1108	1408	1299	1313	692	1624	1301	937	886	1679	1986	1629	2134	2395												
JUNE.	142	115	61	145	90	221	127	201	110	284	297	298	431	434												
JULY.	94	153	39	114	78	77	160	204	184	209	294	229	349	241												
AUG.	195	315	145	203	126	252	183	260	352	434	450	509	421	403												
SEP.	1103	1521	1196	1160	877	1253	976	1036	1190	1458	2135	2135	2301	2374												
OCT.	5987	7263	7537	6440	3530	5470	6390	6242	6595	7750	9260	8831	9407													
NOV.	3964	4533	4862	3479	2488	3714	3208	3448	3385	4188	4830	4769	5056													
DEC.	1513	2183	1681	1081	866	1183	1098	984	1039	1379	1503	1596	1593													
TOTAL	20014	24561	25291	21570	13786	19300	21396	19063	20036	25814	30599	28784	32124													
EXPEDITION IS NOT INCLUDED TREKKERS ONLY.															PRE-(KALI BHADUR RAI) G. SCOUT SNP.											

Fig. 1. Number of persons who visited the Solo Khumbu region (Sagharmatha National Park, Nepal) 1998-2011 (by courtesy of the National Park Office)

Fig. 2. Ascent profile of Mt. Kilimanjaro (5,890m): "Coca cola route" (line) and alternative ascent via Shira Plateau, Southern Circuit, and Barafu Bivouac (dotted line), which follows a nearly ideal ascent profile.

Fig. 3. Altitude profiles of 19 tours, offered by the three biggest German tour operators (from [14])

Fig. 4. Mechanisms of acclimatization (examples, from [14])

of a person's ability to cope with high altitude conditions. HVD is genetically determined. Although a multitude of attempts were done in the past, e.g. for arterial oxygen saturation (SaO_2) [9], a combination of SaO_2 and individual performance, and others, there is no reliable prediction of individual altitude tolerance except for the person's history: if he/she has tolerated high altitude in the past quite well, it is likely that there will be no problem at other sojourns, if the person acclimatizes properly.

But there are other important factors which are responsible for the individual fitness at altitude and the risk of altitude-related diseases as the limitation of diffusion capacity of the alveolar membrane or of minute breathing volume [10], the erythrocytes form, plasticity, size, and age [11], or increased plasma volume or low haematocrit respectively [12]. Again, all of them do not allow to predict the individual altitude or hypoxia tolerance.

For pre-acclimatization an extensive literature research was performed in international databases (e.g. PubMed) with the keywords intermittent hypoxia, simulated altitude, acute mountain sickness, hypoxic ventilatory response, mountaineering, trekking, acclimatization, hypoxic chambers, and isobaric hypoxia. Papers cited in reviews but not listed in the databases and other papers which were known to the authors but also not listed in the databases were also included if there was a substantial contribution to the topic of this paper.

Which group may benefit from pre-acclimatization?

Knowledge about acclimatization strategies and ascent profiles are mainly based on empirical data, but these include >1000 years of high altitude experience [13]. Nevertheless, there is no doubt that proper

acclimatization according to the "Gold Standard" (recommendations published in [3,14] and a multitude of other papers) is the best way to prepare the body for high altitude. There is no evidence that this will change in the next 100 or so years, since any genetic adaptation, if there is some interbreeding between lowlanders and highlanders in the course of the so-called "globalization", will take several generations. Acclimatization is of special importance for any lowlander who will sleep at altitude >2,500 m or who will stay at >4,000 m for 1-3 hours. Persons with pre-existing conditions may need special advice or in some cases restrictions [15]. "Gold Standard" includes slow ascent (+500m sleeping altitude every second day or a maximum of +1,000 m per week, beginning at 2,500 m), sleep with slightly increased upper body, no breathing with pressure and workload below the anaerobic threshold during acclimatization phase [3,14].

If such an ideal ascent profile cannot be realized for any objective reason (e.g. airport of destination at high altitude (e.g. in the Andes or Tibet), urgent and unexpected work has to be done at high altitude like rescue or service, or "critical" mountains where a good altitude profile is difficult to be realized (e.g. Ruwenzori Mountains), a pre-acclimatization for 24-48 hours should be possible for most industrial or business tasks or for travelling. In contrast, the setting for most rescue operations is different. For normal alpine (helicopter) rescue pre-acclimatization is not necessary, mainly because the crews stay too short at altitude and most of them are partially acclimatized. But if international operations should be assisted by a back-up team of unacclimatized lowlanders, the time necessary to organize such operations should be used to pre-acclimatize the team members.

Beside these groups, there are even more people who may benefit from pre-acclimatization: persons with known problems of acclimatization, although the altitude profile was perfect ("slow acclimatizers"), or elite sport teams who are facing competitions at high altitude, which was first discussed for the Olympic Games at Mexico City in 1968.

Pre-acclimatization – how should it be performed?

Some of the mechanisms listed above prevent altitude diseases in the early stage of altitude exposure, while others are responsible for the metabolic stabilization of the body for long stays at altitude [5]. Those which develop over several generations are not of interest for the topic presented here. For pre-acclimatization it does not matter whether it is done by an exposure of the body to real (hypobaric) or simulated altitude (hypobaric or – easier – isobaric), but all procedures are limited in duration. Therefore any pre-acclimatization will influence exclusively those mechanisms which are responsible for the early stage of high altitude sojourns, i.e. to avoid acute mountain sickness (AMS).

It is well known that there are minor physiological differences between isobaric and hypobaric hypoxia. This was already described by Paul Bert 140 years ago and confirmed later by others [16,17]. But these differences do not have any consequences for the tactics of acclimatization, neither in isobaric conditions nor in the mountains [18,19].

The main difference between pre-acclimatization at "real" altitude or in a hypoxic chamber is, that real altitude means, that the person will stay at a given altitude for some time (continuous exposure), while in most cases the stay in a hypoxic chamber will last some hours per day or an overnight stay. Unfortunately there is not much knowledge about acclimatization by intermittent hypoxia with some hours per day in hypoxic environment and therefore actually there is no standard for pre-acclimatization in hypoxic chambers by intermittent hypoxia of some hours. As Bartscher et al. mentioned in detail, studies performed so far show a benefit if the persons are exposed 1-4 hours per day at a corresponding altitude of about 4,000 m ($\text{FiO}_2=12\%$) [20]. On the other hand Bärtsch et al. didn't find any difference in the incidence of AMS of persons ascending to Margherita Hut (4,560 m) after some days with 12% O_2 for 4 hours (personal communication, May 2009). But as stated by Mutschler the subjects of Bärtsch's study didn't follow exactly the altitude profile of the study for several reasons (weather etc.; Mutschler, personal communication, July 2009), which is a major limitation of the study.

Several other recent studies deal with the topic of simulated altitude, in contrast to the legendary "Operation Everest II" in most cases with intermit-

tent hypoxia. Most studies available so far deal with limited numbers of subjects and with significant differences in exposure (altitude, duration of hypoxia and duration normoxia between the hypoxic phases). This prevents a direct comparison of the results. Nevertheless, since Richalet used a hypoxic chamber when he was preparing the Everest expedition in the early 90's [21], some other studies indicate the benefit of pre-acclimatization by intermittent hypoxia to minimize the risk to suffer from AMS [22,23]. In most cases the hypoxic exposure was equivalent to an altitude of 4000 m, but the duration per day and the total period of exposure was very different (3 and more hours per day for 6-20 days) [21-24]. There was no difference between exposure combined with some or without activity reported [23]. At moderate altitude there was no significant influence on several physiological factors by intermittent hypoxia [25], but several changes as usual in normal ("real") hypoxia in the mountains were found when the exposure exceeded a corresponding altitude of 2500 m [21,23,26-28]. In some investigations an increase of performance [21,23,24] or mood status was found [29]. Intermittent hypoxia also increased the vagotonus [30]. Some data indicate that at least 1 week of exposure may be necessary to induce significant pre-acclimatization [25]. In contrast to Katayama's study significant acclimatization was found after 25 days of exposure only [31]. The most prominent effects of intermittent hypoxia with simulated altitude were found for HVD, hyperventilation and arterial oxygen saturation [21-24,27,28,30-33].

Summarized the knowledge about the influence of intermittent hypoxia and here especially the optimal "profile" of equivalent altitude, duration of exposure, the number of exposures and the pause between them on acclimatization AMS, and other factors is not yet clear. Therefore we suggest to follow "traditional" rules for acclimatization and to sleep in hypoxic conditions for some nights [3,14]. Although there are no double-blind controlled studies, there is evidence that the interruption of hypoxia during the day (when the subjects sleep in hypobaric hypoxia only) is of minor effect compared to 24 hrs hypoxia. Our non-systematic data of about 100 mountaineers who summited Mt. Kilimanjaro (5,890 m), Aconcagua (6,962 m), and other relatively high trekking peaks and some expedition summits do not indicate a significant lesser acclimatization (indicated by higher incidence of AMS or failing to reach the summit) when compared to others who spent a couple of days at altitude for acclimatization.

Principally any pre-acclimatization should follow the recommendations of the "Gold Standard" [3]. This can be done in hypoxic chambers as well as during some days in a mountain hut. The latter is more charming, but unfortunately not always realistic.

How high will the final altitude be and shall the pre-acclimatization be combined with activity? What's your goal? Just to pre-acclimatize to avoid AMS or to improve your performance? For the latter planning is crucial: VGEF and mitochondriosis increase only by high intensive training at about 3,650 m [34] and the "threshold" for erythropoietin increase is at about 2,100 – 2,500 m [35,36]. An increase of +5% of erythrocyte volume may need at least 400 hrs (3-4 weeks) at 2,500 – 3,000m and the anaerobic system may get more benefit by altitude than the aerobic system [37,38].

The so-called "slow acclimatizers" are a special problem for preventive altitude medicine. Except for the person's history of previous altitude sojourns as mentioned above there are no procedures available which allow to detect slow acclimatizers with a positive predictive value which is acceptable. For example the hypoxic ventilatory drive, for large collectives well known to be inverse correlated with an increased risk for problems of acclimatization and AMS, cannot be used as predictor because its positive predictive value is only about 60% [39,40]. The monitoring of SaO₂ as described by Thomas and many others is limited by the same problem [9]. Pulse frequency cannot be used as a predictor, but it may be used to monitor the acclimatization: although there are no data there is evidence that slow acclimatizers should have normal pulse rate as normal persons have when they are completely acclimatized for the respective altitude.

Up to now the only chance to identify "slow acclimatizers" is a careful and detailed history of the person's altitude sojourns and the problems which have arisen. Any person who suffered significantly from AMS symptoms although the altitude profile was acceptable or who complained about sleep disturbances significantly more than his or hers companions at the same altitude should be suspected to be "slow acclimatizers". The same should be suspected if a person suffered from HAPE at surprising low altitude (2,500 – 3,000 m) or if a person suffered from recurrent HAPE. It is well accepted that slow acclimatizers should follow a more "defensive" altitude profile than other mountaineers – but unfortunately there are no data or any consensus what "more defensive" is (survey in [14]). Until more detailed data are available we suggest to add at least one more day to every altitude of the profile until an altitude of 4,000 m is reached. Above this altitude the acclimatization process of slow acclimatizers is highly individual and should be monitored clinically (pulse rate, AMS symptoms or Lake Louise Score [41]).

The final altitude of pre-acclimatization depends on the altitude profile later in reality and on the time which is planned to reach that altitude. If a person wants to climb a mountain, the days of ascent can be included in the altitude profile of pre-acclimatization.

This is impossible if the person has to go to altitude at once, e.g. the businessmen or tourists to destinations in the Andes. For high destinations, work, or "critical" altitude profiles the ideal altitude to be reached by pre-acclimatization is the same (or a bit more to get a "safe zone") than the destination. Risk groups ("Slow acclimatizer") should pre-acclimatize to a final altitude which is a bit higher than the highest place planned for sleeping, but a much more "defensive" altitude profile should be chosen. As mentioned above athletes should pre-acclimatize to the height of the competition +300 m. Both, risk group and athletes get a safe margin by doing so with a technique which is not yet evaluated in detail.

For the timing of pre-acclimatization data are limited. Possibly the best scheme for altitude up to 4000 m and healthy persons is as follows: 1st night at 2,500 m equivalent altitude, 2. (-3.) night at 3,000 m, and 1 week later 2 (-3) nights at 3,000 and 3,500 m. This can be done at weekends and therefore it can be easily combined with normal life. It should be as near as possible, but not longer as 2 (-3?) weeks before departure.

Conclusion

Pre-acclimatization decreases the risk of altitude diseases significantly, if acute ascent cannot be avoided. To do so, a minimum of time in hypoxic environment is necessary. The special advantage of hypoxic chambers is the well controlled environment, the safety for persons with individual risks or pre-existing conditions and the easy coordination of the exposure with normal daily life and work. Nevertheless, it must be planned carefully and performed within a short period before departure. Going "not too high too fast" for optimal acclimatization is the "Gold Standard" to avoid health risks and to provide optimal performance at high altitude.

Declaration of interest

The authors report no conflicts of interest.

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A – Study Design

B – Data Collection

C – Statistical Analysis

D – Data Interpretation

E – Manuscript Preparation

F – Literature Search

G – Funds Collection