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Physiological effects of training in hypoxic environments and its benefits for prevention and rehabilitation

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List of Abbreviations

AMS	= acute mountain sickness
BMI	= body mass index
CO_2	= carbon dioxide
ECG	= electrocardiogram
EF	= ejection fraction
F_iO_2	= inspired oxygen fraction
HAPE	= high altitude pulmonary edema
HbA_{1c}	= glycated hemoglobin
HACE	= high altitude cerebral edema
HDL	= high density lipoprotein
HG	= hypoxic group
HH	= hypobaric hypoxia
HIF1α	= hypoxia inducible factor 1α
HIT	= high intensity training
HR	= heart rate
LDL	= low density lipoprotein
NG	= normoxic group
NH	= normobaric hypoxia
O_2	= oxygen
a.s.l	= above sea level
P_B	= barometric pressure
P_iO_2	= inspired oxygen
RR	= blood pressure
SpO_2	= peripheral oxygen concentration measured by pulse-oximetry
T_1	= training 1
T_2	= training 2
VO_{2max}	= maximal oxygen intake
VO_{2peak}	= peak oxygen intake
η^2	= partial eta-square

1. Abstract

Background: The benefits of training in hypoxic environments are widely discussed. Several interventional studies prove its usefulness for different applications. Lately the impact of hypoxia on pre-existing health conditions in middle aged and elderly populations has come into focus. Especially the potential of hypoxic training in reducing the workload during endurance training could withhold great benefits for orthopedically impaired populations like geriatric patients. Furthermore, several studies show beneficial effects of hypoxic training on cardiovascular risk factors and blood perfusion in muscles. This study compound aims at the investigation of physiological effects and potential benefits of hypoxic training interventions in the elderly.

Methods: Three studies and one review are supposed to give an overview of physiological effects and the usability of hypoxia as additive for endurance training in the elderly. Study A evaluates the effects of a commonly practiced hiking prevention program on cardiovascular risk factors in 24 elderly subjects (10 female, age 66.2 ± 4.4 years and 14 male, age 65.6 ± 2.7 years). Study B and C identify possible obstacles and risks when planning rehabilitation or prevention programs in NH. Study B shows the main differences between NH and HH comparing the physiological effects in six subjects (age 28.3 ± 8.2 years) during a "real" and a simulated hike. Meanwhile, paper C gives an overview of possible risks and especially the impact of prolonged hypoxia exposure and its potential impact on cognitive functions. Finally, in Study D, 40 geriatric patients (NG: n = 16, age 82.0 ±7.8 years, HG: n = 19, age 80.2 ± 7.2 years) participated in a single blinded, placebo controlled interventional study, investigating the potential reduction of physical workload during endurance training using NH and its physiological effects.

Results: Only one hiking session per week over a time course of nine months does not lower cardiovascular risk factors in subjects older than 60 years. Systolic blood pressure seems to be lowered only in patients with pathological or borderline values. For prevention- or rehabilitation programs, using normobaric hypoxia, some differences have to be taken into account. In NH, heartrate is lower while peripheral oxygen saturation is higher maintaining a similar physical strain as in HH ($p < 0.05$). Furthermore, NH seems to impair cognitive reaction time after sleep to a certain degree. Physical workload (Watt/kg $p = 0.012$) and

related parameters are significantly reduced in a three week interventional endurance training study on simulated 3000 m in the elderly.

Discussion: NH training lowers physical workload during endurance training in the elderly. Especially for geriatric rehabilitation, where patients and their therapists have only three weeks and rather short training sessions for measurable improvements, NH has great benefits. Furthermore, it seems to provide a safe environment and allows better monitoring than HH for prevention- or rehabilitation programs. Cardiac and pulmonary demands are lower in NH compared to HH. Overnight stays in hypoxia bear some risk for cognitive impairment, which has to be taken into account as possible risk for accidents. Nevertheless, we think during normal daytime training sessions and in quite low altitudes, this is no limiting factor for preventive- or rehabilitative programs. The common hiking routine of only one hiking session per week, practiced by most elderly, seems not to be sufficient to improve cardiovascular fitness. Therefore, the search for new possibilities to use the benefits of hypoxia for this age group is of importance.

Conclusion: Training in hypoxic environments bears a lot of potential for certain patient groups. Especially the use of NH as additive to endurance training either to lower physical workload or to enhance the training intensity seems to be promising. This also could open the field of low volume high intensity training for geriatrics.

2. Introduction

Training in different hypoxic environments has been of special interest to the scientific community since 60 years [43]. The scientific focus lay mainly on the physiological mechanisms accompanying ambient hypoxia as well as the impact and usability of hypoxic stimuli for mountaineers, high altitude workers or elite athletes [43]. Even though several articles have been published in this field, no clear picture regarding different protocols and its resulting effects can be drawn. Even nowadays, the physiological effects of hypoxic training withhold many unanswered questions [40]. While it seems to be debated if hypoxic training can be used to enhance peak performance, more and more investigators long for the exploitation of the few known effects for several different patient groups [43].

Following reports from mountaineers, training in hypoxic environments is thought to promote weight loss and influence adipose tissue as well as fat metabolism [16]. In this context, several studies investigate the impact of hypoxic interventions on obesity and the metabolic syndrome [29,44]. Furthermore, hypoxic preconditioning as well as the promotion of angiogenesis with hypoxic stimuli is thought to improve oxygenation and blood perfusion in the long run [39]. The discovery of the hypoxia inducible factor HIF1α as the main promoter for adaption to hypoxia has widened the field and added new knowledge to the understanding of cancer development and proliferation [9].

A rather new field of interest are changes in physiological adaptions due to hypoxic stimuli, regarding gender differences or different age groups. Considering the increasing numbers of persons reaching certain altitudes, such findings gain more and more practical importance [43]. Especially for older generations, mountaineering and altitude hiking seem to withhold a special fascination [7]. From a physiological point of view, altitude hiking bears a lot of potential for older individuals or even geriatrics. On one hand, there occur several physiological adaptions provoked by the hypoxic environment [43]. On the other hand, hiking is a highly demanding activity requiring balance, strength and attentiveness [41,43].

Interventional studies investigating preventive or rehabilitative use of different hypoxic settings with older subjects are quite scarce. Especially the potential dangers for patients suffering from pre-diagnosed diseases (i.e. coronary heart disease, heart failure, chronic obstructive pulmonary edema) remain unclear. Much more research in this field is needed to provide guidelines for patients and caretakers. Here, normobaric hypoxia

rooms can provide save clinical environments for studies and diagnostics. This study compound aims at investigating the physiological effects of training in hypoxic environments and its benefits for prevention and rehabilitation focusing on the elderly population as well as at the interchangeability of normobaric and hypobaric hypoxia.

The first aim (Study A) was to investigate if a hiking intervention qualifies as prevention-program for metabolic syndrome. The second aim (Study B) was to investigate the interchangeability of hypobaric hypoxia with normobaric hypoxia in order to put it to use in clinical investigations. The third aim (Study C) was to evaluate possible side effects of hypoxia exposure. The fourth aim (Study D) was to show that training in normobaric hypoxia has the potential to improve geriatric rehabilitation.

We hypothesized that different hypoxic environents is useful for prevention- as well as rehabilitation programs in older individuals.

Study A

Gatterer, H., Raab, C., **Pramsohler, S**., Faulhaber, M., Burtscher, M., & Netzer, N. (2015). Effect of weekly hiking on cardiovascular risk factors in the elderly. *Zeitschrift für Gerontologie und Geriatrie, 48(2), 150-153*.

Study B

Netzer, N. C., Rausch, L., Eliasson, A. H., Gatterer, H., Friess, M., Burtscher, M., & **Pramsohler, S**. (2017). SpO2 and Heart Rate During a Real Hike at Altitude Are Significantly Different than at Its Simulation in Normobaric Hypoxia. *Front Physiol. 2017 Feb 13;8:81. 2017.*

Study C

Pramsohler, S., Wimmer, S., Rausch, L., & Netzer, N. (2017). Schlaf in der Höhe. *Pneumologie, 71(03), 146-150.*

Study D

Pramsohler, S., Burtscher, M., Faulhaber, M., Gatterer, H., Rausch, L., Eliasson, A., & Netzer, N. C. (2017). Endurance Training in Normobaric Hypoxia Imposes Less Physical Stress for Geriatric Rehabilitation. *Frontiers in Physiology, 8*.

3. Study A

3.1. Summary

Generally hiking is a rather time-consuming activity. Therefore, it is commonly done at weekends only [7,21,32]. In order to recommend regular hiking as a prevention-program for various diseases it is necessary to evaluate if the stimulus of only one or even less hiking sessions a week provoke measureable adaptions. A great portion of persons aged 60 years and older suffer from hypertension as well as hyperglycemia which are known to lead to more severe diseases like heart failure or stroke [28]. Therefore, we investigated in a 9-month interventional hiking study the effects on BMI, RR, HbA_{1c}, HDL and LDL in older people.

3.2. Material and Methods

10 female (age 66.2 ± 4.4 years) and 14 male (age 65.6 ± 2.7 years) participants were included. Pre- and post-test were performed including measurements of anthropometric data, a resting ECG, RR measurement and HbA_{1c} as well as LDL and HDL determination. Where indicated, an exercise ECG was performed to ensure safety during the intervention.

The intervention consisted in nine month of regular mountain hiking, completing an increase of minimum 500 m altitude within three hours at least once a week. This did not include decent. To stay quite close to common practice, participants were allowed to reach an altitude increase of 1000 m within six hours every two weeks. Resting periods lasting longer than two weeks were not allowed. Exercise was required to be performed at least at 31 of the total 37 weeks. Participants recorded their hiking sessions via journal and performed self-administered resting RR measurements every second day.

Data analysis were performed with SPSS statistical software package (PASW Statistics for Windows version 18.0, SPSS Inc., Chicago, IL, USA). Data are presented as means ± SD. For statistical analyses Kolmogorov-Smirnov, student t-test as well as Wilcoxon test were used were appropriate. The significance threshold was set at 0.05.

3.3. Results

Participants showed a normal cardiovascular risk profile at pre-test. Over the time course of the nine months, no changes in HbA_{1c}, LDL or HDL could be found. Resting RR values did not change as well. After subgroup analysis for pathological or borderline

values at pre-test, only systolic blood pressure tended to improve (from 145.6 ± 7.0 mmHg to 137.0 ± 9.3 mmHg; p= 0.068). According to the age predicted peak oxygen uptake, training intensity was approximately 50%.

Table 1: Changes in measured parameters over the 9-month period for the entire group and in terms of gender, displayed in means ± standard deviation. [13] page 151

	Males			Females			All		
	No. participants	Pretrial	Posttrial	No. participants	Pretrial	Posttrial	No. participants	Pretrial	Posttrial
Body mass (kg)	14	78.7±11.2	79.0±12.0	10	60.4±5.3[a]	60.7±5.1[a]	24	71.1±12.9	71.4±13.3
BMI (kg/m^2)	14	25.0±2.2	25.0±2.5	10	22.8±1.9[a]	22.8±1.9[a]	24	24.1±2.3	24.1±2.5
HR_{rest} (beats/min)	12	60±7	64±8	8	59±6	60±9	20	59±7	62±9
BP_{sys} (mmHg)	14	126.9±14.3	125.6±10.0	10	122.5±13.9	122.4±12.4	24	125.1±14.0	124.2±10.9
BP_{dia} (mmHg)	14	78.0±10.1	76.6±7.6	10	76.9±6.8	75.5±4.9	24	77.6±8.7	76.1±6.5
HbA_{1c} (%)	9	5.4±0.5	5.6±0.4	7	5.5±0.4	5.5±0.3	16	5.5±0.5	5.5±0.3
HDL cholesterol (mg/dl)	14	62.3±19.5	61.9±16.3	10	74.9±16.2	70.3±23.0	24	67.5±18.9	65.4±19.4
LDL cholesterol (mg/dl)	12	135.7±27.5	126.3±33.1	10	149.9±41.2	144.2±41.2	22	142.1±34.3	134.4±37.2

BMI body mass index, HR_{rest} resting heart rate, BP_{sys} systolic blood pressure, BP_{dia} diastolic blood pressure, HbA_{1c} glycated hemoglobin, *HDL* high density lipoprotein, *LDL* low density lipoprotein[a]Indicates gender-specific differences.

3.4. Conclusion

Hiking in lower altitudes and with only one session a week does not seem to be sufficient to provoke relevant adaptions. Supposedly the lack of effect is ought to the low exercise intensity of approximately 50% of VO_{2max} as well as for the low hypoxic stimulus [32]. Furthermore, the recruiting for such a volunteer exercise study protocol often contains a bias in subject selection because usually exercise oriented persons sign up for such studies. Therefore, the subjects were in an overall quite good health state at the beginning of the trial allowing only small adaptions. Nonetheless, the measured risk factors did not worsen during the interventional period and in subjects with pathological or borderline values systolic RR tended to improve. To recommend hiking on a regular basis as prevention for metabolic syndrome it seems to be necessary to practice more often per week [20]. Our subjects reported that the time and money (transport to hiking locations) needed to participate almost exceeded their personal limit. Therefore, we think recommending more frequent hikes is not feasible. Additionally, a higher training intensity as well as altitudes above 2500 m could improve the outcome [8]. These postulations are quite hard to meet at old age and bear logistical as well as physical barriers for a large group of elderly.

4. Study B

4.1. Summary

A practical alternative to real altitude hikes could provide simulated hikes in normobaric altitude chambers. Although, more knowledge regarding differences in physiological reactions between NH and HH is needed for a scientific- and save use of NH in clinical investigations or preventive and rehabilitative programs. The interchangeability of NH and HH is largely discussed [15,22]. Several study groups found slight differences in the two, but the underlying mechanisms leading to those differences are still quite unclear [36]. Therefore, we compared the two conditions longing for a maximum of standardization investigating differences in HR, SpO_2 and the occurrence of AMS.

4.2. Material and Methods

Six healthy subjects (age 28.3 ± 8.2 years) with a self-reported fitness routine of 1-4 hours per week participated in two hikes. None of the subjects have been to altitudes above 2,000 m a.s.l during the last six months. Participants completed two trials (T_1 and T_2). The study design was controlled for worn cloth, fluid and food intake as well as carried weight to maximize comparability of T_1 and T_2. Temperature and humidity were continually measured in both settings. During both hikes SpO_2 and HR were measured by self-administered pulse oximetry every 15 min by the participants.

At T_1 the 7-hour hike (including breaks) was simulated in a normobaric altitude room, mimicking the exact same parameters as on the Humu'ula trail on the mountain Mauna Kea in Hawaii. It consisted of a 7-hour treadmill walk including breaks (h/p Cosmos Mercury and Quasar) with an inclination of 14.2% and a constant speed of 1.6 km/h. NH was provided by an oxygen expulsion system (Low Oxygen Systems; Berlin-Buch, Germany). The expulsion system (oxygen exchange through nitrogen) allows a mixture of fresh air to keep controlled CO_2 levels comparable to the levels in HH. Participants started walking at a simulated altitude of 2,800 m. The FiO_2 in the chamber was modified automatically, which led to the completion of the treadmill task at a simulated altitude of 4,200m.

Four weeks after T_1 the actual hike in HH (T_2) was performed by the same subjects. Parameters as P_B, temperature, energy- and fluid-intake were constantly measured. Data were expressed as means and standard deviation or as medians with 95% confidence intervals as appropriate. Nonparametric tests (Wilcoxon) were used for HR, SpO2, and

AMS scores at each time point comparing NH and HH. The significance threshold was set at 0.05.

4.3. Results

The simulation did mimic the conditions in HH quite well as shown in Figure 1. Temperature ranged in both conditions at all altitude levels around 20 °C (19–24 °C) and humidity was between 50 and 60 % (average on Mauna Kea 58%; in the chamber 55%). HR and SpO_2 differed significantly in most of the measured time points as show in Table 2 (HR 66%, SpO_2 62% of the time points). An overall statistical difference between NH and HH regarding HR and SpO_2 was detected ($p < 0.05$). HR values were significantly higher while SpO_2 values were significantly lower in HH. AMS scores did not differ significantly between the chamber and the mountain. Self-reported Borg scale values showed no difference for rate of perceived exertion in both NH (12.33 ± 2.07) and HH (12.33 ± 1.75).

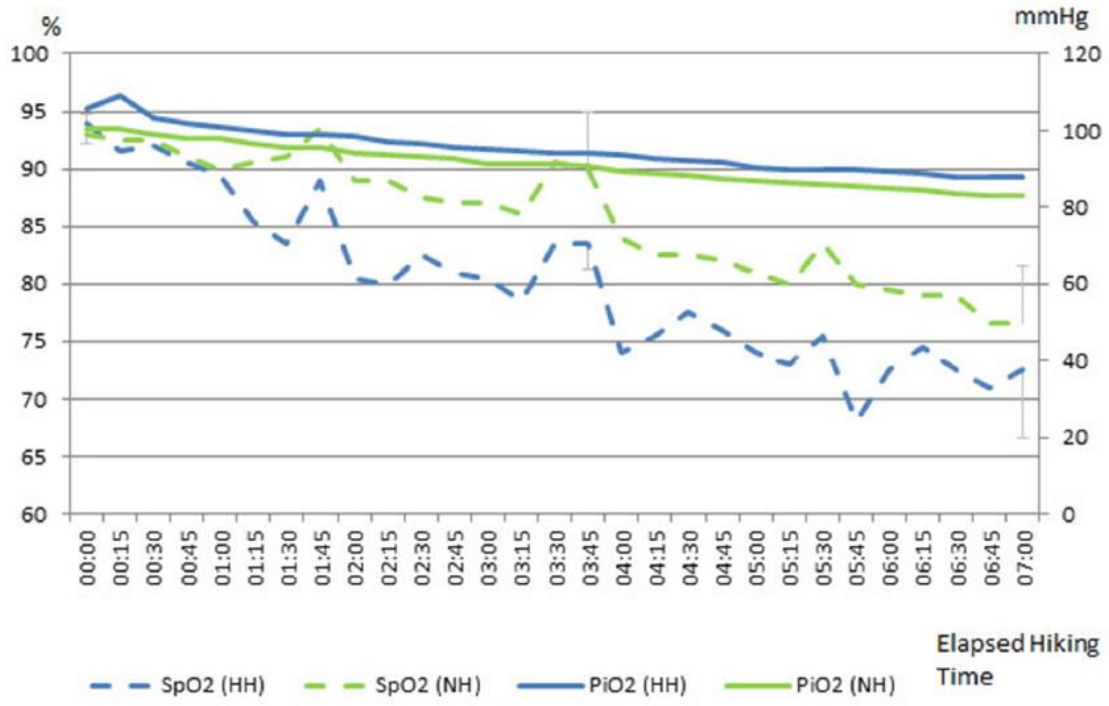


Figure 1: Comparison of inspired oxygen (P_iO_2 and peripheral oxygen saturation (SpO_2) during the hikes in normobaric (NH) and hypobaric hypoxia (HH).
Legend: Break 1 at 3,100 m altitude, break 2 at 3,500 m altitude, break 3 at 3,900 m altitude; % = SpO2 %; mmHg = PiO2 mmHg. [27] page 4

Table 2: Actual fraction of inspired oxygen (FiO2) in normobaric hypoxia (NH) and barometric pressure (P_B) in hypobaric hypoxia (HH).Medians (confidence intervals, CI) of heart rate (HR)and peripheral oxygen saturation (SpO_2) and p-values between NH and HH. [27] page 5

F_iO_2 %	P_B mmHg	Altitude (m)	HR median (bpm) and 95% CI		NH vs. HH
			NH	HH	*p*-value
14.57	550	2,800	93 (77–109)	87 (72–102)	0.225
14.57	566	2,850	108 (100–115)	123 (109–137)	0.028
14.33	539	2,900	104 (93–114)	110 (93–126)	0.249
14.25	533	2,950	101 (91–111)	122 (101–143)	0.046
14.21	527	3,000	102 (89–114)	120 (104–136)	0.027
14.02	523	3,050	103 (91–114)	125 (109–140)	0.027
13.89	518	3,100	103 (88–118)	122 (112–131)	0.027
13.85	518	3,150	84 (69–99)	94 (76–111)	0.080
13.66	516	3,200	103 (92–114)	131 (114–148)	0.028
13.56	509	3,250	104 (95–113)	122 (105–139)	0.028
13.50	506	3,300	105 (94–116)	122 (96–148)	0.028
13.46	503	3,350	104 (94–114)	125 (107–142)	0.027
13.24	500	3,400	103 (90–115)	129 (108–149)	0.028
13.24	497	3,450	105 (93–116)	133 (112–153)	0.028
13.21	496	3,500	80 (62–98)	87 (68–105)	0.115
13.18	496	3,550	75 (59–90)	87 (69–105)	0.046
12.97	493	3,600	107 (95–119)	130 (96–164)	0.173
12.91	489	3,650	111 (97–124)	131 (114–148)	0.027
12.80	486	3,700	109 (91–126)	135 (105–165)	0.046
12.69	483	3,750	109 (92–126)	128 (115–141)	0.028
12.63	478	3,800	111 (93–128)	136 (120–152)	0.027
12.52	476	3,850	110 (93–127)	138 (118–158)	0.028
12.49	476	3,900	87 (67–107)	94 (77–111)	0.058
12.37	476	3,950	112 (94–129)	126 (91–161)	0.173
12.33	473	4,000	113 (95–131)	122 (108–136)	0.115
12.26	470	4,050	115 (98–132)	115 (96–133)	0.345
12.10	467	4,100	121 (106–135)	125 (106–144)	0.173
12.08	465	4,150	114 (93–134)	132 (107–157)	0.046
12.03	465	4,200	114 (92–135)	130 (105–155)	0.046
		Mean	103 (93–114)	121 (106–135)	

F_iO_2 %	P_B mmHg	Altitude (m)	S_pO_2 median (%) and 95% CI		NH vs. HH
			NH	HH	*p*-value
14.57	550	2,800	93 (91–95)	94 (92–96)	0.336
14.57	566	2,850	93 (91–94)	92 (88–95)	0.399
14.33	539	2,900	93 (90–95)	92 (89–95)	0.248
14.25	533	2,950	91 (89–93)	91 (85–96)	0.786
14.21	527	3,000	90 (88–92)	90 (85–94)	0.854
14.02	523	3,050	91 (86–95)	86 (83–88)	0.078
13.89	518	3,100	91 (85–97)	84 (79–88)	0.027
13.85	518	3,150	94 (90–97)	89 (86–92)	0.027
13.66	516	3,200	89 (84–94)	81 (75–86)	0.028
13.56	509	3,250	89 (85–93)	80 (78–82)	0.026
13.50	506	3,300	88 (83–93)	83 (78–87)	0.026
13.46	503	3,350	87 (82–92)	81 (75–87)	0.058
13.24	500	3,400	87 (82–92)	81 (75–86)	0.172
13.24	497	3,450	86 (81–91)	79 (72–85)	0.046
13.21	496	3,500	91 (88–93)	84 (79–89)	0.028
13.18	496	3,550	90 (86–94)	84 (75–92)	0.075
12.97	493	3,600	84 (79–89)	74 (68–80)	0.027
12.91	489	3,650	83 (77–88)	76 (71–81)	0.027
12.80	486	3,700	83 (78–88)	78 (72–83)	0.112
12.69	483	3,750	82 (77–87)	76 (70–82)	0.027
12.63	478	3,800	81 (75–87)	74 (70–78)	0.027
12.52	476	3,850	80 (75–85)	73 (64–82)	0.046
12.49	476	3,900	84 (79–88)	76 (64–87)	0.028
12.37	476	3,950	80 (74–86)	68 (61–75)	0.027
12.33	473	4,000	80 (73–86)	73 (71–74)	0.046
12.26	470	4,050	79 (74–84)	75 (70–80)	0.058
12.10	467	4,100	79 (74–84)	73 (67–78)	0.027
12.08	465	4,150	77 (71–82)	71 (64–78)	0.027
12.03	465	4,200	77 (71–82)	73 (68–78)	0.027
		Mean	86 (82–90)	80.2 (77–83)	

4.4. Conclusion

There are significant differences in physiological reactions between NH and HH. Both, HR and SpO_2, behave significantly different even when keeping P_iO_2 levels constant. Concurring with the argumentation of other study groups, these differences are most likely ought to a higher dead space ventilation caused by a higher breathing frequency and lower tidal volume compared to NH [36,37]. The underlying mechanisms causing those changes remain unclear. Unfortunately, logistical constraints did not allow a randomization to the different study stages nor blinding the subjects to the experimental conditions which limits our study outcome. Furthermore, we did not measure urine concentrations to exclude higher fluid loss due to higher ventilation rates. Nevertheless, monitoring and measuring of the subjects as well as eventual emergency measures seem far easier to execute in NH. This allows a maximum of safety, which makes NH a useful alternative to hiking in real altitude. Moreover, our findings indicate that NH, when it comes to HR as well as SpO_2, does not bare higher risks for usability in prevention or rehabilitation programs. Those two parameters do not indicate a higher cardiac or pulmonary stress for NH compared to HH.

5. Study C

5.1. Summary

Besides the additional stress to the heart, hypoxia supposedly bears also other risks. Hypoxia has been known for decades as troublemaker. This is ought to the fact, that in clinical settings usually severe diseases lead to hypoxic states [4]. Obviously, here immediate treatment is necessary to prevent serious consequences. At altitude the cause for the hypoxic state is known and fully reversible with leaving the hypoxic environment [12,43]. In this case and for a short time, the healthy human body is able to compensate the hypoxic state and even adapt to some degree, avoiding damage due to hypoxia up to certain altitudes [43]. Nevertheless, hypoxia withholds serious dangers even for healthy persons as AMS, HAPE and HACE [43]. Their occurrence depends on the protocol of ascent, the degree of acclimatization as well as genetics [43]. In order to recommend hiking in altitude for prevention and rehabilitation, it is necessary to gain more knowledge about the downsides of hypoxia. Sleep at altitude seems to play an important role for the development of altitude related diseases because most problems in altitude hikes occur after the first or second night in hypoxia [1,46]. Therefore, we aimed at reviewing current literature on sleep at altitude and conducted small experiments investigating its pathological consequences.

5.2. Material and Methods

Literature search was conducted to identify relevant articles and to give an overview on sleep at altitude and its pathological consequences. The data of two own studies were integrated. One case report investigating the influence of β-blocker dose on altitude sleep, as well as a small sample size study (11 subjects) to show the impact of hypoxia on cognition as well as gender differences. The 11 subjects slept at three different simulated altitudes in normobaric hypoxia (3500 m, 4500 m, 5500 m). Directly after awakening a reaction testing with the “RT Schufried” was performed to assess motoric- and cognitive reaction time.

5.3. Results

Hypoxia induced periodic breathing characterizes sleep at high altitudes. Reaching a certain altitude, almost all individuals develop periodic breathing [3]. However, its role is not sufficiently explored. On one hand it seems to have a protective effect, on the other

hand it impairs sleep drastically [19]. Especially high doses of β-blockers cause periodic breathing to occur already at lower altitudes as shown in our case report. Nevertheless, periodic breathing and impaired sleep in general does not seem to be solely responsible for the development of AMS. More likely, the exposure time to low oxygen levels plays the bigger part in the development of altitude sicknesses [2]. Currently, the impact on cognitive functions of prolonged and acute hypoxia exposure is largely discussed [26,30]. Hypoxia seems to influence cognitive functioning to a certain degree depending on altitude, exposure time, gender and genetics.

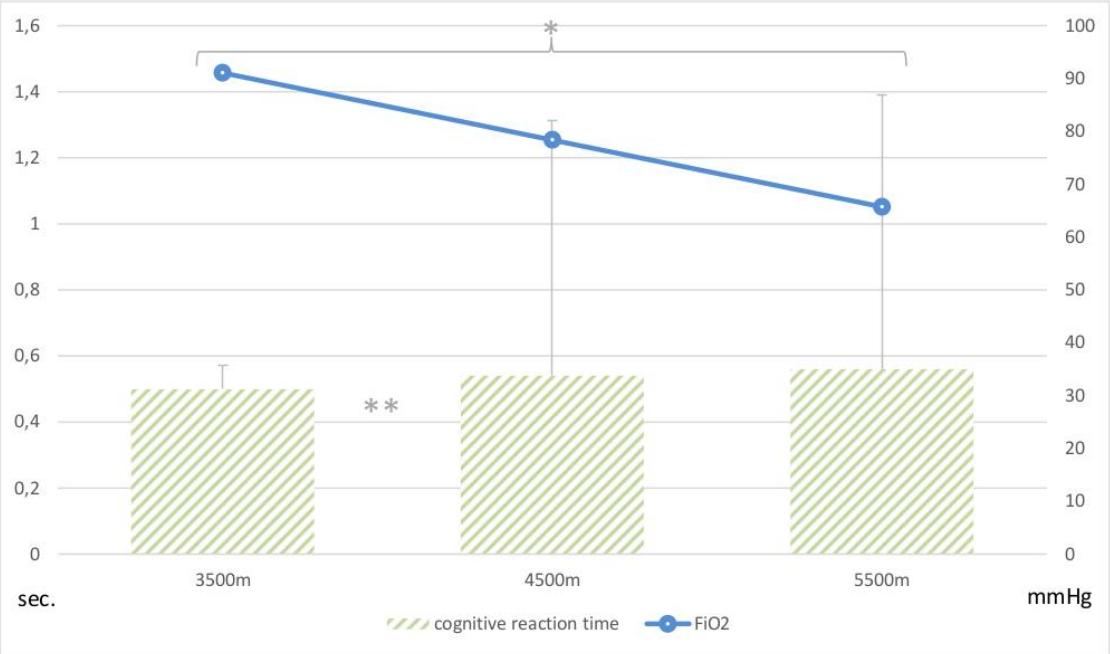


Figure 2: Inspired oxygen fraction (F_iO_2) and cognitive reaction time in seconds (sec.) after the three nights on different altitude levels.
*Legend: * $p \leq 0.05$, ** $p \leq 0.025$. [34] page 149 (modified in agreement with "Georg Thieme Verlag KG Stuttgart")*

5.4. Conclusion

The hypoxia occurrence during altitude hikes bears some dangers. The brain strongly depends on oxygen and seems to be affected by hypoxia. Nevertheless, to our knowledge most studies assessed cognition only in quite high altitudes above 3500 m. We cannot exclude the possibility of the impairment of cognitive functions also in lower altitudes. Conclusively, possible preventive or rehabilitative programs should as precaution, only use low altitudes. Furthermore, in our opinion, keeping training sessions short, minimizes the impact on cognition.

6. Study D

6.1. Summary

Summarizing those previous findings, we aimed at designing and evaluating a normobaric hypoxic training intervention with geriatric patients at 3000 m simulated altitude as rehabilitation program. Especially for geriatric rehabilitation, normobaric hypoxia holds a lot of potential. Above the age of 65, mountaineering and altitude hiking carries more and more logistical barrier's and safety concerns as mentioned in Study A. Training in normobaric hypoxia rooms could provide a practicable setting for the elderly. Hypoxia leads to elevated heart rate and breathing frequency while physical impact on the locomotor system is correspondingly low [38]. HIT has shown to provoke bigger adaptions than the commonly used moderate intensity endurance training [42]. Therefore, normobaric hypoxia interventions seem to provide both, higher training intensities as well as low impact on the locomotor system. Main parameters should be Watt, Watt/kg, Velocity, EF, HR, Grade, walking distance, RR and SpO_2.

6.2. Material and Methods

At pre-test, anthropometric data were collected and echocardiography was performed. Spiroergometry with ECG monitoring was conducted using a standard protocol for heavily impaired patients. The testing was interrupted following current criteria [31]. The testing was also interrupted upon attaining subjective exhaustion equivalent to 18 on the BORG-Scale [5]. Target training intensity was set as HR at 80% of VO2peak with 5 bpm added to account for the conversion from cycle to treadmill training [18]. 40 recruited patients were randomly assigned in equal numbers to the HG or the NG. The main parameters were EF by echocardiogram, peak HR, O2 saturation, VO2peak, and peak O2/HR.

Each group performed 7 training sessions during their 3-week stay in the geriatric rehabilitation center in a normobaric hypoxic chamber. The HG trained at a simulated altitude of 3000 meters (FiO2 = 15.27%) while the NG trained in sham hypoxia (room air at F_iO_2 = 20.94%). Patients were blinded to the different conditions though the investigators were not (single-blinded). Each training included a stay of at least 30 min within the hypoxic room. Of this 30 min stay, active training had to be performed for a minimum of 10 min and a maximum of 30 min. The treadmill (h/p/cosmos, Traunstein, Germany) offered forearm supports for more impaired patients and a safety belt to stop

the movement in an emergency. Considering the physical and medical impairments of each patient, the therapists tried to reach the target HR, taking care not to exceed the given limit. RR (Omron M400 IT) was measured before each training session, while HR (Polar Heart Rate Sensor T31) and O2 saturation (NONIN Go 2) were monitored continuously during training. The intervention protocol was designed to be practicable and achievable for geriatric patients. Seven sessions of at least 10 min of endurance training over a 3-week period corresponds to common practice in geriatric rehabilitation hospitals. All subjects also participated in the normal therapy offering of the geriatric rehabilitation center, consisting of 30 min of individual physiotherapy and 30 min of group therapy per day. At the end of the intervention outcome, measurements were repeated as they had been performed at pre-test.

6.3. Results

Altogether, 40 patients (26 women) were recruited. Of the 40 patients recruited, 35 (87.5%) were able to complete the trial. Reasons for dropout were unwillingness to continue (4) and termination for medical reasons (1). (NG: n = 16, age 82.0 ±7.8 years, sex 11 women/5 men, and BMI 25.8 ± 6.2 kg/m^2) (HG: n = 19, age 80.2 ± 7.2 years, sex 12 women/7 men, and BMI 25.2 ± 5.3 kg/m^2) Statistical analysis showed no significant differences between the groups pre-trial.

The patients showed a multimorbid disease profile and most were prescribed cardiovascular-relevant medications as well as diuretics, anticoagulant medication, cholesterol and blood sugar lowering drugs. During the study period, slight changes in medication were made by the hospital's physicians but these medication changes occurred in both groups equally.

From pre-test to post-test, there were no changes in anthropometric parameters. There was also no change in the measured cardiologic parameters. The group mean ejection fraction for the HG showed a non-significant decrease compared to the NG. Oxygen uptake was enhanced in both groups. The ratio of oxygen uptake and heart rate was higher in the HG but this difference was not statistically significant. However, the maximum performance from baseline to study completion increased significantly in both groups (NG: $p = 0.03$; HG: $p = 0.02$). There were no sex differences regarding the effect of the intervention. Overall both groups showed similar responses from baseline to study completion though the training intensity was significantly lower in the HG. ($p=0.008$).

See Table 3. All intensity related parameters showed a significant reduction in training effort for the HG as listed in Table 2. Resting blood pressure in both normoxic and hypoxic environments did not change over the time course of the seven units. (Figure 3)

Table 3: Physiological and training-intensity related parameters during the intervention for the hypoxic group (HG) and normoxic group (NG).
*Legend: Values are means from training 1 (Tr1) and training 7 (Tr7) ± SD. Training intensity = % of peak heart rate; BP = blood pressure; SpO2 = oxygen saturation, *p ≤ 0.05, **p ≤ 0.025, ***p ≤ 0.001 levels of significance, effect size is displayed as η2. [33] page 4*

Item	Hypoxic group (HG)			Normoxic group (NG)			Cond. p (η^2)	Time p (η^2)	Int. p (η^2)
	Tr1	Tr7	Δ Tr1-7 (%)	Tr1	Tr7	Δ Tr1-7 (%)			
Watt (W)	18.53 (±6.54)	22.84 (±13.52)	23.26	23.00 (±11.51)	34.75 (±14.90)	51.09	0.058	<0.001*** (0.56)	0.005*** (0.18)
Watt/kg (W)	0.27 (±0.07)	0.32 (±0.15)	18.52	0.33 (±0.11)	0.50 (±0.13)	51.52	0.012 (0.35)	<0.001*** (0.53)	0.001*** (0.21)
Training intensity (%)	79.45 (±7.96)	80.67 (±5.80)	1.54	68.12 (±9.03)	74.43 (±8.33)	9.26	0.012** (0.35)	0.059	0.739
BP systolic (mmHg)	140.47 (±22.78)	140.32 (±23.32)	−0.11	148.44 (±17.95)	141.88 (±19.94)	−4.42	0.350	0.163	0.605
BP diastolic (mmHg)	77.32 (±19.27)	76.68 (±10.24)	−0.83	82.06 (±8.21)	75.75 (±11.83)	−7.69	0.609	0.616	0.465
Velocity (km/h)	1.37 (±0.29)	1.37 (±0.36)	±0.00	1.44 (±0.29)	1.71 (±0.23)	18.75	0.070	<0.001*** (0.32)	0.001*** (0.21)
Grade (%)	0.12 (±0.46)	1.65 (±2.21)	1.275	1.13 (±1.75)	3.88 (±2.42)	243.36	0.005** (0.42)	<0.001*** (0.46)	0.066
Walking distance (m)	263.16 (±99.12)	381.23 (±251.04)	44.87	285.63 (±105.42)	505.42 (±178.25)	76.95	0.358	<0.001*** (0.63)	0.492
SpO_2 (%)	88.28 (±9.00)	90.11 (±11.47)	2.07	94.42 (±2.98)	95.15 (±2.33)	0.77	<0.001*** (0.72)	0.027* (0.14)	0.776

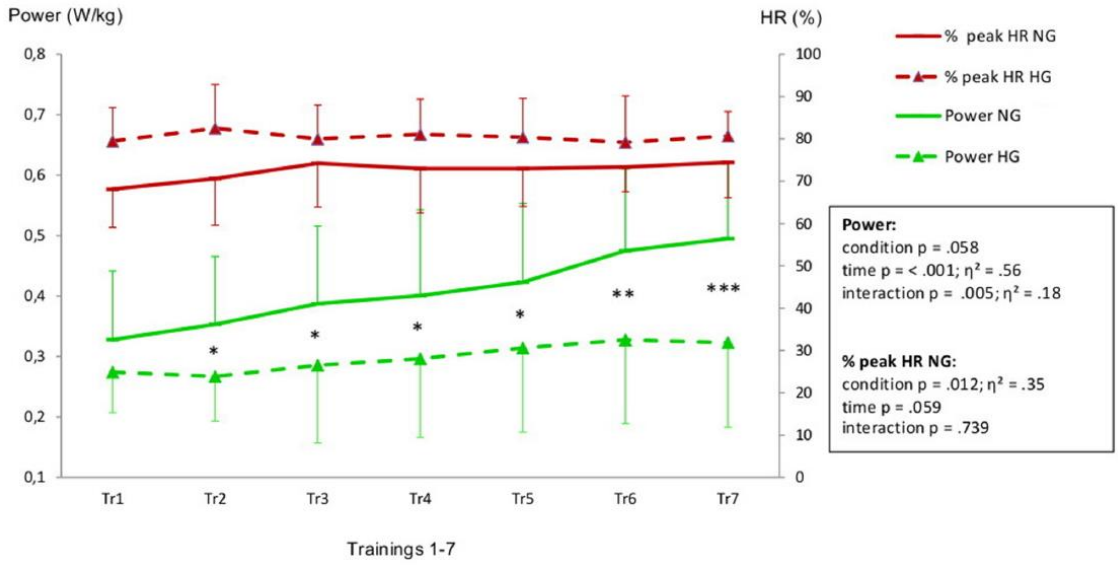


Figure 3: Heart rate (expressed in % of HR peak) and power values (W/kg) recorded during the training intervention Trainings 1 to 7 (Tr1-Tr7).
*Legend: *p ≤ 0.05, **p ≤ 0.025, ***p ≤ 0.001 levels of significant differences between HG and NG in Tr1 to Tr7. Effect size is displayed as η^2. [33] page 5*

6.4. Conclusion

Training in normobaric hypoxia with geriatric patients provides the possibility to lower physical stress on the locomotor system and still provoke adaptions commonly expected from endurance training. In geriatric rehabilitation, usual recommendations for effective endurance training are often hard to meet. Slow walking speeds, insecurity and ache often prevent high endurance training intensities [23]. Lately, the scientific community collects more and more evidence, that higher training intensities maximize the beneficial effects of endurance training on several risk factors and diseases [24,42,45]. Normobaric hypoxia has the potential not only to lower physical strain, but also to elevate training intensity and supposedly cardiac and pulmonary effects, keeping physiological strain constant in both groups. Of course the variety of primary diagnoses as well as multiple co-morbid conditions influenced our study outcome. Nonetheless, we see the complex medical histories of our patients as strength of this study since the results are more likely to pertain to usual clientele served by geriatric rehabilitation programs. The rather short study period and short hypoxic bouts were not challenging enough to provoke cardiopulmonary adaptions in either of the study groups. Furthermore, a larger study population would have allowed subset analyses. Nevertheless, our findings indicate that hypoxic endurance training is very likely to be more effective than normoxic training. Conclusively, training in NH withholds a great potential for prevention and rehabilitation.

7. Discussion

This study compound shows different possible approaches for preventive and rehabilitative use of both NH and HH in the elderly. The common hiking practice at old age, with a maximum of one session a week, does not seem to be sufficient to provoke physiological adaptions. Furthermore, our training protocol in NH, did not provoke the expected physiological adaptions. Nevertheless, our investigations show the effectiveness of NH in its ability to lower physical workload while keeping physiological effects equal to training in sham hypoxia. This leads us to believe that, when keeping physical workload equal, cardiac and pulmonary adaptions to training would be enhanced. According to several study groups, high intensity training is superior to common moderate endurance training and provokes greater and more pronounced adaptions [14,35]. Especially VO_{2max}, adaptions in skeletal muscles, metabolic control and changes in cardiovascular functions seem to be enhanced in response to low volume high intensity training [14,35]. With hypoxia as additive in prevention- and rehabilitation programs, such high intensity training could be put into effect for groups with special demands as geriatrics. This age group often tolerates only low training volumes and is in special need for the beneficial physiological adaptions endurance training provides [17]. The main focus in geriatrics lays on gait ability and gait quality [6]. With the help of NH this goal could be followed by treadmill training while also pursuing cardiac and pulmonary goals. There is a need for new approaches to make hypoxic training accessible, effective and practicable for this age group. Here, varieties of protocols have to be tested and evaluated in order to give adequate recommendations.

In search for new possibilities to organize preventive- and rehabilitative programs, training in normobaric hypoxic rooms as additive to hiking sessions or as sole training program, gives a new and promising perspective. NH provides a safe and manageable setting as shown in study B. Physical strain as well as cardiac, pulmonary and metabolic demands seem to be lower and better assessable in NH compared to HH. In direct confront to HH, NH has proven to impose lower HR and SpO_2 stress. Furthermore, an American study group found a lower risk for the development of AMS symptoms in NH compared to HH [10]. In line with literature, our study outcome suggests an impact of normobaric hypoxia exposure on cognitive functions [11]. Since studies investigating the recovery of such momentary cognitive impairment are quite scarce, we recommend only low altitudes for the use of NH in preventive- or rehabilitative programs. Further investigations regarding cognition and cerebral blood flow as well as its consequences

following training in hypoxic environments are necessary. Conclusively, we think training in hypoxic environments does bare grate benefits for preventive- and rehabilitative purposes.

In hypoxic research and especially for training interventions the recruitment of participants to reach statistically meaningful numbers is quite hard. Therefore, low subject numbers limit our study outcome. Furthermore, each study suffers from its own small limitations discussed above. This study compound is aiming at the evaluation of possible use of HH and NH stimuli in prevention and rehabilitation and to lay a first basis for further investigations.

8. Perspectives

Low volume high intensity training has gained a stand in almost all training disciplines. Studies investigating this promising training prove great effects also for patients suffering from several diseases [14,35]. Especially the promotion of VEGF's via the HIFα1 pathway and its impact on blood flow seems to be responsible for several positive consequences of HIT [25]. Making this kind of training accessible to populations with impairments in their ability to perform regular HIT as geriatrics, obese or generally weak patients, could provide great benefits. Pursuing this aim we plan to repeat the experiment from study D. In contrast to the previous study, we want to recruit 60 patients and conduct a similar intervention standardized by physical workload. Considering the short time rehabilitation centers have to improve the physical status of their patients this effort could maximize the outcome.

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10. Appendix

11.1 Study A including author contributions

Hereby I declare my contributions to the following article “effect of weekly hiking on cardiovascular risk factors in the elderly.”

I was involved in several stages of the development of this study:

- Data sighting
- Statistical analysis
- Literature search
- Writing and finalizing the manuscript

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Effect of weekly hiking on cardiovascular risk factors in the elderly

Introduction

It is well established that regular physical activity provides numerous health benefits, including reducing the risk for a variety of diseases (e.g. coronary heart disease, stroke, cancer, diabetes) and improvements in functional ability [14]. Nowadays, scientific literature recommends regular (≥3 days/week) moderate- to vigorous-intensity physical activity, with a total volume of ≥150 min/week for healthy adults, the elderly and even for different patient groups [1, 4, 14]. However, due to time constraints, some individuals may choose to compress their weekly exercise into a single prolonged session. Studies addressing such a practice are scarce and outcomes are ambiguous [14]. It seems that performing just one long-lasting weekly session of moderate-intensity exercise does not reduce mortality among elderly persons already having at least one cardiovascular risk factor [9]. Conversely, men without any major risk factors may profit from such a practice in terms of reduced mortality [9] and possibly by achieving endurance gains comparable to those achieved with regular training (five sessions per week) [10].

In Alpine regions and the many areas with low mountain ranges, hiking is a very popular activity among the elderly population (>60 years) [3]. Regular hiking performed three times per week was shown to have positive effects on all key markers of metabolic syndrome [7, 15]. However, due to the time (several hours) that is usually associated with such an activity, as well as the travel sometimes required to reach the mountain or upland regions, hiking is often only undertaken at the weekend. As mentioned above, evidence for the health benefits of this practice is lacking [14]. Particularly in light of the fact that more than 6 million elderlies (>60 years) undertake mountain activities in the Alps every year [3], as well as the finding that the elderly hiker has a cardiovascular disease prevalence of >35% [6] and is at higher risk of sudden cardiac death during hiking [5], additional information on this population group could be valuable in order to adequately prescribe physical activity patterns. Therefore, the present investigation aims to study the effects of a single weekly hiking session on major cardiovascular risk factors in the elderly (age >60 years) over a period of several months. We hypothesized that the single weekly hiking session would improve cardiovascular risk profile in the elderly.

Materials and methods

Participants

Participants were recruited via a call for participants published in various local media. Inclusion criteria for the study were age >60 years and the capability to undertake easy hiking (i.e., according to their habits, participants estimated their capability to achieve a 500-m altitude increase within 3 h). Exclusion criteria were: inability to perform the hike within the given timeframe; New York Heart Association (NYHA) class 2–4; myocardial infarction or stroke occurring within the 6 months preceding the start of the study; instable angina pectoris; multivessel coronary disease; hypertension treated with more than two medications; major surgery performed within the 6 months prior to the start of the study; all forms of cancer except prostate cancer; chronic obstructive pulmonary disease (COPD) with functional lung capacity <2 l and/or forced expiratory volume in the first second of <1 l; resting oxygen saturation <90%; alcohol abuse (>100 g/d) and smoking.

The call for participation was followed by 27 elderly males and 25 elderly females. Of these, 14 males (age 65.6±2.7 years; weight 78.7±11.2 kg; height 177.1±7.5 cm; body mass index, BMI 25.0±2.2 kg/m^2) and 10 females (age 66.2±4.4 years; weight 60.4±5.3 kg; height 163.0±4.2 cm; BMI 22.8±1.9 kg/m^2) were eligible and completed the entire study protocol. At the start of the study, 23 participants reported undertaking hiking on a regular basis, whereas one participant hiked only occasionally. Regarding medication, seven males and seven females were receiving drug therapy comprising medication targeting either the cardiovascular risk profile—males (n=4): two angiotensin converting enzyme (ACE) inhibitors, calcium antagonist, diuretics; females (n=3): ACE inhibitor, β-blocker, cholesterol-lowering drug—or other drugs, e.g., non-steroidal antirheumatics (NSARs), thyroid, asthma and osteoporosis medica-

Tab. 1 Changes in measured parameters over the 9-month period for the entire group and in terms of gender

	Males			Females			All		
	No. participants	Pretrial	Posttrial	No. participants	Pretrial	Posttrial	No. participants	Pretrial	Posttrial
Body mass (kg)	14	78.7±11.2	79.0±12.0	10	60.4±5.3[a]	60.7±5.1[a]	24	71.1±12.9	71.4±13.3
BMI (kg/m^2)	14	25.0±2.2	25.0±2.5	10	22.8±1.9[a]	22.8±1.9[a]	24	24.1±2.3	24.1±2.5
HR_{rest} (beats/min)	12	60±7	64±8	8	59±6	60±9	20	59±7	62±9
BP_{sys} (mmHg)	14	126.9±14.3	125.6±10.0	10	122.5±13.9	122.4±12.4	24	125.1±14.0	124.2±10.9
BP_{dia} (mmHg)	14	78.0±10.1	76.6±7.6	10	76.9±6.8	75.5±4.9	24	77.6±8.7	76.1±6.5
HbA_{1c} (%)	9	5.4±0.5	5.6±0.4	7	5.5±0.4	5.5±0.3	16	5.5±0.5	5.5±0.3
HDL cholesterol (mg/dl)	14	62.3±19.5	61.9±16.3	10	74.9±16.2	70.3±23.0	24	67.5±18.9	65.4±19.4
LDL cholesterol (mg/dl)	12	135.7±27.5	126.3±33.1	10	149.9±41.2	144.2±41.2	22	142.1±34.3	134.4±37.2

BMI body mass index, HR_{rest} resting heart rate, BP_{sys} systolic blood pressure, BP_{dia} diastolic blood pressure, HbA_{1c} glycated hemoglobin, *HDL* high density lipoprotein, *LDL* low density lipoprotein[a]Indicates gender-specific differences.

tion: males (n=6); females (n=6). All participants were informed about the study goals and provided their written informed consent. The study was carried out in accordance with the ethical standards laid down in the declaration of Helsinki and the study protocol was approved by the local ethics committee (approval nr: SB-GLand/UNI/24/04/2006).

Procedure

Before commencing the 9-month hiking program, a routine medical examination was performed to establish major cardiovascular risk factors. The examination included measurement of weight, a resting electrocardiogram (ECG) recording (to guarantee safety during the hiking session, an exercise ECG was performed in some participants where indicated), blood pressure and HbA1c, high-density (HDL) and low-density lipoprotein (LDL) level determination. All laboratory testing was performed in accredited laboratories. The hiking program consisted of completing a 500-m altitude increase within 3 h, once a week. According to the age-predicted peak oxygen uptake [16], the corresponding work intensity was approximately 50%. This intensity can be sustained for several hours [3] and should be adequate and safe for this study population. The downhill walk back to the starting point was not included in the 3-h timeframe. Performing a 1000-m altitude increase within 6 h every 2 weeks was also allowed. Resting periods lasting longer than 2 weeks were not permitted and during the 9 months (approximately 37 weeks), exercise was required to be performed during at least 31 weeks. Participants were not supervised during the study period, but had to complete a hiking protocol. Additionally, participants were regularly questioned regarding lifestyle modifications supplementary to those intended by the study. Every second day, participants were required to perform morning blood pressure measurements. A qualified person demonstrated and trained participants in the correct handling of the automatic blood pressure measurement device (Boso medistar S, Bosch, Jungingen, Germany) before the start of the study. For the final analyses, the mean blood pressure values over the first and the ninth months were taken. Energy expenditure for the 500-m altitude increase hike was calculated based on the formula by Burtscher [3], i.e., VO_{2rel} =(0.133Dh +2.0Dv)/t +3.5, where VO_{2rel} = relative oxygen consumption (ml/min/kg), Dh = horizontal distance (m), Dv = vertical distance (m), t = time (min). Hiking equipment weighing 3 kg and an optimal gradient of 15% for mountain paths was assumed [3, 11]. After the 9-month hiking period, the same measurements were performed as before the program.

Statistical analysis

Data are presented as means ± standard deviation (SD). Due to missing values, sample size differs slightly (**Tab. 1**). Data analyses were performed with the SPSS statistical software package (PASW Statistics for Windows version 18.0, SPSS Inc., Chicago, IL, USA). In the case of normally distributed data (Kolmogorov–Smirnov test) and a sample size (n) >10, parametric statistics were used; otherwise nonparametric statistics were applied. As a result, unpaired student t-tests were applied to investigate gender differences and paired student t-tests or Wilcoxon tests (n<10) were applied to identify changes over the 9-month period. To obtain information on whether or not outcomes of such a hiking program vary between participants with different cardiovascular risk profiles, two groups were identified. One group included participants with normal values and the second group included participants with borderline or pathological values (blood pressure >140/90 mmHg, LDL >130 mg/dl, HDL<40 mg/dl [1]) at the start of the study. The Mann–Whitney U test was used to investigate whether or not there was a significant difference over time (calculated as posttrial minus pretrial values) between these groups. Significance level was set at p<0.05.

Results

There were no gender-specific differences in the established parameters, except for the anthropometric parameters (in that males were heavier and taller than females). Therefore, the net (without basal) energy expenditure for the 500-m altitude increase was higher for males than females (574±79 kcal vs. 446±38 kcal, p<0.001). Medication remained unchanged and lifestyle changes, others than those pre-

scribed by the study protocol, were not reported during the intervention period. No changes over the 9-month period were found in any investigated parameter, either for the entire group or for either of the gender groups (◘ **Tab. 1**). When analyzing the participants who had pathological or borderline values at the beginning of the study, only systolic blood pressure tended to improve (from 145.6±7.0 to 137.0±9.3 mmHg, p=0.068; n=4). Changes over time differed between the two groups (−8.7±9.1 vs. 0.7±6.8 mmHg, p=0.023).

Discussion

To our knowledge, this is the first study reporting data on cardiovascular risk factors in older subjects performing regular, but only once weekly moderate-intensity mountain hiking sessions. The main findings of the present investigation were that, in contrast to our hypothesis, such a practice does not improve classical cardiovascular risk factors in elderly persons not suffering from major cardiovascular diseases. However, in elderly persons who suffer from systemic hypertension, once weekly hiking sessions might lower blood pressure.

With respect to the unaffected risk factors, the present results support the findings of Lee et al. [9], who showed that being active only at the weekends does not reduce mortality among elderly persons already suffering from at least one cardiovascular risk factor. Nonetheless, a potential positive effect on the present population cannot be excluded, as risk factors did not worsen and even improved in hypertensive participants. Besides these measured risk factors, a high fitness level is important in view of the findings that low cardiovascular fitness represents an important risk factor for cardiovascular diseases and is associated with increased mortality [2, 12]. Kohl et al. [8] showed that persons who are active at a moderate intensity only 1–2 days per week are more likely to be classified as having low fitness compared to persons who exercised three or more times each week at the same intensity. Additionally, Burtscher et al. [4] found that more than two exercise sessions are necessary to improve exercise capacity. Unfortunately, exercise capacity

Abstract · Zusammenfassung

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Effect of weekly hiking on cardiovascular risk factors in the elderly

Abstract

Background. Hiking is one of the most popular activities among the elderly in Alpine regions. Due to the long-lasting, moderately intensive nature of this form of physical activity, hiking is generally considered to be beneficial to health. However, it is currently unclear whether once-weekly hiking—as commonly practiced at weekends—really does yield such positive effects in elderly persons aged 60 years and over.

Objectives. This study investigated the effect of a single weekly mountain hiking session on cardiovascular risk factors.

Materials and methods. A 9-month mountain hiking program was completed by 14 male (age 65.6±2.7 years) and 10 female (age 66.2±4.4 years) elderly participants. The program consisted of a single weekly hiking session with the goal of achieving a 500-m altitude increase within 3 h. Before and after the 9-month program, an electrocardiogram (ECG) was performed and blood pressure, glycated hemoglobin (HbA1c), high-density (HDL) and low-density lipoprotein (LDL) measurements were made.

Results. The elderly participants showed a normal cardiovascular risk profile at the start of the investigation. The estimated net energy expenditure for one hiking session was approximately 521±91 kcal. Over the 9-month period, no changes were found in any of the investigated parameters for the entire group. However, participants with untreated hypertension showed a reduced systolic blood pressure.

Conclusion. The present investigation showed that moderate-intensity activity only at weekends does not improve cardiovascular risk factors in elderly persons with a relatively normal cardiovascular risk profile. Conversely, elderly persons suffering from hypertension might profit from such a practice.

Keywords

Hypertension · Exercise · Cardiovascular disease · Blood pressure · Electrocardiogram

Auswirkungen wöchentlicher Bergwanderungen auf kardiovaskuläre Risikofaktoren bei älteren Menschen

Zusammenfassung

Hintergrund. Im alpinen Raum zählt Wandern bei älteren Menschen zu den beliebtesten Aktivitäten. Aufgrund der länger andauernden, körperlichen Aktivität mit moderater Intensität werden dem Wandern positive gesundheitliche Effekte zugeschrieben. Jedoch ist unklar, ob 1-mal Wandern pro Woche, wie es häufig an den Wochenenden praktiziert wird, diese positiven Effekte hervorruft.

Ziel. Ziel dieser Studie war es, die Auswirkungen einer Wandereinheit pro Woche auf kardiovaskuläre Risikofaktoren zu untersuchen.

Material und Methoden. An dem Wanderprogramm, das sich über einen Zeitraum von 9 Monaten erstreckte, nahmen 10 weibliche (Alter: 66,2±4,4 Jahre) und 14 männliche (Alter: 65,6±2,7 Jahre) ältere Menschen teil. Das wöchentliche Wanderprogramm beinhaltete einen Aufstieg von 500 Höhenmetern 1-mal pro Woche innerhalb von 3 Stunden. Vor und nach den 9 Monaten wurden ein EKG aufgezeichnet, der Blutdruck gemessen und HbA1c-, HDL- und LDL-Werte bestimmt.

Ergebnisse. Zu Beginn der Untersuchung lag das kardiovaskuläre Risikoprofil der Teilnehmer durchweg im Normalbereich. Der Energieverbrauch während der Wandereinheit betrug durchschnittlich 521±91 kcal. In der Gesamtgruppe konnten keine Veränderungen der erhobenen Risikoparameter gefunden werden. Jedoch zeigte sich, dass Teilnehmer mit unbehandeltem Bluthochdruck eine Reduktion des systolischen Blutdrucks erfuhren.

Schlussfolgerung. Bei älteren Personen mit einem relativ normalen kardiovaskulären Risikoprofil dürfte Bergwandern, an einem Tag in der Woche, keinen Effekt auf kardiovaskuläre Risikofaktoren haben. Andererseits zeigte sich, dass ältere Personen mit Bluthochdruck von den wöchentlichen Wandereinheiten profitieren können.

Schlüsselwörter

Hypertonie · Bewegung · Kardiovaskuläre Erkrankungen · Blutdruck · Elektrokardiogramm

was not assessed in the present investigation, but on the basis of the findings from Kohl et al. [8] and Burtscher et al. [4], increases in exercise capacity are unlikely to have occurred. It has to be mentioned that participants of the present investigation expended only approximately 521±91 kcal for every 500-m altitude increase during the hike. This amount does not meet the recommendation of accumulating at least 1,000 kcal expended per week with physical activity in order to achieve health benefits [1]. Nonetheless, participants performed moderate-intensity activity lasting ≥150 min/week and even small increases in the volume of physical activity might provide important health gains according to the "some activity is better than none" maxim [1, 13, 14]. However, the presented practice did not improve cardiovascular risk factors, except in four hypertensive participants, who showed a greater improvement in systolic blood pressure when compared to those with normal blood pressure. This indicates that such exercise frequencies and/or intensities are too low to achieve health/fitness benefits in elderly persons with a normal risk profile [1], but might improve measurements in persons with inadequately treated risk factors [14]. Naturally, the study has some limitations which should be mentioned. The call for participation throughout the local press possibly led to a selection bias. Most participants answering the call reported to have already been regularly active before the study and were thus adequately medically adjusted. Therefore, their cardiovascular risk profile was largely normal at the start of the study, which might have been the reason why the implemented hiking program had no additional effect. Furthermore, it cannot be excluded that some participants over- or underperformed in the hiking exercise without recording this. We do not think that these limitations greatly impacted the outcome of the study or the overall approach to test a moderate-intensity hiking program in the elderly, since our study protocol came close to what would be feasible for a hiking program in this age group.

Conclusion

In conclusion, the present investigation shows that being active at a moderate intensity only at the weekend does not improve classical cardiovascular risk factors in elderly persons not suffering from major cardiovascular diseases. However, elderly persons suffering from hypertension might benefit from such a practice.

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Compliance with ethical guidelines

Conflict of interest. H. Gatterer, C. Raab, S. Pramsohler, M. Faulhaber, M. Burtscher and N. Netzer state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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11.2 Study B including author contributions

Hereby I declare my contributions to the following article "SpO2 and Heart Rate During a Real Hike at Altitude Are Significantly Different than at Its Simulation in Normobaric Hypoxia."

I was involved in all stages of the development of this study:

- Planning and study design
- Obtaining ethics approval
- Recruiting of subjects
- Execution of the measurements and testing in normobaric hypoxia
- Execution of the measurements and testing in hypobaric hypoxia
- Statistical analysis
- Writing and finalizing the manuscript

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SpO_2 and Heart Rate During a Real Hike at Altitude Are Significantly Different than at Its Simulation in Normobaric Hypoxia

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Rationale: Exposures to simulated altitude (normobaric hypoxia, NH) are frequently used in preparation for mountaineering activities at real altitude (hypobaric hypoxia, HH). However, physiological responses to exercise in NH and HH may differ. Unfortunately clinically useful information on such differences is largely lacking. This study therefore compared exercise responses between a simulated hike on a treadmill in NH and a similar field hike in HH.

Methods: Six subjects (four men) participated in two trials, one in a NH chamber and a second in HH at an altitude of 4,205 m on the mountain Mauna Kea. Subjects hiked in each setting for 7 h including breaks. In NH, hiking was simulated by walking on a treadmill. To achieve maximal similarity between hikes, subjects used the same nutrition, clothes, and gear weight. Measurements of peripheral oxygen saturation (SpO_2), heart rate (HR) and barometrical pressure (P_B)/inspired oxygen fraction (F_iO_2) were taken every 15 min. Acute mountain sickness (AMS) symptoms were assessed using the Lake-Louise-Score at altitudes of 2,800, 3,500, and 4,200 m.

Results: Mean SpO_2 values of 85.8% in NH were significantly higher compared to those of 80.2% in HH ($p = 0.027$). Mean HR values of 103 bpm in NH were significantly lower than those of 121 bpm in HH ($p = 0.029$). AMS scores did not differ significantly between the two conditions.

Conclusion: Physiological responses to exercise recorded in NH are different from those provoked by HH. These findings are of clinical importance for subjects using simulated altitude to prepare for activity at real altitude.

Trial registration: Registration at DRKS. (Approval No. 359/12, Trial No. DRKS00005241).

Keywords: normobaric hypoxia, hypobaric hypoxia, altitude, heart rate, oxygen saturation

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INTRODUCTION

The popularity of using normobaric hypoxia (NH) to prepare for hypobaric hypoxia (HH) experienced during mountaineering activities at real altitude raises the question about the comparability between the effects of NH and HH. The primary condition that differs between NH and HH is the mechanism by which partial pressure of inspired oxygen (P_iO_2) is reduced, with P_iO_2 defined as inspired oxygen fraction (FiO_2) × (P_B-47 mmHg). Reductions in P_iO_2 can be achieved by altering the barometric pressure (P_B) in HH or the inspired fraction of oxygen (F_iO_2) in NH (Conkin and Wessel, 2008). Since seminal work by Paul Bert in 1878, lower P_iO_2 has been assumed to be the primary stimulus for adapting to any hypoxic state (Bert, 1878; Conkin and Wessel, 2008). More recently, a direct relationship between lower arterial partial pressure of carbon dioxide ($PaCO_2$) and the reduction of P_B was found, proposing a synergistic effect of environmental pressure and F_iO_2 (Saltzman et al., 1971; Savourey et al., 2003). This effect has been used to explain differences regarding the physiological responses in HH compared to NH environments (Tucker et al., 1983; Roach et al., 1996; Loeppky et al., 2005).

Peripheral oxygen saturation (SpO_2) and arterial blood oxygen saturation (SaO_2) have been found to be significantly lower in HH compared to NH. This has been speculated to be due to increased dead space ventilation, provoked by a lower tidal volume (V_t) and a higher breathing frequency (f) (Savourey et al., 2003, 2007). Accordingly, $PaCO_2$ decreases with alkalemia as a consequence, shifting the oxyhemoglobin dissociation curve to the left (Savourey et al., 2003). A recent review describes the variations in ventilation in NH and HH (Coppel et al., 2015). The heart rate (HR) is increased in HH (Savourey et al., 2007; Self et al., 2011; Faiss et al., 2013). The severity of acute mountain sickness (AMS) as a result of physiological differences in HH appears to be greater as well (Tucker et al., 1983; Roach et al., 1996; Loeppky et al., 2005).

After years of altitude research most differences between NH and HH appear to be sufficiently explored.

However, one aspect that is still debated is the interchangeability of the HH and NH environments regarding their effects on physiological responses. Previous studies often lack standardization or detailed documentation and do not provide comparability of study designs (Millet et al., 2012a,b; Mounier and Brugniaux, 2012; Saugy et al., 2016). Most of the studies conducted used laboratory settings for both NH and HH (Millet et al., 2012a) Since the advent of chamber research on hypoxia, questions have remained regarding the comparability between conditions of the simulated chamber environment and the real-life mountain environment.

According to a recent review, several studies have compared NH and HH but the comparison of laboratory (NH) and field (HH) environments in a single standardized study has not yet been performed (Coppel et al., 2015). To show differences in SpO_2, HR, and AMS between laboratory NH and field HH conditions we conducted measurements of these parameters during a hike in simulated altitude and again in real altitude, standardizing variables as much as possible to allow for maximal comparability over the course of a 7-h exposure time. We hypothesized that we could verify the significant differences in SpO_2, HR, and AMS previously reported by other researchers from laboratory research and research at fixed altitudes by performing a study protocol with continuously increasing altitude in the field.

METHODS

Subjects

Six healthy participants who usually resided at an altitude between 500 and 650 m (4 men and 2 women, ages 24–45 years) were recruited for the study. They were students of the Department of Sports Science of the University of Innsbruck and reported a moderate fitness routine of 1–4 h per week of training in various disciplines. Descriptive characteristics of participants are shown in **Table 1**. All subjects gave their written informed consent prior to the participation in the study. None of the participants had been at an altitude above 2,000 m for 6 months prior to the study.

Protocol

Participants completed two trials (T_1 and T_2). T_1 took place in a normobaric hypoxia chamber. Normobaric hypoxia was provided by an oxygen expulsion system (Low Oxygen Systems; Berlin-Buch, Germany). The expulsion system (oxygen exchange through nitrogen) allows a mixture of fresh air to keep controlled CO_2 levels comparable to the levels measured in HH. Four weeks after the first trial, participants went through an equivalent testing protocol (T_2) under hypobaric hypoxia conditions on the mountain Mauna Kea, Hawaii, USA. Mauna Kea was chosen for the experiment for a number of important reasons. The mountain's altitude with a moderate continuous inclination allowed the simulated treadmill hike to be programmed to a high degree of comparability. Constant climatic conditions on the mountain with temperatures around 20°C paralleled the temperatures in the normobaric hypoxia room. Road access to the summit facilitated transport of gear and descent of the participants. Participants were asked to wear the same clothes and use the same equipment during each trial. The amount of food and beverage intake was weighed and recorded for each person at breakfast and dinner before T_1. The subjects were instructed to follow the same food and beverage intake in T_2. Participants carried the same weight consisting of snacks and beverage in a backpack during both trials. Energy and fluid intake were measured individually during T_1 and kept the same for T_2. Temperature and humidity were continually measured in both settings.

T_1 Protocol

The first trial in NH conditions (T_1) involved a 7-h stay in the chamber with 6 h walking on a treadmill (h/p Cosmos Mercury and Quasar). The built-in calibrating sensor of the treadmills were checked for accuracy by a mechanic prior to testing (error < 0.2 m per 100-m interval). The treadmill hike was set at an average incline of 14.2% and a constant speed of 1.6 km/h. These parameters were calculated to simulate the hike on top of the

TABLE 1 | Subjects' Characteristics.

Subject	Sex (m/f)	Age (yr)	Height (cm)	Weight (kg)	Weight + backpack (kg)	BMI (kg/m^2)
1	f	24	169	66	73	23.1
2	m	25	180	62	76	19.1
3	f	26	174	68	71	22.4
4	m	25	174	72	84	23.8
5	m	25	189	82	91	22.9
6	m	45	175	75	81.4	24.5
Mean Values ± *SD*		28.3 ± 8.2	176.8 ± 6.9	70.8 ± 7.1	79.2 ± 7.5	22.6 ± 1.9

Mauna Kea Mountain. The average incline was determined as the ratio between the difference in altitude (1,405 m) and the walking distance (9,894 m). The treadmill speed was calculated as a function of the duration of walking (6 h) and the walking distance. Participants started walking at a simulated altitude of 2,800 m. The F_iO_2 in the chamber was modified automatically, which led to the completion of the treadmill task at a simulated altitude of 4,200 m. During the testing, participants had 3 breaks; a 15-min break after 75 min of walking, a 30-min break after 195 min of walking and another 15-min break after 315 min of walking. During the breaks, participants stayed in the chamber, resting, drinking, and eating snacks. An investigator was present throughout all testing in NH, controlling the simulated altitude, time, walking distance, and F_iO_2 (measured by O_2 and CO_2 probes in the room, Dräger Germany).

T_2 Protocol

In the second trial, participants arrived on the Big Island Hawaii and rested for 4 days after arrival with at least 8 h of sleep per night. Participants then hiked the Humu'ula trail on top of the Mauna Kea Mountain. The subjects were brought to the starting point of the hike via a 30-min car drive. The experiment started at 09:00 AM local lime. The trail starts at an altitude of 2,800 m and ends at 4,200 m. Participants used a GPS receiver (Forerunner® 305, Garmin, Garching, Germany) to measure time and walking distance. The PM 90 monitor (Beurer GmbH, Ulm, Germany) was used to evaluate barometric pressure and altitude as well as to keep a constant walking speed. We report each 15-min measurement interval as 50 m in altitude gain. Two 15-min breaks and one 30-min break were made after the same time of walking as in T_1. Participants rested, ate snacks and drank fluids during the breaks just as in T_1.

Measurements

Anthropometric measurements were made and participants were weighed with and without their backpacks before T_1. For at least 1 min every 15 min during the hike, measurements of HR and SpO_2 were conducted by the participants themselves. The measurements were done using fingertip pulse oximeters (PULOX® PO-100, Novidion GmbH, Cologne, Germany, accuracy for SpO_2 = 70–100 ± 2% and for HR = 30–250 ± 2 beats per min). Participants avoided solar radiation on the devices and noted the stable SpO_2 at the end of the 1 min measurement (Luks and Swenson, 2011). Self-reported recordings were visually checked by one investigator and one other participant independently for possible artifacts. Only one value, a SpO2 in subject 5, had to be corrected. The rate of perceived exertion was assessed via Borg scale directly after the hike.

Subjective symptoms of AMS were assessed using the Lake-Louise-Score (LLS) Questionnaire at altitudes if 2,800, 3,500, and 4,200 m (Roach et al., 1993). The following AMS categories were assessed: (1) headache, (2) gastrointestinal symptoms (e.g., nausea), (3) fatigue and/or weakness, (4) dizziness/lightheadedness. According to the literature, the 5th symptom complex of the LLS, i.e., the quality of sleep, was excluded from the self-report section (Macinnis et al., 2013). Participants rated the severity of AMS symptoms from 0 (no discomfort) to 3 (severe discomfort). AMS was diagnosed when headache occurred together with one other symptom from the categories mentioned above, and a total LLS of >3 (Hackett and Roach, 2001). Walking time, distance, speed, and altitude were assessed the same way in T_1 and T_2.

Statistics

Although sample size was primarily based on logistical considerations, a power analysis was performed with G-Power Version 3.1.9.2 (University of Kiel) for dependent samples (correlation coefficient set at 0.5) with expected values of mean SpO_2 90 ± 3% for NH and 85 ± 3% for HH based on previous study results (Savourey et al., 1997, 2003, 2007; Boos et al., 2016). The power analysis yielded a sample size of six subjects. Statistical analysis was performed using IBM SPSS Statistics 23 (PASW Statistics for Windows version 21.0, SPSS Inc., Chicago, IL, USA). Data were expressed as means and standard deviations or as medians with 95% confidence intervals as appropriate. Nonparametric tests (Wilcoxon) were used for HR, SpO_2, and AMS scores at each time point comparing NH and HH. The significance threshold was set at 0.05.

Study Approval

The Ethics Committee at the Leopold-Franzens-University of Innsbruck, Austria approved the study protocol on the October 1, 2014. Participants gave their written informed consent prior to inclusion in the study.

RESULTS

All participants completed the two exposure trials successfully. During ascent in NH, F_iO_2 was lowered continuously from 14.6% at 2,800 m, 13.2% at 3,500 m to 12.1% at 4,205 m (P_B = 767.3 mmHg). The room air CO_2 concentration was kept relatively constant during the experiment at 884 ppm ± 325 within limits that did not influence ventilation. On the mountain, P_B was measured with a value of 550 mmHg at 2,800 m, 496 mmHg at 3,500 m and 465 mmHg at 4,205 m (**Figure 1**). Temperature ranged in both conditions (at Mauna Kea between sunrise and sunset) at all altitude levels around 20°C (19–24°C) and humidity was between 50 and 60% (average on Mauna Kea 58%; in the chamber 55%). Wind speed on Mauna Kea was below 5 mph.

An overall statistical difference between NH and HH regarding HR and SpO_2 was detected ($p < 0.05$; **Tables 2**, **3**). However, AMS scores did not differ significantly between the chamber and the mountain. Self-reported Borg scale values showed no difference ($p = 1.00$) for rate of perceived exertion in both NH (12.33 ± 2.07) and HH (12.33 ± 1.75).

Heart Rate

The HR showed significant differences in 66% of the measured time points between NH and HH (p-values varied from p = 0.027–0.046, **Table 2**). In both NH and HH, the lowest values of individual HR were observed during or after the three walking breaks around 3,100, 3,500, and 3,900 m (**Figure 2**). Minimum HR values ranged from 53 to 93 beats per min (bpm) in NH and from 68 to 103 bpm in HH. Peak values extended from 106 to 137 bpm in NH and from 130 bpm to 159 in HH.

Peripheral Oxygen Saturation

Significant differences in SpO_2 were seen between NH and HH in 62% of the measured time points (**Table 3**). Most significant p-values for SpO_2 were detected (p-values ranged from p = 0.027–0.046) from 3,100 to 3,300 m and from 3,750 to 4,000 m. The SpO_2 values for each participant decreased with increasing altitude (**Figure 3**). Highest values of SpO_2 were reached during or after the 3 breaks around 3,100, 3,500, and 3,900 m. Peak values ranged from 95 to 97% in NH and from 93 to 95% in HH. Lowest SpO_2 values ranged from 68 to 82% in NH and from 61 to 75% in HH.

In the two women (subjects 1 and 3), SpO_2 in HH was higher compared to NH around the break at 3,500 m with values ranging from 90 to 93% in HH compared to 88 and 91% in NH. Subjects 2 and 6 were the only participants in whom the SpO_2 values in HH were lower throughout the whole protocol except for the beginning at 2,800 m. In subject 6, the SpO_2 values stayed higher in HH up to 3,050 m. Subject 5 randomly showed one higher SpO_2 value of 85% in HH compared to 82% in NH at 3,700 m. Therefore, we consider the one time measurement of 61% at 3,950 m an artifact. The largest difference in SpO_2 values was found in subject 4 varying from 95% at 2,800 m to 60% at 3,850 and 4,150 m in HH.

Acute Mountain Sickness

There was no significant difference in AMS scores examined ($p >$ 0.05) between NH and HH. The severity of AMS was mild (LLS 3 to 4) in almost all subjects in both NH and HH. On average, median AMS scores were lower than 3, except for the increased median value of 3.5 at an altitude of 4,200 m in HH which is not statistically significant. Half of the subjects reported an AMS

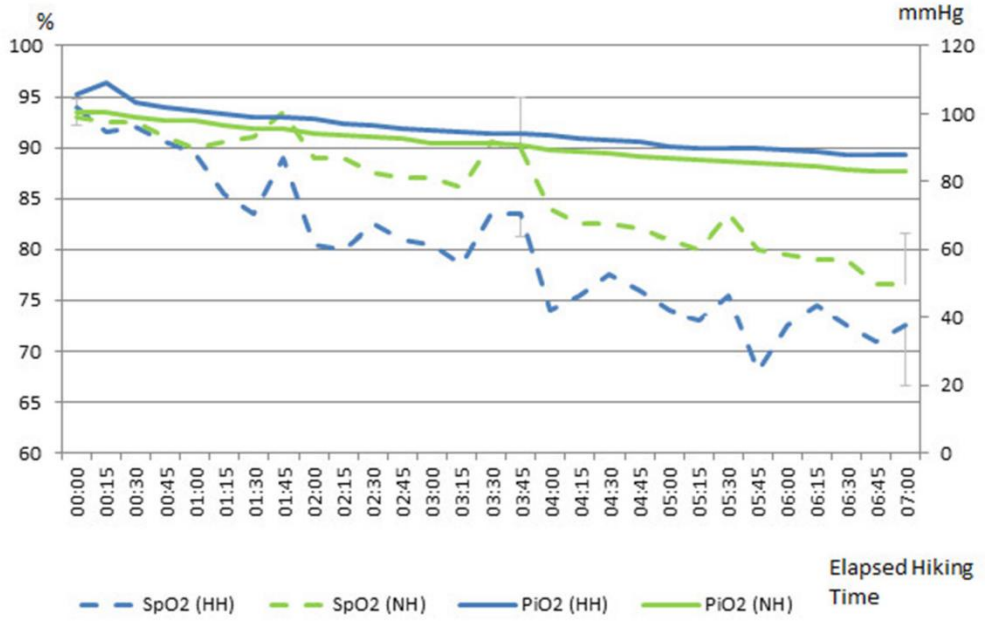


FIGURE 1 | Comparison of inspired oxygen (P_iO_2) and peripheral oxygen saturation (SpO_2) during the hikes in normobaric hypoxia (NH) and hypobaric hypoxia (HH). Legend: Break 1 at 3,100 m altitude, Break 2 at 3,500 m altitude, Break 3 at 3,900 m altitude; % = SpO_2%; mmHg = P_iO_2 mmHg.

TABLE 2 | Actual fraction of inspired oxygen (F_iO_2) in normobaric hypoxia (NH) and barometric pressure (P_B) in hypobaric hypoxia (HH). Medians (confidence intervals) of heart rate (HR) and *p*-values between NH and HH.

F_iO_2 %	P_B mmHg	Altitude (m)	HR median (bpm) and 95% CI		NH vs. HH
			NH	HH	*p*-value
14.57	550	2,800	93 (77–109)	87 (72–102)	0.225
14.57	566	2,850	108 (100–115)	123 (109–137)	0.028
14.33	539	2,900	104 (93–114)	110 (93–126)	0.249
14.25	533	2,950	101 (91–111)	122 (101–143)	0.046
14.21	527	3,000	102 (89–114)	120 (104–136)	0.027
14.02	523	3,050	103 (91–114)	125 (109–140)	0.027
13.89	518	3,100	103 (88–118)	122 (112–131)	0.027
13.85	518	3,150	84 (69–99)	94 (76–111)	0.080
13.66	516	3,200	103 (92–114)	131 (114–148)	0.028
13.56	509	3,250	104 (95–113)	122 (105–139)	0.028
13.50	506	3,300	105 (94–116)	122 (96–148)	0.028
13.46	503	3,350	104 (94–114)	125 (107–142)	0.027
13.24	500	3,400	103 (90–115)	129 (108–149)	0.028
13.24	497	3,450	105 (93–116)	133 (112–153)	0.028
13.21	496	3,500	80 (62–98)	87 (68–105)	0.115
13.18	496	3,550	75 (59–90)	87 (69–105)	0.046
12.97	493	3,600	107 (95–119)	130 (96–164)	0.173
12.91	489	3,650	111 (97–124)	131 (114–148)	0.027
12.80	486	3,700	109 (91–126)	135 (105–165)	0.046
12.69	483	3,750	109 (92–126)	128 (115–141)	0.028
12.63	478	3,800	111 (93–128)	136 (120–152)	0.027
12.52	476	3,850	110 (93–127)	138 (118–158)	0.028
12.49	476	3,900	87 (67–107)	94 (77–111)	0.058
12.37	476	3,950	112 (94–129)	126 (91–161)	0.173
12.33	473	4,000	113 (95–131)	122 (108–136)	0.115
12.26	470	4,050	115 (98–132)	115 (96–133)	0.345
12.10	467	4,100	121 (106–135)	125 (106–144)	0.173
12.08	465	4,150	114 (93–134)	132 (107–157)	0.046
12.03	465	4,200	114 (92–135)	130 (105–155)	0.046
		Mean	103 (93–114)	121 (106–135)	

TABLE 3 | Fractions of inspired oxygen (F_iO_2) in normobaric hypoxia (NH), barometric pressure (P_B) in hypobaric hypoxia (HH), medians (confidence intervals) of peripheral oxygen saturation (SpO_2) and *p*-values between NH and HH.

F_iO_2 %	P_B mmHg	Altitude (m)	S_pO_2 median (%) and 95% CI		NH vs. HH
			NH	HH	*p*-value
14.57	550	2,800	93 (91–95)	94 (92–96)	0.336
14.57	566	2,850	93 (91–94)	92 (88–95)	0.399
14.33	539	2,900	93 (90–95)	92 (89–95)	0.248
14.25	533	2,950	91 (89–93)	91 (85–96)	0.786
14.21	527	3,000	90 (88–92)	90 (85–94)	0.854
14.02	523	3,050	91 (86–95)	86 (83–88)	0.078
13.89	518	3,100	91 (85–97)	84 (79–88)	0.027
13.85	518	3,150	94 (90–97)	89 (86–92)	0.027
13.66	516	3,200	89 (84–94)	81 (75–86)	0.028
13.56	509	3,250	89 (85–93)	80 (78–82)	0.026
13.50	506	3,300	88 (83–93)	83 (78–87)	0.026
13.46	503	3,350	87 (82–92)	81 (75–87)	0.058
13.24	500	3,400	87 (82–92)	81 (75–86)	0.172
13.24	497	3,450	86 (81–91)	79 (72–85)	0.046
13.21	496	3,500	91 (88–93)	84 (79–89)	0.028
13.18	496	3,550	90 (86–94)	84 (75–92)	0.075
12.97	493	3,600	84 (79–89)	74 (68–80)	0.027
12.91	489	3,650	83 (77–88)	76 (71–81)	0.027
12.80	486	3,700	83 (78–88)	78 (72–83)	0.112
12.69	483	3,750	82 (77–87)	76 (70–82)	0.027
12.63	478	3,800	81 (75–87)	74 (70–78)	0.027
12.52	476	3,850	80 (75–85)	73 (64–82)	0.046
12.49	476	3,900	84 (79–88)	76 (64–87)	0.028
12.37	476	3,950	80 (74–86)	68 (61–75)	0.027
12.33	473	4,000	80 (73–86)	73 (71–74)	0.046
12.26	470	4,050	79 (74–84)	75 (70–80)	0.058
12.10	467	4,100	79 (74–84)	73 (67–78)	0.027
12.08	465	4,150	77 (71–82)	71 (64–78)	0.027
12.03	465	4,200	77 (71–82)	73 (68–78)	0.027
		Mean	86 (82–90)	80.2 (77–83)	

severity of 4 at 4,200 m in HH, whereas one participant suffered from mild AMS (LLS = 4) at a lower altitude of 3,500 m on the mountain. Two subjects experienced a LLS $\geq$ 3 in NH. None of the participants noted severe nausea and vomiting or severe fatigue or dizziness.

DISCUSSION

This is the first study to compare a 7-h simulated high altitude hike in a normobaric hypoxia chamber and a mountain hike at real altitude. This study provides a descriptive comparison of physiological parameters (HR and SpO_2) and AMS scores measured in a chamber (NH) and on the mountain (HH). Our findings do verify previously reported differences for SpO_2 and HR, with SpO_2 values significantly lower and HR values significantly higher in a HH environment compared to NH. However, in contrast to prior reports, AMS severity did not differ significantly between the two settings.

Using a study design similar to our protocol, Savourey et al. also found SpO_2 to be significantly lower in a hypobaric chamber (HH) compared to NH with a simulated altitude exposure to 4,500 m (Savourey et al., 2003). The Savourey study was performed at a fixed altitude for a limited time only. However, ventilation was measured and revealed increased dead space ventilation in HH due to a lower tidal volume (V_t) and a higher frequency of breathing (f). This breathing pattern caused a lower $PaCO_2$, alkalemia, and a lower SpO_2 than in NH (Savourey et al., 2003). Other studies reported a direct relationship between a lower $PaCO_2$ and the reduction of P_B (Saltzman et al., 1971). To explain the findings of

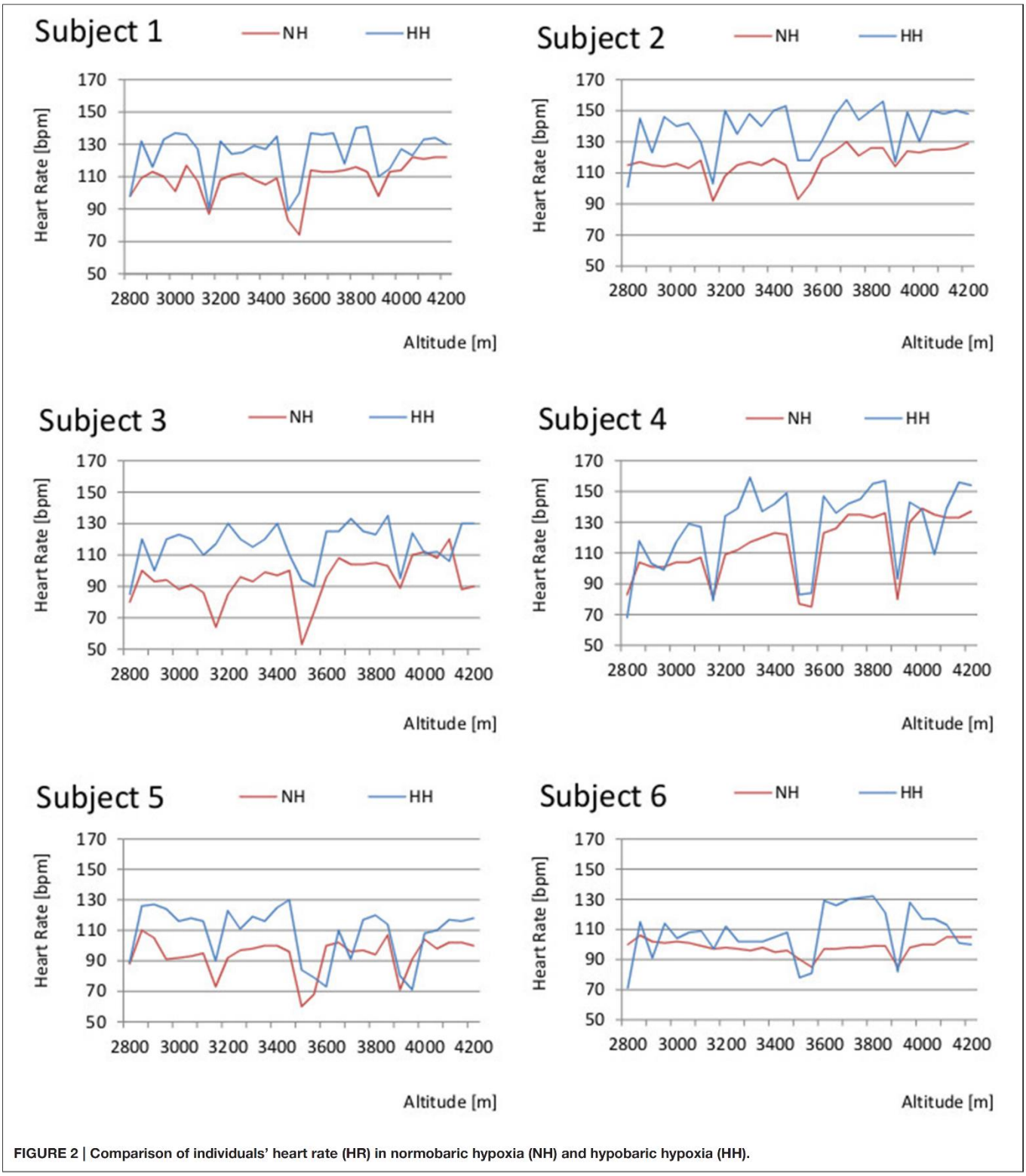


FIGURE 2 | Comparison of individuals' heart rate (HR) in normobaric hypoxia (NH) and hypobaric hypoxia (HH).

significantly lower SaO_2 values in HH compared to NH at a simulated altitude of 7,620 m a synergistic effect of hypoxia and hypobaria was proposed (Levine et al., 1988; Self et al., 2011).

The studies cited above were characterized by a short exposure time to hypoxia (<1 h) at fixed altitudes. The importance of exposure time was emphasized in a review of five long-term hypoxia exposure studies (>1 h) which

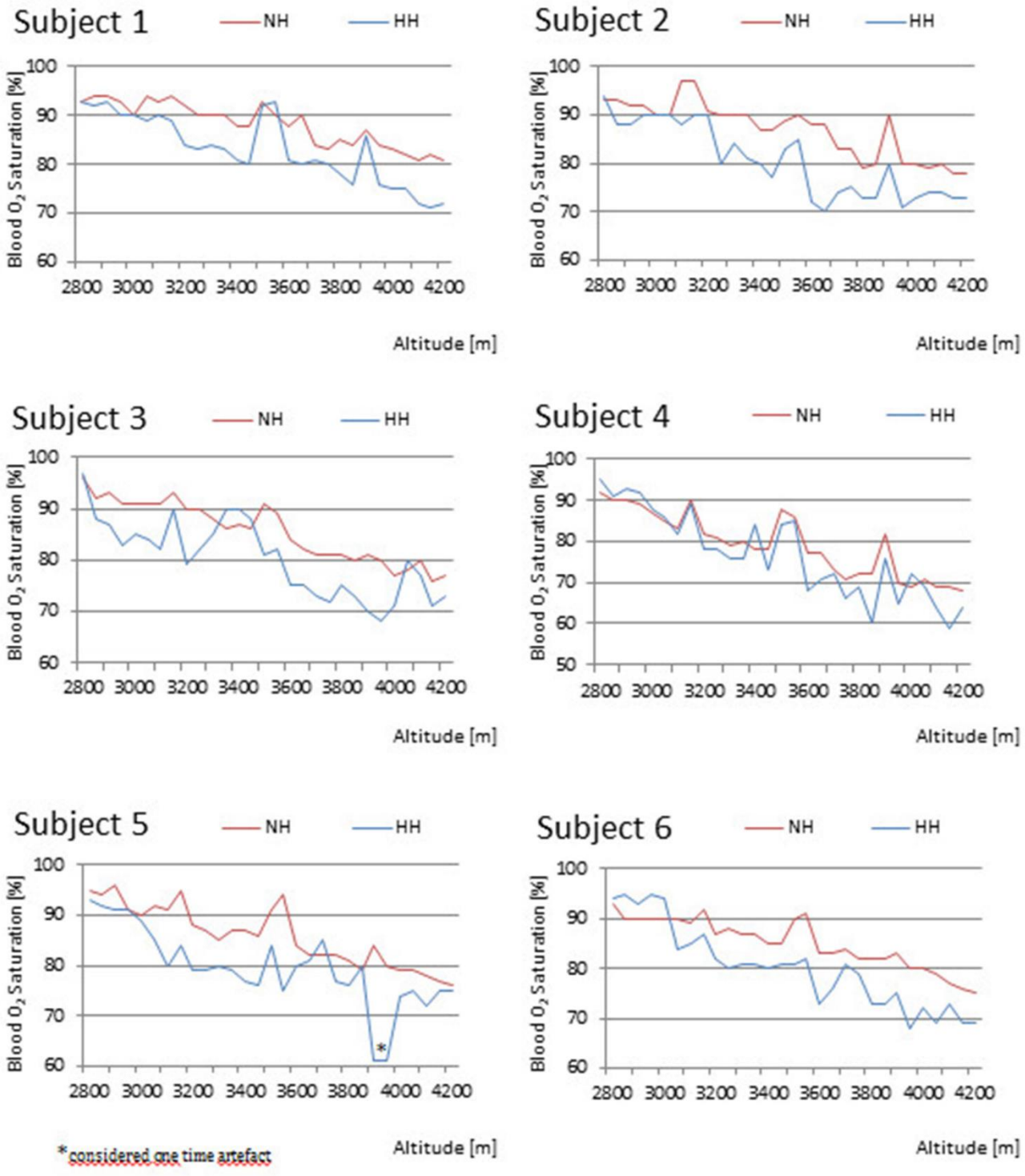


FIGURE 3 | Comparison of individual's peripheral oxygen saturation (SpO_2) between normobaric hypoxia (NH) and hypobaric hypoxia (HH).

did not show any differences in SpO_2 between NH and HH,(Tucker et al., 1983; Roach et al., 1996; Loeppky et al., 1997, 2005; Faiss et al., 2013) possibly due to acclimatization to hypoxia (Coppel et al., 2015). What sets our study apart from prior research is that the study design incorporated a long exposure time at increasing altitudes with movement and exercise performance utilizing actual mountaineering conditions.

Subjects 1 and 3 reacted with values ranging from 90 to 93% in HH compared to 88 and 91% in NH around the 3,500 m break. Because both participants were women, a likely explanation of this finding may be increased respiratory drive due to higher progesterone levels in these participants.

In previous short-term as well as in long-term exposure studies, heart rate values tended to be higher in HH, but showed inconsistent results compared to NH (Savourey et al., 1997). In their first study, Savourey et al. recorded HR values that were significantly higher in HH, whereas in their second study no significant differences in HR were found, despite using a very similar protocol (Savourey et al., 2003, 2007). While the subjects of Savourey et al. were exposed to altitude for only 40 min, Faiss et al. conducted a 24-h exposure study at 3,000 m and did not find any significant differences in HR at rest or during moderate physical activity between conditions of NH and HH (Faiss et al., 2013). In our study HR was significantly higher in HH for the duration of 7 h. The increased HR values may be explained by a need for higher cardiac output due to a lower minute ventilation (V_E) from faster and shallower breathing in HH as has often reported in studies (Savourey et al., 2007; Self et al., 2011; Faiss et al., 2013).

There are other possible explanations for the increased HR we demonstrated during the mountain trail hike: (a) the ground surface on the Humu'ula trail is uneven compared to a treadmill and could have elicited higher exercise performance, (b) ultraviolet light radiation of the sun could have led increased fluid loss on the mountain trail compared to the chamber conditions. With restrictions on fluid intake to maintain comparability of intake between study settings, volume depletion with consequent tachycardia may have occurred, and (c) participants reported marked differences in group dynamics between the settings with more group pressure on Mauna Kea.

Our finding regarding the lack of difference in severity of AMS symptoms between NH and HH agrees with previous research (Richard et al., 2014). There are two factors that affect the generalizability of this finding. First, there was high inter-subject variability with the LLS probably due to the subjective nature of this questionnaire. Second, AMS becomes fully manifest after 6–96 h of hypoxic exposure at moderate to high altitudes (Debevec and Millet, 2014) Therefore, the 7-h exposure duration used in our study design may have had an impact on the participants' experiences of AMS during NH and HH. Limited exposure duration may explain the discrepancies between our observations and those studies reporting the opposite finding with exposure durations longer than 8 h (Debevec and Millet, 2014).

As is true of all studies with high altitude field observations, our study has limitations. Due to logistical problems, it was not possible to randomize assignments to the different study stages. It was also not possible to blind subjects to the experimental conditions in this crossover trial comparing NH in a chamber with natural HH on a mountain. However, due to the fact that the study results are based predominantly on objective parameters as SpO_2 and heart rate the likelihood of influencing results with personal bias is low. A minor limitation is the potential confounding effect of hypobaric acclimatization during the flights to Hawaii (10 and 5 h with 14 h lay-over between flights) as well as the jetlag effect on circadian rhythms. However, 4 days of rest at sea level on Hawaii with extended sleep times and time for sun exposure on the beach diminished these potential cofounding effects (Reilly and Edwards, 2007). Another minor limitation is that we did not measure urine concentrations after the hikes such that we cannot determine the possible contribution of a greater degree of volume depletion during the mountain hike.

In conclusion, our study describes physiological differences in HR and S_pO_2 during a mountain hike at altitudes from 2,800 to 4,200 m compared to a simulated hike in a normobaric hypoxia chamber. These differences must receive consideration when high altitude studies are performed or when mountaineers train for hikes at high altitude using normobaric chambers. The results of our trial also provide important data for aviation medicine and intensive care medicine, environments that confront the critical issue of hypoxia.

AUTHOR CONTRIBUTIONS

NN: designing research study, conducting experiment, providing material, writing manuscript LR: conducting experiment, writing manuscript, acquiring data, analyzing data Manuscript AE, Writing final version of manuscript; HG, analyzing data, writing manuscript; MF, conducting experiment, acquiring data; MB, writing manuscript, analyzing data; SP, designing research study, conducting experiment, analyzing data, acquiring data, writing.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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11.3 Study C including author contributions

Hereby I declare my contributions to the following article “Schlaf in der Höhe“.

I was involved in all stages of the development of this review:

- Literature search
- Execution of the measurements and testing in the several small examples
- Graphic design
- Statistical analysis
- Writing and finalizing the manuscript

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Thieme

Schlaf in der Höhe

Sleep at Altitude

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ZUSAMMENFASSUNG

Mit der besseren Erschließung der Bergregionen begeben sich nicht nur vorbereitete Sportler, sondern auch ältere Menschen mit Vorerkrankungen in größere Höhen. Aufgrund der Hypoxie erreichen die Bergsteiger dabei oft Sättigungstiefstwerte, die ernste Hypoxämie im Gewebe zur Folge haben. Auch in mittleren Höhen treten Symptome der akuten Bergkrankheit auf, welche sich im Schlaf manifestieren. Dabei sind vor allem Schlafapnoepatienten gefährdet, da zusätzlich zur obstruktiven Ventilationsstörung ein geringerer Sauerstoffpartialdruck vorhanden ist. Gleichzeitig spielen Geschlechterunterschiede eine maßgebende Rolle. Aufgrund der atemstabilisierenden Wirkung von Östrogen, passen sich Frauen schneller an Höhenunterschiede an als Männer. Die objektive Schlafqualität kann in normo- oder hypobaren Hypoxiekammern erfasst werden. In Hypoxie zeigt sich eine Verkürzung der Gesamtschlafdauer und verlängerte Wachphasen nach dem ersten Einschlafen, wodurch eine verringerte Schlafeffizienz erklärt werden kann. In größeren Höhen nimmt der Arousal-Index zu. Die großen, interindividuellen Unterschiede bei der Verträglichkeit von Höhenexposition fordern eine genaue Untersuchung höhenbezogener Problematiken sowie individuelle Akklimatisationsprotokolle. Durch eine gute Vorakklimatisation können weitgehend höheninduzierte Schlafprobleme behandelt werden.

ABSTRACT

Advancing infrastructure of mountain regions allows not only well-prepared mountaineers, but also elderly people with pre-existing illness the stay at high altitudes. Based on the hypoxic conditions, low oxygen saturation values are reached, which cause severe hypoxemia in the tissue. Symptoms of acute mountain sickness appear even at moderate altitude, which are manifested during sleep. Patients suffering from sleep apnea are at high risk, because of the obstructive ventilation disorder in combination with less oxygen availability. Concurrently, gender differences play a decisive role. Due to the respiratory stabilizing impact of estrogen, women are faster in adapting to altitude differences. A reduction of sleep duration and extended wake phases are shown, which causes lower sleep sufficiency. With continued rise of altitude, the arousal-index increases. For individual differences concerning altitude induced problems, individual acclimatization protocols are needed. Well prepared pre-acclimatization could prevent altitude induced sleep problems, as well as the treatment of such.

Physiologische Höhenreaktion

Die Höhe ist vor allem durch einen geringen Gesamtluftdruck und damit auch einen geringen Sauerstoffpartialdruck (pO_2) gekennzeichnet. Dies führt insgesamt zu einem erniedrigten arteriellen Sauerstoffpartialdruck (paO_2) im Körper und folglich zu Hypoxämie in der Zelle. Diesem Umstand setzt der Körper eine Reihe von Anpassungsreaktionen entgegen. Als akute Maßnahme erhöht sich die Herzfrequenz und eine durch den niedrigen paO_2 bedingte Hyperventilation setzt ein. Je nach genetischer Prädisposition, dem allgemeinen Trainingszustand sowie der Akklimatisationserfahrung des Organismus ist dies personenbedingt unterschiedlich stark ausgeprägt. Zusätzlich wird die Atemtiefe und Atemfrequenz der Hyperventilation durch schwankende oder extreme Temperaturunterschiede, Stresssituationen oder emotionale Faktoren beeinflusst. Die geringe arterielle Sauerstoffsättigung hat eine Unterversorgung der Zelle mit Sauerstoff zur Folge. Diese führt vor allem in Sauerstoff-sensiblen Bereichen wie im Gehirn und im Auge zu spürbaren Einschränkungen (im Extremfall Höhenhirnödem HACE). Für das Höhenlungenödem (HAPE) ist dagegen der Euler-Liljestrand Reflex verantwortlich, der mit einer Vasokonstriktion im Lungengewebe zu einem Rückstau im rechten Ventrikel führt und damit eine pulmonale Hypertonie provoziert [1, 2].

Bis zu einem kritischen pO_2 von etwa 50 mmHg (etwa 8000 m) ist die alveoläre O_2-Diffusion noch möglich und erfährt dann durch den geringen Druck allmählich eine Flussumkehrung [3]. Dies ermöglicht das Weitersteigen nur noch bei ausgezeichneter Höhenanpassung und bei besonders günstigen Wetterlagen.

Die Anpassung des Organismus an die Hypoxie unterliegt stark genetischen Faktoren. Diese Mechanismen scheinen sich nicht nur zwischen Flachlandbewohnern und Höhenbewohnern zu unterscheiden, sondern funktionieren auch unterschiedlich unter den verschiedenen Höhenbewohnern wie Tibetern, Andenbewohnern oder Äthiopiern [4, 5]. Mitteleuropäer sind grundsätzlich genetisch sehr durchmischt und reagieren daher unterschiedlich auf verschiedene Höhen.

Grundsätzlich kann man die verschiedenen Höhenreaktionen in vier Bereiche einteilen:

Mittlere Höhe Höhenexpositionen zwischen dem Meeresspiegel und Zugspitze (2962 m) sind für Gesunde weitgehend als unproblematisch einzustufen. Bei anfälligen Personen treten Symptome der akuten Bergkrankheit (AMS) wie Kopfschmerz, Schwindel, Übelkeit, Müdigkeit und Schlafprobleme oft schon in geringen Höhen auf und werden teilweise fälschlich einer schlechten Tagesform oder leichter Krankheit zugeschrieben. Es gibt Hinweise darauf, dass bei Personen mit hoher β-Blocker Medikation bereits in diesen Höhen periodische Atmung verstärkt auftritt. Bei vorbestehender Cheyne-Stokes-Atmung verstärken sich die Symptome. Des Weiteren birgt die erhöhte Herzfrequenz ein höheres Schlaganfallrisiko und der geringe paO_2 das Risiko der Unterversorgung bereits schlecht versorgter Areale. In diesen Höhen bewegt sich die weitaus größte Gruppe von Bergsteigern. Hier ist eine genaue Evaluierung der Schlafqualität auf Zielhöhe nötig [1].

Große Höhe Von 3000 m bis 5000 m (z. B. Elbrus) treten vermehrt Symptome der AMS auf. Der menschliche Organismus kann sich zwar noch vollständig adaptieren, aber es treten in der Anfangsphase der Anpassung unweigerlich Symptome auf. Bei schnellem Aufstieg (< 2 Tage) kann hier auch bei Gesunden in der Nacht verstärkt die periodische Atmung erscheinen. Tiefschlaf- und REM-Phasen werden zunehmend kürzer, und die Arousal-Häufigkeit nimmt zu. Perfekt angepasst kann in diesem Bereich allerdings noch weitgehend symptomfrei Bergsport betrieben werden [6].

Sehr große Höhe Von 5000 m bis in eine Höhe von 7500 m (z. B. Muztagh Ata) kann sich der Körper nicht mehr vollständig anpassen. Symptome bahnen sich unweigerlich ihren Weg, und die Leistungsfähigkeit nimmt ab.

Todeszone In der Todeszone ab 7500 m kann der Körper trotz guter Vorakklimatisation nur noch kurze Zeit aushalten. Der Kreislauf kann nicht genügend Sauerstoff aufnehmen, um die Versorgung, insbesondere der Muskulatur und des Gehirns, noch ausreichend zu gewährleisten.

Der Höhenschlaf

Dem Höhenschlaf wurde bereits 1890 eine heilsame Wirkung zugesprochen. Spätere grundlegende Untersuchungen mit händisch geführten Schlafprotokollen stellten längere Schlafperioden und häufige Unterbrechungen des Höhenschlafs fest [7]. Erst um 1970 wurde es möglich, den Schlaf auf einer Höhe von über 4000 m mittels Elektroenzephalogramm (EEG), Elektrokardiogramm (EKG) und der Schlafphasenklassifizierung nach Rechtschaffen & Kales qualitativ und quantitativ zu untersuchen [8, 9]. Die Feststellung, dass die subjektive sowie objektive Schlafqualität fast linear zur Höhe abnimmt, räumte der Schlafmedizin auch bezüglich der Erforschung verschiedener Höhenkrankheiten einen neuen Stellenwert ein [10, 11]. Wesentlich niedrigere arterielle Sauerstoffsättigungswerte, welche den Höhenschlaf charakterisieren, tragen zum Entstehen der AMS bei.

Subjektive Schlafqualität

Von vielen Bergsteigern wird der Schlaf ab 3000 m als schlecht eingestuft, durchsetzt mit subjektiv empfundenen Wachphasen. Wie auch für die Höhenkrankheit, gibt es bei der Ausprägung dieser gefühlten Störung des Schlafes individuelle Unterschiede. In größeren Höhen können zusätzliche Komplikationen wie Übelkeit, Schwindel oder Atemnot als Symptome der AMS noch hinzukommen [12]. Eine Fragebogenstudie bestätigte diese subjektiven Einschätzungen vieler Bergsteiger, und es konnte nachgewiesen werden, dass Probleme bei der Schlafinduktion und häufiges nächtliches Erwachen schon in Höhen ab 3000 m eintreten [13].

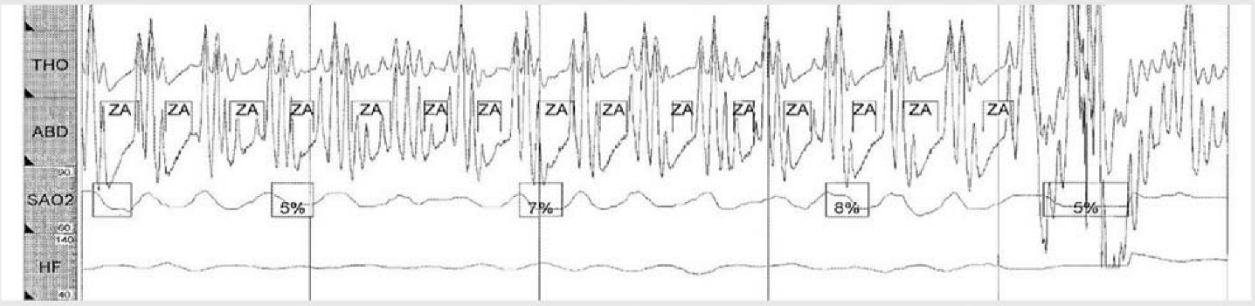
Objektive Schlafqualität

Die objektive Schlafqualität in der Höhe wird nicht nur am Berg erfasst, sondern auch in normobaren und hypobaren Hypoxiekammern. Die Durchführung einer standardisierten Schlaferfassung in einer normbaren Umgebung erhöht die Vergleichbarkeit und Validität der Messung. Dabei wird entweder der räumliche Luftdruck abgesenkt (hypobar) oder der Stickstoffanteil in der Raumluft erhöht (normobar), um die gewünschte Höhe zu erzielen. In den meisten bislang durchgeführten Studien zeigten sich übereinstimmend eine Verkürzung der Gesamtschlafdauer und verlängerte Wachphasen nach dem ersten Einschlafen (WASO), wodurch eine verringerte Schlafeffizienz erklärt werden kann. Neben der Schlafdauer verändert sich auch die Schlafarchitektur. So nimmt mit fortschreitender Höhe der Anteil von Stadium N1 zu, während Delta-Schlaf und REM Schlafanteile abnehmen. Auffällig ist auch eine Zunahme des Arousal-Indexes bei einem weiteren Anstieg der Höhe und damit der Hypoxämie der betreffenden Probanden [10].

Pathologie des Höhenschlafens

Periodische Atmung

Während im Wachen jederzeit die Möglichkeit besteht, die Atemfrequenz willentlich zu steuern, wird die Atemtätigkeit nachts weitgehend autonom gesteuert. Messfühler dafür sind Chemorezeptoren an der Arteria Carotis, welche die Zusammensetzung der Blutgase (CO_2, O_2, Säure-Basen-Haushalt und ph-Wert) errechnen. Ein reduzierter pO_2 erhöht den Atemantrieb und führt zur Hyperventilation. Dabei wird verstärkt CO_2 abgeatmet, wodurch der zunächst gesteigerte Atemantrieb wieder gebremst wird. Ab einer gewissen Höhe kommt es zu respiratorischer Instabilität, basierend auf einer Disbalance des chemischen Feedbacks in den Chemorezeptoren. Die korrektive Atemantwort (Hyperventilation) auf den niedrigen pO_2 ist größer als die ausgehende Störung (Hypoxie). Die Korrektur übersteigt das notwendige Maß und verstärkt die Atemstörung, anstatt sie zu beheben (dies hat vor allem auch mit der



▶ **Abb. 1** Ausschnitt aus einer Polysomnografie (Sidas GS, Fa. Stimotron, Wendelstein) im Höhenschlaflabor bei einem gesunden männlichen Probanden in simulierten 5000 m Höhe. Das Atemmuster zeigt bei den Thorax- und Abdomenbewegungen das typische Muster der anschwellenden und abschwellenden periodischen Atmung mit einer Atempause. Die SaO_2-Kurve zeigt das typische an- und abschwellende Muster für zentrale Apnoen, ähnlich wie bei Hypopnoen (vgl. dazu auch Netzer N, Eliasson AH, Netzer C, Kristo DA. Overnight pulse oximetry for sleep-disordered breathing in adults: a review. Chest 2001; 120: 625 – 633).

Verzögerung der Sauerstoffmessung am Chemorezeptor und der daraus resultierenden Nachregulation zu tun). Es stellt sich eine periodische Atmung ein, welche durch Phasen der Hyperventilation, gefolgt von Hypoventilation oder zentralen Apnoen, gekennzeichnet ist (▶ **Abb. 1**). Das Atemmuster ist der Cheyne-Stokes-Atmung ähnlich [2].

Das Phänomen ist grundlegend durch die Verzögerung und Abschwächung des Ausgangswertes des effektiven $PaCO_2$ während des Weges zu den Chemorezeptoren zu erklären. Dies führt zu einer Verzögerung und Fehlregulation an den Rezeptoren gemessen an der eigentlichen Situation und somit zu einer weiteren Eskalation der Atmung [14]. Im Resultat führt dies zu einer Phasendifferenz zwischen dem apnoeischen Teil der periodischen Atmung und der minimalen SaO_2. So beträgt in 5400 m Höhe die Verzögerung zwischen der maximalen Atemantwort und der maximalen SaO_2 bereits 12 Sekunden im Vergleich zu 6,8 bis 9,4 Sekunden auf Meereshöhe.

Der Loop Gain, also die Stärke der Atemantwort auf die Apnoe und den Anstieg des $PaCO_2$, ist von verschiedenen individuellen Faktoren abhängig (genetische Voraussetzungen, Geschlecht, Alter, Vorspannung und Kraft der Atemmuskulatur, Sensibilität der Sensorik in der Atemmuskulatur u. a.). Je höher der Loop Gain, desto mehr wirkt sich die Phasendifferenz aus, und es kommt zur Wiederholung von Apnoen mit der typischen Periodik der an- und abschwellenden Atmung bei der hypoxiebedingten periodischen Atmung.

Die häufigen nächtlichen Arousals in mittlerer und großer Höhe werden hauptsächlich durch periodische Atmung verursacht [12, 15]. Weder die physiologischen Grundlagen der Atmungsregulation beim Schlaf in der Höhe sind im Detail erforscht noch ist geklärt, inwieweit die periodischen Atemmuster unter Hypoxie als pathologisch zu interpretieren sind, oder ob sie einen protektiven Faktor darstellen, der das Überleben in der Höhe sichert [2].

Durch die Hypoxämie erhöhen sich die sympathische Aktivierung und der Adrenalinspiegel und lassen die Arousal-Schwelle weiter absinken. Ab extremen Höhen erfolgt eine so starke sympathische Aktivierung, dass ein regulärer Schlaf kaum mehr möglich ist. Neben der periodischen Atmung sind Umweltfaktoren wie Kälte, Wind, unbequeme Schlafumgebung, höhenbedingte Kopfschmerzen, gesteigerte Nykturie oder aversive Emotionen weitere Gegenspieler des erholsamen Schlafes.

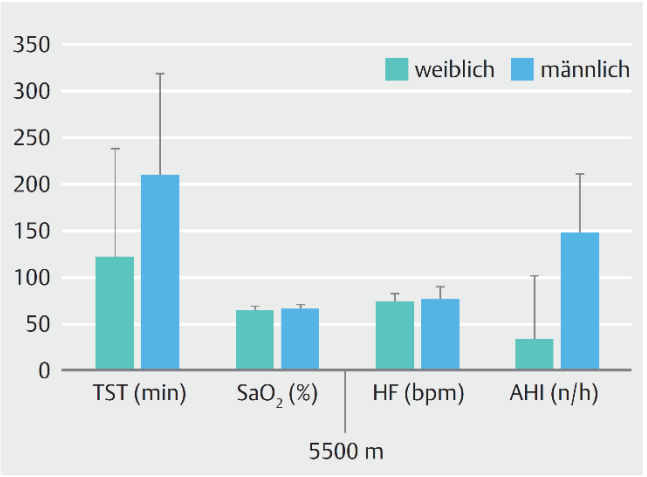
Schlafapnoe

Lautes Schnarchen ist das akustische Symptom der Schlafapnoe, welches durch die Verschließung der Atemwege erzeugt wird. Diese Atemstörung ist nicht nur eine Geräuschbelastung, sondern vor allem eine enorme Beeinträchtigung des Schlafes. Eine Gefährdung stellen vor allem die mittleren Höhen für Schlafapnoepatienten dar, weil sich zu der ohnehin schon bestehenden, schlafbezogenen, obstruktiven Ventilationsstörung der reduziert verfügbare Sauerstoff dazu gesellt. In großen Höhen übernimmt die zentrale Atemstörung mit ihren periodischen Atemmustern die Regie, sodass obstruktive Atemstörungen weniger ins Gewicht fallen [16]. Da in der Höhe am Berg ein nCPAP-Gerät zur Atemtherapie meist nicht zur Verfügung steht, sind atemsteigernde Medikation, wie bspw. der Carboanhydrasehemmer Acetazolamid, zu empfehlen, die einer nächtlichen, zentralen Atemregulationsstörung entgegenwirken [17]. Auch Benzodiazepine und deren Derivate, die neben ihrer schlaffördernden Wirkung einen leicht atemdepressiven Effekt haben, können zur Verbesserung des Höhenschlafs eingesetzt werden. Dabei macht man sich den atemdepressiven Effekt insofern zunutze, dass dieser einem waxing und waning entgegenwirkt. Dabei scheinen Benzodiazepine, insbesondere Temazepam, keinen negativen Effekt auf Vigilanz, Reaktionszeit oder andere kognitive Funktionen zu haben [18].

Geschlechtsunterschiede

Wie in vielen Bereichen spielen auch beim Schlafen in Hypoxie Genderdifferenzen eine maßgebende Rolle. So unterscheiden die Geschlechter sich in der Atemregulation und daher in der Höhenanpassung. Lombardi et al. zeigen bei einer Untersuchung im Himalaya, dass bei gleicher Sauerstoffsättigung in der Höhe, Frauen weniger zu periodischer Atmung tendieren als Männer und sich auch schneller an die Höhenbedingungen anpassen [19]. Es wird vermutet, dass Östrogen sowie Proges-

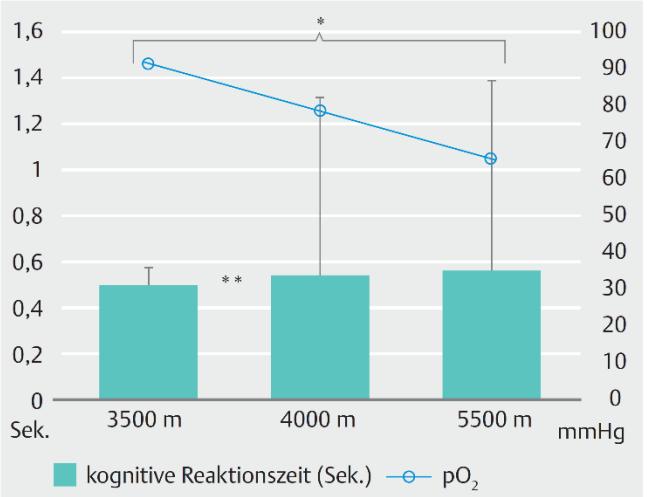
teron und deren atemstabilisierende Wirkung eine maßgebliche Rolle dabei spielen. Diese vermindern den zerebralen Gefäßtonus und sorgen für eine Steigerung des zerebralen Blutflusses durch die Erhöhung der Ausschüttung von endothelial abgeleitetem Nitrooxid und Prostacyclin. Das Testosteron hingegen wirkt gegenteilig und destabilisiert somit die Atemkontrolle [16]. Des Weiteren konnte eine verringerte zerebrovaskuläre Reaktivität auf Grund des $PaCO_2$-Abfalls bei Schlafapnoe-Patienten festgestellt werden. In sehr großen Höhen verkürzen sich außerdem die Länge der Atemzyklen bei Männern, nicht so bei Frauen. Die dafür ausschlaggebende Interaktion zwischen hypoxie-induzierter Hyperventilation und Chemoreflex-Aktivität erfordert jedoch weitere Untersuchungen. Die periodische Atmung scheint hingegen in manchen Fällen eine SpO_2 stabilisierende Rolle einzunehmen und wird zurzeit als eventueller Vorteil für die Höhe diskutiert [2]. ▶ **Abb. 2** zeigt die Unterschiede zwischen Männer und Frauen beim Höhenschlafen auf 5500 m simulierter Höhe in normobarer Hypoxie. Hier weisen die Männer einen deutlich höheren AHI (apopnea/hypopnea Index) auf, während die mittlere Sauerstoffsättigung vergleichbar mit der der Frauen sogar etwas höher liegt. Eventuell wirkt sich in diesem Beispiel die periodische Atmung sogar auf die Gesamtschlafzeit (TST) positiv aus.



▶ **Abb. 2** PSG-Daten von 6 jungen Männern und 5 jungen prämenopausalen Frauen. AHI = Apnoe-Hypopnoe Index, SaO_2 = Arterielle Sauerstoffsättigung, TST = Totale Schlafzeit, HF = Herzfrequenz.

Beeinträchtigung der Kognition

Beeinträchtigte Kognition, bedingt durch schlafbezogene Atmungsstörungen, ist ein bekanntes Phänomen. Da Höhenschlafen, wie beschrieben, periodische Atemmuster provoziert, ist eine Einschränkung der Kognition bei Höhenaufenthalten denkbar. In diesem Zusammenhang wurde bereits eine Reihe von Untersuchungen durchgeführt [20]. Nimmt man etwa Reaktionstests nach Nächten auf 3500 m, 4500 m und 5500 m in simulierter Höhe, zeichnet sich ein interessantes Bild. Zwar scheinen die Reaktionszeiten insgesamt nicht sonderlich verlangsamt, aber die kognitive Komponente verlangsamt sich signifikant in allen Höhenstufen. Je niedriger der pO_2 fällt, umso ausgeprägter fallen Einschränkungen in kognitiver Reaktionszeit aus (▶ **Abb. 3**). Im vorliegenden Datensatz korreliert die Abnahme der kognitiven Reaktionszeit nicht mit der mittleren Sauerstoffsättigung über Nacht, daher bleibt die Ursache für die Einschränkung vorerst unklar. Allerdings könnte dieser Umstand mit ein Faktor für Unfälle in großen Höhen sein [21].



▶ **Abb. 3** Kognitive Reaktionszeiten von 6 jungen Männern und 5 jungen prämenopausalen Frauen bei steigernder simulierter Höhe. pO_2 = Sauerstoffpartialdruck in der Einatemluft.

Fazit

Mit der Popularität des Bergsteigens und der Attraktivität der Alpenregionen nehmen Fragestellungen zum Thema Schlafen in der Höhe kontinuierlich zu. Für Gesunde gibt es in der Regel keine Einschränkungen, was das Schlafen in mittleren und großen Höhen betrifft, solange die Akklimatisationszeiten lange genug sind. Die großen, interindividuellen Unterschiede bei der Verträglichkeit von Höhenexposition fordern eine individuelle Untersuchung einzelner höhenbezogener Problematiken sowie individuelle Akklimatisationsprotokolle. Durch eine gute Vorakklimatisation können weitestgehend alle durch die Höhe verursachten Schlafprobleme behandelt werden. Eventuell ist eine Anpassung von vorhandener Medikamentation notwendig, um physiologische Höhenreaktionen nicht zu behindern (β-Blocker). Bei bekannter Anfälligkeit für AMS sind eine genaue Anamnese und höhenspezifische Untersuchungen notwendig. Patienten, die an Herzinsuffizienz oder schlafbezogenen Atmungsstörungen leiden und Aufenthalte in mittleren bis großen Höhen planen, sollten ihre Höhenverträglichkeit in einem Höhenschlaflabor untersuchen. Nach genauer Kenntnis der individuellen Reaktion auf die Höhe können hier Empfehlungen für eine therapeutische Maßnahme (PAP-Therapie, Medikamente) ausgesprochen werden. Besonders bei anfälligen Personen und einer starken Ausprägung periodischer Atmung in der Höhe ist eine umfangreiche Vorakklimatisation anzuraten. Ein langsamer Aufstieg und ein nicht größerer Höhenunterschied als 500 m pro Nacht sind hier anzuraten [22].

Interessenkonflikt

Die Autoren geben an, dass kein Interessenkonflikt besteht.

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11.4 Study D including author contributions

Hereby I declare my contributions to the following article "EHAK-65."

I was involved in all stages of the development of this study:

- Planning and study design
- Obtaining ethics approval
- Recruiting of subjects
- Execution of the measurements and testing in normoxia
- Execution of the measurements and testing in normobaric hypoxia
- Statistical analysis
- Writing and finalizing the manuscript

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Endurance Training in Normobaric Hypoxia Imposes Less Physical Stress for Geriatric Rehabilitation

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Rationale: Evidence suggests that training in hypoxia can be very effective even while requiring less physical effort. We therefore aimed to measure the effect of endurance training under hypoxic conditions on pulmonary and cardiovascular parameters in an elderly population undergoing inpatient rehabilitation.

Methods: Forty patients over age 65 years with multiple co-morbid conditions were recruited during a 3-week stay in a geriatric rehabilitation center. Using a randomized, single-blinded, placebo-controlled design, patients were assigned to a hypoxic (HG) or normoxic (NG) group. HG patients completed seven training sessions of 30 min duration on a treadmill in a normobaric chamber with inspired oxygen fraction (FiO_2) of 15.27%, with 10–30 min active training. Training was conducted with target heart rate at 80% of peak oxygen consumption (VO_2-peak). NG group performed similar training in sham hypoxia (room air or $FiO_2 = 20.94\%$). At pre- and post-test completion, measures included: (1) cycle ergometry with ECG monitoring and measurement of VO_2-peak, and (2) echocardiography for ejection fraction.

Results: The physical effort required of patients to reach target heart rate was reduced significantly (-28%, $p = 0.043$) in the HG compared to NG. Cardiopulmonary parameters showed no differences between groups.

Conclusion: Endurance training at 3,000 meters elevation imposes less stress on the locomotor systems while resulting in a similar physiological strain (i.e., heart rate). Hypoxic training holds promise for successful geriatric rehabilitation by being more accommodating to physical limitations in geriatric patients.

Trial registration: Registration at DRKS. (Approval No. 359/12, Trial No. DRKS00005241).

Keywords: hypoxia, training with geriatrics, low external load, training, geriatrics

INTRODUCTION

With the aging population, rehabilitative training for the elderly is gaining humanitarian and economic importance (Poterba, 2016). A major goal is to keep the elderly as fit and active as possible to prevent immobility and hospitalization (Jamour et al., 2014). This effort has the potential to improve quality of life and decrease burdens on the medical system. Despite intensive investigations into methods for training and therapy, there is a paucity of data and evidence-based guidelines for endurance training in the elderly ≥75 years (Meusel, 2000). However, endurance training does show positive results (Meusel, 2000; Oster et al., 2005; Fiogbe et al., 2017; Pandey et al., 2017). For common diseases such as coronary heart disease, stroke, cancer and diabetes, endurance training has proven to be effective in younger individuals <75 years (Buchner et al., 1997; Cornelissen and Fagard, 2005; Ventura-Clapier et al., 2007). Since those diseases have a high prevalence among geriatric patients, the question is raised regarding the benefit of such endurance training in the elderly. Restrictions in endurance capacity have a direct impact on immobility, muscle atrophy and frailty, all of which relate to activities of daily living (Avila-Funes et al., 2011). Recent studies in the field of endurance training suggest a greater effect of training at higher intensities (Hayashi et al., 2005; Swain and Franklin, 2006; Pokan et al., 2009). Higher intensities of training are especially hard to reach with geriatric patients because of physical and medical limitations. High-intensity training is even harder in rehabilitation settings such as after surgery. At times tolerance of active training may be reduced to 10–20 min per day. For endurance training to provoke adaptive responses in the cardiopulmonary systems in such a short time period, it may be necessary to conduct the training at 60–80% of peak oxygen (O_2) consumption (VO_2-peak) (Hayashi et al., 2005; Swain and Franklin, 2006; Pokan et al., 2009). Attaining this intensity level of training in the elderly may not be possible without substantial risk (Oster et al., 2005).

Positive effects of hypoxic training have been shown in prior investigations notably in obese subjects (Piehl Aulin et al., 1998; Netzer et al., 2008; Schipfer et al., 2008; Haufe, 2010; Gatterer et al., 2014). Initially, endurance performance in hypoxia is reduced, but even when applying a lower external load, such hypoxic training can result in cardiovascular and metabolic responses that are similar to high-intensity training in normoxia (Kong et al., 2017).

These observations suggest that hypoxic training may be useful to increase training intensity for geriatric patients while maintaining a low impact on locomotor systems. Hypoxic training may also have positive effects on ejection fraction (EF), heart rate (HR) to power ratio, O_2 consumption (VO_2), and revascularization of the myocardium (Knuth, 2008). In this study our aim was to measure the effect of endurance training under hypoxic conditions on pulmonary and cardiovascular parameters in an elderly population undergoing inpatient rehabilitation. We hypothesized that endurance training in normobaric hypoxia may induce a lower physical stress for a similar physiological strain compared to similar training in normoxia. As such, this may safely support targeted endurance training while respecting physical restriction in geriatric patients.

METHODS

Subjects were recruited from the geriatric rehabilitation hospital (Fachklinik Ghersburg für Geriatrische Rehabilitation, Bad Aibling, Germany) attached to the study center. Inclusion criteria for participation were: (1) age > 65 years, (2) cognitive ability to give informed consent and to participate in the study, (3) sufficient peripheral blood flow for pulse oximetry, (4) heart failure symptoms no worse than NYHA Class III, and (5) dosages of cardiovascular-relevant medications (ß-blockers, ACE inhibitors, etc.) that would allow at least a 10% increase of HR to physical stress. An exclusion criterion was any orthopedic condition that precluded performance of a cycle ergometry test.

Of the 40 patients recruited, 35 (87.5%) were able to complete the trial. Reasons for dropout were unwillingness to continue ($n = 4$) and termination for medical reasons ($n = 1$).

Descriptive means for the normoxic group (NG, $n = 16$) were: age 82.0 (±7.8) years, sex 11 women/5 men, and BMI 25.8 (±6.2) kg/m^2. Descriptive means for the hypoxic group (HG, $n = 19$) were: age 80.2 (±7.2) years, sex 12 women/7 men, and BMI 25.2 (±5.3) kg/m^2.

Exercise Testing

At pre-test, anthropometric data were collected and echocardiography was performed. Cycle ergometry with ECG monitoring was conducted using a standard protocol for heavily impaired patients (Pokan et al., 2009). After 3 min of rest and 3 min of reference pedaling at 15 watts, the test started at 27 watts and was increased by 7 watts each minute until subjective exhaustion (Pokan et al., 2009). Criteria that would trigger interruption of the test were: (1) HR higher than maximal predicted, calculated using the formula 220 bpm—age, (2) systolic blood pressure (BP) higher than 220 mmHg, (3) any ST-segment changes, (4) ventricular extrasystoles, or (5) angina pectoris. The testing was also interrupted upon attaining subjective exhaustion equivalent to 18 on the BORG-Scale (Borg, 1982). After pre-test, patients were randomly assigned in equal numbers to the HG or the NG.

Training Phase

The subsequent target HR for training was set as 80% of VO_2-peak (maximum O_2 consumption achieved during the pre-test ergometry test) with 5 bpm added to account for the conversion from cycle to treadmill training (Kroidl et al., 2015). The more standard conversion factor of 10 bpm was not used because patients most commonly train with their arms resting on the treadmill handrails. The main parameters that were used to assess training effects were EF by echocardiogram, peak HR, O_2 saturation, VO_2-peak, and peak O_2/HR. Patients were asked to perform 7 training sessions during their 3-week stay in the geriatric rehabilitation center. The normobaric hypoxic chamber was set to contain either hypoxic air equivalent to an altitude of 3000 meters ($F_iO_2 = 15.27\%$) or sham hypoxia (room air at $F_iO_2 = 20.94\%$). Normobaric hypoxia was produced using

a device called "Low Oxygen Systems" (Berlin-Buch, Germany) which provided a controlled mixture of fresh air and nitrogen to keep O_2 and carbon dioxide (CO_2) levels constant. This allowed patients to exercise without wearing a mask and to concentrate fully on the intervention. Patients were blinded to the different conditions though the investigators were not (single-blinded). Each of the 7 training sessions in the chamber included a stay of at least 30 min with a minimum of 10 min and a maximum of 30 min of active training on a treadmill. The treadmill (h/p/cosmos, Traunstein, Germany) offered forearm supports for more impaired patients and a safety belt to stop the movement in an emergency. The therapists tried to reach the target HR considering the physical and medical impairments of each patient and taking care not to exceed the target HR. BP (Omron M400 IT) was measured before each training session, while HR (Polar Heart Rate Sensor T31) and O_2 saturation (NONIN Go 2) were monitored continuously during training.

The intervention protocol was designed to be practicable and achievable. The prescription of seven sessions of at least 10 min of endurance training over a 3-week period corresponded to common practice in geriatric rehabilitation hospitals. Both HG and NG subjects also participated in the other prescribed rehabilitation programs in the hospital, consisting of one 30-min individual physical therapy session and another 30-min group physical therapy session (e.g., strength, gait, balance training) per day. The mean time elapsed between training sessions as well as pre- and post-tests was 1.56 days in HG and 1.57 days in NG. At the conclusion of the 7 sessions of endurance training, outcome measurements were repeated as they had been performed at pre-test.

STATISTICS

Evidence from published research suggested that for the main outcome parameter of VO_2-peak, we would detect a mean difference of 0.23 l/min (SD ± 0.36 l/min) between intervention group and control group (Vaitkevicius et al., 2002; Vogt et al., 2002). To reach a significance level set a priori at $p < 0.05$ and a power of 80%, it would be necessary to enroll 17 subjects in each arm of the study. To account for possible dropouts, the study enrollment was set at 40 subjects in total. Data are presented as means ± standard deviation (SD). For all analyses a two-way ANOVA for repeated measures was performed. To identify the magnitude of statistical difference between the groups in each training session (Tr1-Tr7) a student *t*-Test was used. Data analyses were performed with the SPSS statistical software package (PASW Statistics for Windows version 21.0, SPSS Inc., Chicago, IL, USA). Effect size, using ANOVA, was calculated as partial eta-squared (η^2). $\eta^2 < 0.06$ accounts for a small effect, $0.06 < \eta^2 > 0.14$ accounts for a medium effect and $\eta^2 > 0.14$ accounts for a big effect.

STUDY APPROVAL

The study protocol was reviewed and approved by the institutional review board of the University of Ulm on the January 19, 2015 and was registered as a clinical trial with the German Clinical Trials Register (DRKS). (Approval no. 359/12, Trial no. DRKS00005241) Participants gave their written informed consent prior to inclusion in the study.

RESULTS

Thirty five patients (23 women) were able to finish the trial. Among these patients the most common diagnoses were coronary heart disease, diabetes types I and II, hypertension, chronic obstructive pulmonary disease, peripheral arterial occlusive disease, hip replacement, fractures, congestive heart failure, osteoporosis, stroke and myocardial infarction. The majority of patients were prescribed cardiovascular-relevant medications as well as diuretics, anticoagulant medication, cholesterol and blood sugar lowering drugs. During the study period, slight changes in medication were made by the hospital's physicians but these medication changes occurred in both groups equally.

The endurance training was well tolerated and there were no complaints regarding the intervention. For some patients, transfer to the cycle ergometer for ergospirometry was hard to accomplish. The gas analyzer mask was reported to be uncomfortable but tolerable for the short testing period.

Outcome Measurements before and after the Intervention

Statistical analysis showed no significant differences between groups. From pre- to post-test, there were no changes in anthropometric parameters (**Table 1**). There was also no change in the measured cardiologic parameters. Mean EF for the HG showed a non-significant decrease compared to the NG. Although not significant, peak VO_2 was higher in post-test in both groups. The peak O_2 /-HR was higher in HG but this difference was not statistically significant. However, the maximum performance increased significantly in both groups from pre- to post-test ($p = 0.004$) (**Table 1**). There were no sex differences regarding the effect of the intervention. Overall, both groups showed similar responses from pre- to post-test though the training intensity (% of peak VO_2) was significantly lower in HG ($p = 0.012$) (**Table 2**).

Intervention

Aiming for a mean training intensity at 80% of VO_2-peak the NG had to be pushed harder and only reached an average intensity of 74%. The HG had to be restrained to prevent them from exceeding their target HR resulting in a mean training intensity of 80%.(**Figure 1**). All intensity related parameters showed a significant reduction in training effort for HG as displayed in **Table 2**. Resting BP in both normoxic and hypoxic environments did not change over the time course of the seven training sessions (**Figure 2**).

DISCUSSION

This is the first study of endurance training in normobaric hypoxia with exclusively geriatric patients. The present study

TABLE 1 | Anthropometrical and physiological values at baseline (pre-) and after (post-) the endurance training for the hypoxic group (HG) and normoxic group (NG).

Item	Hypoxic group (HG)		Normoxic group (NG)		Condition	Time	Interaction
	Pre-	Post-	Pre-	Post-	*P*	*p* (η^2)	*p*
Weight (kg)	67.74 (±18.92)	68.21 (±19.34)	68.38 (±16.49)	67.78 (±17.75)	0.56	0.608	0.254
BMI (kg/m^2)	25.23 (±5.26)	25.41 (±5.39)	25.83 (±5.71)	25.64 (±6.43)	0.457	0.827	0.287
EF (%)	42.83 (±9.28)	39.87 (±9.31)	46.61 (±15.70)	44.2 (±9.46)	0.493	0.169	0.931
Peak Power (W)	41.18 (±13.53)	46.19 (±14.43)	43.38 (±10.41)	46.24 (±11.41)	0.737	0.004** (0.43)	0.289
Peak HR (bpm)	120.05 (±30.12)	120.37 (±24.48)	116.56 (±22.92)	120.31 (±20.41)	0.296	0.118	0.459
Peak VO_2 (ml/min)	929.68 (±325.6)	1003.37 (±342.02)	938.13 (±218.01)	969 (±296.74)	0.858	0.375	0.703
Peak O_2/HR (ml)	8.86 (±2.83)	9.4 (±3.14)	8.61 (±2.54)	8.66 (±2.59)	0.655	0.544	0.574

Values are means ± SD.
*BMI, body mass index; EF, ejection fraction of the heart; peak HR, peak heart rate; peak VO_2, peak oxygen consumption; peak O_2/HR, peak fraction of oxygen to heart rate; **$p \leq 0.025$ levels of significance effect size is displayed as η^2.*

TABLE 2 | Physiological and training-intensity related parameters during the intervention for the hypoxic group (HG) and normoxic group (NG).

Item	Hypoxic group (HG)			Normoxic group (NG)			Cond. *p* (η^2)	Time *p* (η^2)	Int. *p* (η^2)
	Tr1	Tr7	Δ Tr1-7 (%)	Tr1	Tr7	Δ Tr1-7 (%)			
Watt (W)	18.53 (±6.54)	22.84 (±13.52)	23.26	23.00 (±11.51)	34.75 (±14.90)	51.09	0.058	<0.001*** (0.56)	0.005*** (0.18)
Watt/kg (W)	0.27 (±0.07)	0.32 (±0.15)	18.52	0.33 (±0.11)	0.50 (±0.13)	51.52	0.012 (0.35)	<0.001*** (0.53)	0.001*** (0.21)
Training intensity (%)	79.45 (±7.96)	80.67 (±5.80)	1.54	68.12 (±9.03)	74.43 (±8.33)	9.26	0.012** (0.35)	0.059	0.739
BP systolic (mmHg)	140.47 (±22.78)	140.32 (±23.32)	−0.11	148.44 (±17.95)	141.88 (±19.94)	−4.42	0.350	0.163	0.605
BP diastolic (mmHg)	77.32 (±19.27)	76.68 (±10.24)	−0.83	82.06 (±8.21)	75.75 (±11.83)	−7.69	0.609	0.616	0.465
Velocity (km/h)	1.37 (±0.29)	1.37 (±0.36)	±0.00	1.44 (±0.29)	1.71 (±0.23)	18.75	0.070	<0.001*** (0.32)	0.001*** (0.21)
Grade (%)	0.12 (±0.46)	1.65 (±2.21)	1.275	1.13 (±1.75)	3.88 (±2.42)	243.36	0.005** (0.42)	<0.001*** (0.46)	0.066
Walking distance (m)	263.16 (±99.12)	381.23 (±251.04)	44.87	285.63 (±105.42)	505.42 (±178.25)	76.95	0.358	<0.001*** (0.63)	0.492
SpO_2 (%)	88.28 (±9.00)	90.11 (±11.47)	2.07	94.42 (±2.98)	95.15 (±2.33)	0.77	<0.001*** (0.72)	0.027* (0.14)	0.776

Values are means from Tr1 and Tr7 ± SD.
*Training intensity, % of peak heart rate; BP, blood pressure; SpO_2, oxygen saturation, *$p \leq 0.05$, **$p \leq 0.025$, ***$p \leq 0.001$ levels of significance, effect size is displayed as η^2.*

demonstrates that endurance training performed in hypoxia in geriatric patients requires less physical effort to produce an effective and comparable physiological strain (i.e., higher HR) than with similar training in normoxia. Of particular relevance in elderly, the significant reduction in mean power output by more than 25% during such hypoxic endurance training offers a gentler rehabilitation process for specific orthopedic limitations.

While endurance training could also be performed using an arm ergometer or similar ergometers depending on the patient's injury, it is noteworthy that the main goals of most geriatric patients are to get back on their feet and avoid future falls (Buchholz and Kohlmann, 2013). Combining gait training and endurance training during a stay in a rehabilitation center may improve therapy even while taking into consideration the reduced tolerance of physical training experienced by most geriatric patients. In view of this lowered tolerance for physical training, hypoxic training—which appears to be well tolerated, without provoking any complications—provides a new opportunity to enhance cardiac capacity while focusing on classical therapeutic goals (e.g., improvement in gait performance and postural stabilization) in geriatrics.

With the exception of peak power output, both groups reacted with the same non-significant physiological changes: a slightly increased VO_2-peak, a decrease in peak O_2/-HR and no change in EF. Evidence from related studies suggest that hypoxic exposure normalizes hypertension, improves myocardial angiogenesis or ventricular remodeling and decreases the risk for ischemic heart disease (Millet et al., 2016). Hypoxia also seems to positively affect hematological parameters as well as cognitive functioning (Schega et al., 2016). The outcomes of the present study are in line with these findings. Nevertheless, the lack of significant changes in cardiac parameters suggest that the training stimulus

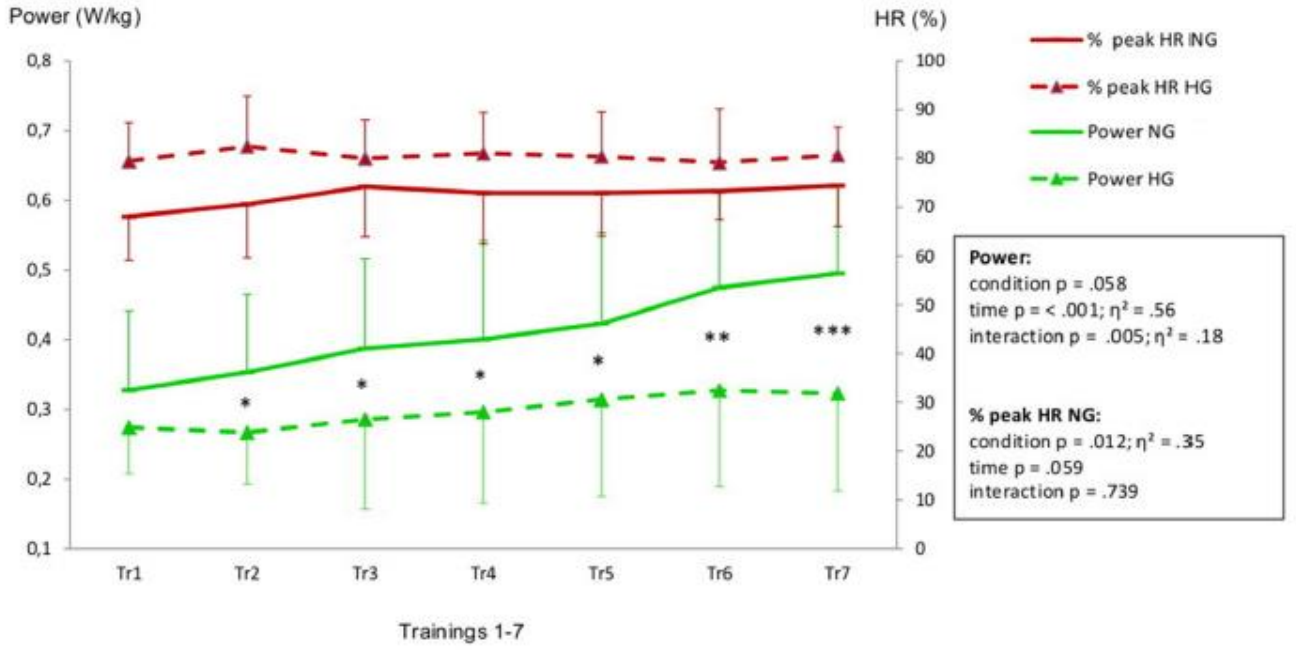


FIGURE 1 | Heart rate (expressed in % of HR peak) and power values (W/kg) recorded during the training intervention (Tr1-Tr7). Legend: $^{*}p \leq 0.05$, $^{**}p \leq 0.025$, $^{***}p \leq 0.001$ levels of significant differences between HG and NG in Tr1 to Tr7. Effect size is displayed as η^2.

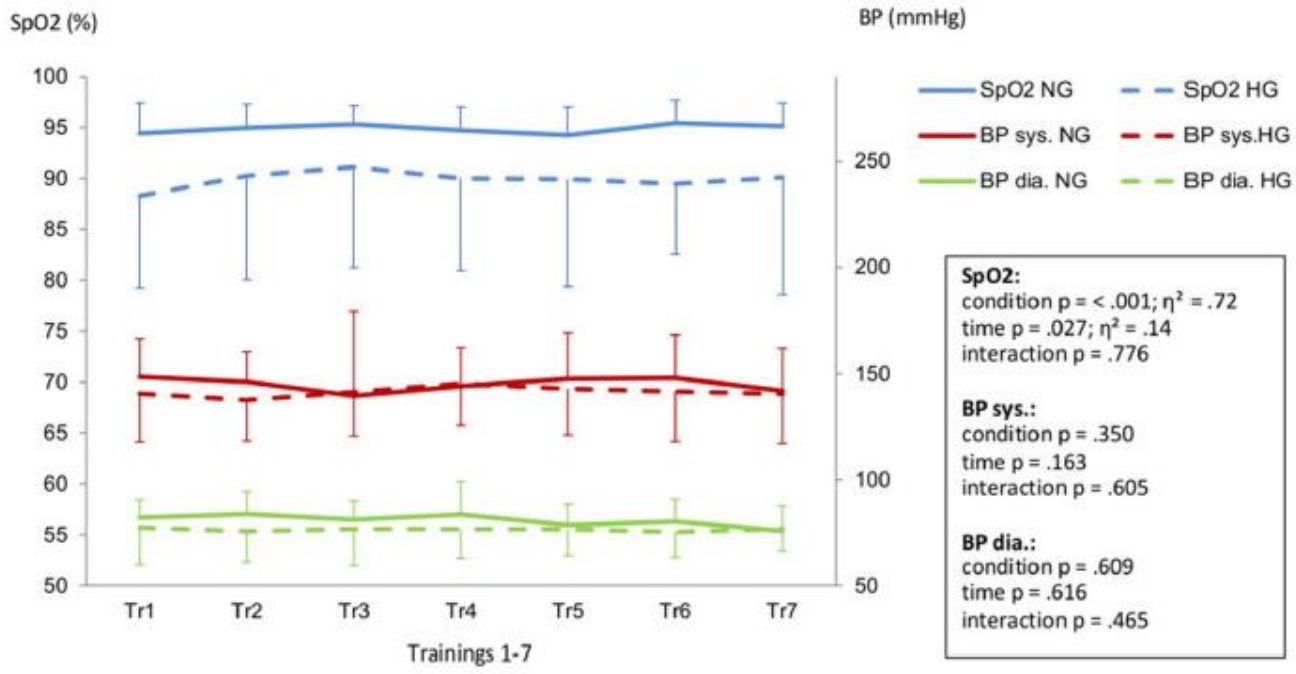


FIGURE 2 | Peripheral oxygen saturation (SpO_2) and systolic (BP sys.) aswell as diastolic blood pressure (BP dia.) in Hypoxic Group (HG) and Normoxic Group (NG) during the training intervention (Tr1-Tr7). Legend: Effect size is displayed as η^2.

for our population was not challenging enough to provoke measurable cardiac adaptations to the training. However, the endurance training reflected the routines commonly employed in geriatric rehabilitation programs. Therefore, it would not have been practical to prolong the training stimulus in our patients (Meusel, 2000). Rather than improving training stimulus (e.g.,

volume and/or intensity), we suggest that, depending of patients' health and fitness status, implementing longer "time in hypoxia" without training may be beneficial to provoke bigger changes in cardiac and pulmonary parameters. Alternatively, more frequent interventions, with sufficient regeneration time, during a single day may prove to be more effective (Bernardi et al., 2001; Vogt et al., 2002; Foster et al., 2005). More investigations are warranted using this specific population.

An increase in maximum power output was measured in both groups after the intervention. This finding is likely due in most part to the rehabilitation routine each subject underwent during their stay. The rehabilitation intervention included physical strength training, gait training, balance training and other common physical therapy methods. The relatively lower HR observed in HG during the post-test may be an early signal of an emerging higher stroke volume and improved O_2 utilization that has been demonstrated in other studies (Levine and Stray-Gundersen, 1997; Vissers et al., 2015; Lundby and Calbet, 2016; Moon et al., 2016). These positive outcomes may be attributed to the combined effects of the endurance training with an impactful target HR as well as the O_2 deprivation.

There are limitations to our study. The study was conducted in geriatric patients with a variety of primary diagnoses, multiple co-morbid conditions and complex medication regimens. These circumstances naturally influenced the outcomes of the study. Nevertheless, geriatric patients typically have complex medical conditions which cannot be standardized. The complex medical histories of our patient population is a strength of this study in that the results are more likely to pertain to usual clientele served by geriatric rehabilitation programs. As stated by the World Health Organization, several diseases that our health system aims to cure in young people can be seen as a disability when it comes to old age (WHO, 2001). In order to develop an applicable hypoxic endurance training program for geriatric patients, it is important not to exclude particular medical conditions or medications. Second, the rather short hypoxic protocol was not challenging enough to provoke significant cardiopulmonary adaptations in either randomized group. Third, a larger study population may have allowed for subset analyses to identify patients with particular characteristics that would be more responsive to this intervention. Fourth, the NG did not reach the estimated 80% VO_2 peak of training-intensity. The mean difference between NG and HG was 5.9 ± 4.2 bpm, which in our opinion does not influence the study outcome substantially. Nevertheless, the inability of the NG to reach the target training-HR validates the need for new methods to enhance training intensity.

In conclusion, the main outcome of this study demonstrated that endurance training in normobaric hypoxia demands less physical effort from the geriatric patient for the same degree of target HR response than similar training in normoxia. Our findings suggest that hypoxic endurance training is very likely to be more effective than normoxic training. Hypoxia has already been proposed to positively impact several common diseases in geriatric patients, such as hypertension, obesity, cognitive impairment and cardiopulmonary diseases (Burtscher, 2004; Millet et al., 2016; Schega et al., 2016). The great challenge for future investigations is to find a suitable and achievable training-protocol which provokes the expected beneficial adaptations for such population. Such a protocol should enhance geriatric rehabilitation while also taking into account the physical conditions that often limit the geriatric patients.

AUTHOR CONTRIBUTIONS

SP: designing research study, acquiring data, analyzing data, conducting experiment, writing manuscript. MB, MF and HG: writing manuscript, analyzing data. LR and AE: reviewing data, writing manuscript. NN: designing research study, conducting experiment, providing material, writing manuscript.

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Curriculum Vitae

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