University of Applied Sciences and Arts of Southern Switzerland
Department of Business Economics, Health and Social Care

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Originally in German, translated into English

The Psychophysiological Effect of Terrestrial Altitude and Normobaric Hypoxia - a randomized clinical trial

Clinical Trial Protocol

Short title	Effect of Terrestrial Altitude and Normobaric Hypoxia
Study Type:	Other clinical trial with a certified Category A device
Study Categorisation:	Another clinical trial Cat. pursuant to Art. 61 of the Ordinance
Study Registration:	-
Study Identifier:	-
Sponsor:	**University of Applied Sciences** **Department of Business Economics, Health and Social Care** **Physiotherapy Graubünden** Weststrasse 8 7302 Landquart +41 81 300 01 70
Investigator:	***Contact / Director of Studies*** **Dr. Clijsen Ron**, PhD University of Applied Sciences and Arts Southern Switzerland Physiotherapy Graubünden Weststrasse 8, 7302 Landquart +41 81 300 01 75 ron.clijsen@supsi.ch
Investigational Product:	Cloud 9
Protocol Version and Date:	Study protocol – Version 02 – 1.5.2019

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CONFIDENTIALITY

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SIGNATURE OF THE PERSON RESPONSIBLE FOR THE STUDY

Study number	-
Study Title	The Psychophysiological Effect of Terrestrial Altitude and Normobaric Hypoxia - A Randomized Clinical Trial

Sponsor:

I have reviewed this study protocol, version 02 of 01.05.2019, and confirm that the study complies with the World Medical Association Declaration of Helsinki, ICH-GCP Guidelines, the ISO 14155 standard (where applicable), as well as the locally applicable Swiss Ordinance on Clinical Trials KlinV.

University of Applied Sciences Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden

Sponsor (Thim van der Laan AG)

Thim van der Laan jr.

Landquart, 01.05.2019

Place/Date Signature

Investigator:

I have reviewed this study protocol, version 02 of 01.05.2019, and confirm that the study complies with the World Medical Association Declaration of Helsinki, ICH-GCP Guidelines, the ISO 14155 standard (where applicable), as well as the locally applicable Swiss Ordinance on Clinical Trials KlinV.

University of Applied Sciences Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden

Investigator

Dr. Ron Clijsen

Landquart, 01.05.2019

Place/Date Signature

SUPSI

TABLE OF CONTENTS

SUPSI

SUPSI

SUPSI

SUPSI

Study Synopsis

Sponsor / Sponsor-Investigator	**Sponsor** **Thim van der Laan AG** **Thim van der Laan jr.** Weststrasse 8 / CH-7302 Landquart **Investigator** **University of Applied Sciences** **Department of Business Economics, Health and Social Care** Physiotherapy Graubünden Attn: Dr. Ron Clijsen Weststrasse 8 CH-7302 Landquart
Study Title:	The Psychophysiological Effect of Terrestrial Altitude and Normobaric Hypoxia - A Randomized Clinical Trial
Short Title / Study ID:	The Effect of Terrestrial Altitude and Normobaric Hypoxia
Protocol Version and Date:	Version 02 from 01.05.2019
Trial registration:	Cantonal Ethics Committee Zurich
Study category and Rationale	Other clinical trials of category A according to the ClinV (Art. 20)
Clinical Phase:	-
Background and Rationale:	Research has consistently shown that exposure to extreme environments (i.e., cold, at altitude) can impair cognitive function (Taylor, Watkins, Marshall, Dascombe, & Foster, 2015). For logistical reasons and to control the study set-up in which the test is carried out, studies that want to investigate the effect of "height" are usually carried out in laboratories. By testing under such controlled conditions, researchers can remove any co-founding factors and isolate a specific stressor, allowing them to better understand the mechanisms by which impairment can occur. However, when people are exposed to such environments as "height" in the "real world", they often experience a number of other additional stressors at the same time, which could produce different results compared to laboratory studies. Surprisingly, however, little attention has been paid to the study of these additional stressors in combination (Tipton, 2012). The best example of multiple stressors that occur In combination Is when climbing to high altitudes. Although the percentage of oxygen remains constant at different altitudes (20.93%), the air pressure decreases exponentially as the altitude increases. As a result, the oxygen partial pressure in the arterial blood and tissues is reduced (hypoxia), which leads to a deterioration in both physical and cognitive performance.

SUPSI

Objective(s):	The aim of this study is to compare the psychophysiological effects of terrestrial altitude with a normobaric, hypoxic situation.
Outcome(s):	Primary results: **Physiological measurements** - Perfusion of the skin microcirculation (flux) - Blood oxygen saturation (%) - Oxygen saturation of the muscles (%) - Oxygen saturation of the brain (%) - Heart rate (b/min) - Blood pressure (mm/Hg) - Skin temperature (°C) - Lactate (mmol/l) - Creatine kinase (U/L) - Balance test (° & m/sec) - Pain sensation (N) **Psychological measurements** - Sleep Disorder Questionnaire - Lake Louis Altitude Sickness Questionnaire - Dyspnea questionnaire - State of mind questionnaire - Stanford Sleepiness Questionnaire - Automated, cognitive test battery Secondary results: - Thermal comfort and heat perception
Study design:	Randomized, clinical, crossover study

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Inclusion / Exclusion criteria:	Inclusion criteria: - Healthy, adult aged 18 to 50 years - No cardiovascular diseases and/or interventions - no surgical interventions on the cardiovascular system. - No current injuries and/or pain conditions - Regular and sufficient sleep - No terrestrial altitude of 1000 m exceeded in the last month (including flights) - Not exposed to any form of hypoxia in the last month **Exclusion criteria:** - Age over 50 years - Current injuries of any kind and/or pain conditions - Acute and/or chronic pain conditions - Known general diseases (e.g. diabetes mellitus) - Fear of hypoxia - Fear of heights or sensitivity to terrestrial altitude - Regular intake of medication (including self-purchased medication), with the exception of anticonception drugs - Cardiovascular disease or abnormalities - Abnormalities of blood analysis or ECG - Psychological illnesses - Pregnancy / breastfeeding
Preparation	Subject recruitment The subject information and declaration of consent are submitted. Questions may be asked. If the subject agrees with the information, he or she will be summoned to the first day of contact. This includes the explanations on site, the signature of the declaration of consent and the completion of the health questionnaire. The pregnancy test must be negative (women only). If all tests are passed, an appointment is made for the intervention. Test Subject Preparation Measurement Day The test subject lies down on a couch in his underwear. This is followed by the 20-minute room acclimatization phase in the same storage. The room temperature is kept as constant and neutral as possible (deviation of +/-2°C).

SUPSI

Measurements and procedures:	During the 20-minute acclimatization phase, the application areas are drawn (skin-friendly pen) and the appliances are attached. If necessary, the hypoxia mask is then put on, the treatment is started and the baseline measurements are carried out. After the baseline measurement, the 5-minute step-up task is performed. After this task, the physiological parameters are measured again. These measurements were followed by a 5-minute cold water bath of the hand. Afterwards, the physiological measurements are carried out up to 30 minutes after the cold water bath (5 min interval) and the questionnaires are filled out afterwards. In the terrestrial altitude situation, the test subject spends the night in the Hohsaas mountain restaurant (**https://www.hohsaas-bergrestaurant.ch**, canton of Valais) and the measurements are repeated the next day. Perfusion of skin microcirculation The perfusion of the skin microcirculation is visualized using the Laser Speckle Contrast Imager (moorFLPI 2, moor instruments, www.moor.co.uk). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval). Oxygen saturation of the muscles and brain The oxygen saturation of the muscles and brain is measured non-invasively with a deep tissue oxygenation monitor (moorVMS-NIRS, moor instruments, www.moor.co.uk). For this purpose, adhesive electrodes are attached over the muscle and forehead. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval). Oxygen saturation of the blood The oxygen saturation of the blood is measured with a portable pulse oximeter with finger clip probe (Nonin 7500, Nonin medical B.V., Plymouth, USA). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval). Blood pressure and heart rate The heart rate is measured with a heart rate belt and an additional 2-point ECG (Actiheart, Camntech Ltd., Cambridge, UK). Blood pressure is determined by means of an electronically automated upper arm blood pressure meter (Boso-Medicus uno). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval). Skin temperature Skin temperature is measured via the iButton system (www.ibuttonlink.com). The self-adhesive sensors transmit the information about the skin temperature wirelessly to a computer. Furthermore, the skin temperature is recorded by means of a thermal imaging camera (FLIR). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

SUPSI

Measurements and procedures:	Lactate and creatine kinase The lactate and creatine kinase measurement are carried out by capillary blood measurement (Accutrend, Roche Diagnostic, Rotkreuz, Switzerland & Reflotron, Roche Diagnostic, Rotkreuz, Switzerland). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval). Balance measurement The fluctuations of the hull are recorded and evaluated with the Sway Star™ System (www.b2i.info). The Sway Star™ is a measuring instrument that contains gyroscopes. It is attached to a belt that is placed around the patient's waist. The data is evaluated with the associated Sway Star ™software and transferred to the data sheet. This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand. Pain sensation The pain threshold is measured using a pain pressure algometer (NOD, www.to-nod.com). This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand. Psychological measurements The psychological measurements (sleep disorder, altitude sickness, dyspnea, state of mind, drowsiness) are evaluated on the basis of written questionnaires. The cognitive test battery consists of 8 tasks (ANAM, US Department of Defence, Vista Life Sciences, USA), which are carried out on a laptop computer. These measurements are carried out after the baseline measurement and after the cold water bath immersion of the hand. Thermal comfort and temperature perception These parameters are measured using a scale. This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand . **Further processing of the data** Windows uses Excel for data pooling and the graphical representation of the end data® .
Study Product / Intervention:	Cloud 9
Control Intervention (if applicable):	As a control, the subjects are observed under normobaric and normoxic conditions.
Number of Participants with Rationale:	We limit the number of subjects to n = 24 study participants due to the available financial resources and due to the power analysis carried out.

Study Duration:	June 2019-December 2020

SUPSI

Study Schedule:	June 2019: planned start of measurements December 2020: planned end of measurements
Investigator(s):	Examiner - Dr. Ron Clijsen1,2,3 - Dr. Erich Hohenauer1,2,3 - Rahel Stoop, MSc1,2 - Carlina Deflorin, MSc.[1] 1.) University of Applied Sciences and Arts Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden, Weststrasse 8, 7302 Landquart 2.) THIM the International University of Physiotherapy, Weststrasse 8, 7302 Landquart 3.) Vrije Universiteit Brussel, Department of Movement and Sport Sciences, Pleinlaan 8, 1050 Brussels ***Contact / Director of Studies*** **Dr. Clijsen Ron**, PhD University of Applied Sciences and Arts Southern Switzerland Department of Business Economics, Health and Social Care Physiotherapy Graubünden Weststrasse 8, 7302 Landquart +41 81 300 01 75 ron.clijsen@supsi.ch
Study Centre(s):	Single Centre Study: University of Applied Sciences and Arts Southern Switzerland Physiotherapy Graubünden Weststrasse 8 7302 Landquart

SUPSI

Statistical Considerations:	Psychophysiological changes between terrestrial altitude and normobaric hypoxia - a randomized clinical trial. Repeated measures analysis of variance (MANOVA) 2 Factors (Physiological Parameters) - Situation (terrestrial altitude vs. simulated altitude) - Time (baseline, after step-up task, 0, 5, 10, 15, 20, 25, 30 min post-cold water immersion of the hand) 2 factors (psychological parameters, balance, thermal comfort, temperature perception) - Situation (terrestrial altitude vs. simulated altitude) - Time (baseline, post-cold water immersion of the hand) - The significance level is set at $P < 0.05$, and the statistical data analysis is carried out with SPSS V. 26.
GCP Statement:	This study will be conducted in compliance with the protocol presented here, the current version of the Declaration of Helsinki, the ICH-GCP, ISO EN 14155 (where applicable), and the Swiss Human Research Ordinance HFV.

SUPSI

Overview of the study

It has already been shown in previous studies that various environmental conditions can change both the physiology and psychology of humans (Taylor et al., 2015). For logistical reasons and due to other scientific considerations such as the comparability of results, investigations such as the investigation of "height" are carried out under laboratory conditions. By testing under such controlled conditions, researchers can remove any co-founding factors and isolate the cause of stress, allowing them to better understand the mechanisms by which impairment can occur. However, when exposed to such "real world" environments, they often experience a number of other additional stressors at the same time, which can also affect their performance. Surprisingly, however, little attention has been paid to the study of these additional stressors in combination (Tipton, 2012).

The best example of multiple stressors that occur in combination is when climbing to high altitudes. Although the percentage of oxygen remains constant at different altitudes (20.93%), the air pressure decreases exponentially as the altitude increases. As a result, the oxygen partial pressure in the arterial blood and tissues is reduced (hypoxia), which leads to a deterioration in both physical and cognitive performance. However, in addition to the stressful effects of hypoxia, there can also be other extreme stressors, such as temperature fluctuations, which are known to significantly affect cognitive function (McMorris, Hale, Barwood, Costello, & Corbett, 2017).

The reduced oxygen level in the blood during exposure at high altitude leads to a disturbance of sleep. This happens through changes in breathing during sleep. Consequently, sleep at altitude is characterized by a reduction in total sleep, sleep efficiency, and sleep quality (de Aquino Lemos et al., 2012).

While both hypoxia and sleep deprivation are reported to have negative effects on cognitive performance at rest, this may not be true when a person is exercising or moving. A light activity (such as a step-up task) may be enough to change the psychophysiological responses. It is known that cognitive performance improves with normoxia with light moderate exercise (Chang, Labban, Gapin, & Etnier, 2012). In addition, there is growing evidence that exercise can even cancel out the negative effects of hypoxia on cognitive performance (Ando et al., 2013; Komiyama et al., 2017). Another point that gives rise to further investigations in the field of hypoxia is the sensation of pain. It has already been shown in previous studies that the sensation of pain differs between normoxic and hypoxic situations (Noel-Jorand, Bragard, & Plaghki, 1996). To the knowledge of the authors, however, there are only limited studies that compare these parameters in a laboratory condition with the reactions in the real world. Many people suffer from lung dysfunction (such as COPD) and are therefore at least partially under hypoxic conditions. With this study, we can contribute to understanding the psychophysiological reactions under hypoxia.

Aim of the study

The aim of this study is to evaluate and compare the psychophysiological changes during terrestrial and simulated altitude. These changes will be investigated after a 5-minute step-up task and after a 5-minute cold water immersion of the hand in a) a normobaric, normoxic situation, b) normobaric, hypoxic situation and c) hypoxic, hypobaric situation.

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Abbreviations

CEC	Competent Ethics Committee
GCP	Good Clinical Practice
Ho	Zero hypothesis
H1	Alternative hypothesis
KlinV	Ordinance on Clinical Trials in Human Research
Masl.	meters above sea level
hPa	Hectopascals

SUPSI

Study Schedule

The completion of the measurement series is planned for October 2019, and the completion of the entire project for December 2020.

Table 1: Schedule

	January-February	March	April-June	July-October	November-December
2019			Subject information, screening, planning, data collection	Subject information, screening, planning, data collection	Statistics
2020	Writing the article	Writing the Article	Writing the Article	Publishing the article	Publishing the article

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1 STUDIEN-ADMINISTRATION

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1.3 Examiner

Investigator

Dr. Ron Clijsen, PhD1,2,3 *(GCP Module I – III & GCP Basic Course, Advanced Course Sponsor-Investigator)*

Selection of subjects, obtaining consent to study participation, study administration, implementation of the Measurements – collecting data, analyzing data, interpreting data, writing a report

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SUPSI

Other examiners

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Selection of subjects, obtaining consent to study participation, study administration, implementation of the Measurements – collecting data, analyzing data, interpreting data, writing a report

Rahel Stoop, MSc1 *(GCP Module I-III & GCP Basic Course)*
Data analysis, *carrying out measurements – collecting data* , interpreting results

Carlina Deflorin1 *(GCP Module I-III & GCP Basic Course)*
Data analysis, *execution of measurements – collection of data*, interpretation of results

1 University of Applied Sciences and Arts Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden, Weststrasse 8, 7302 Landquart
2 THIM the International University of Physiotherapy, Weststrasse 8, 7302 Landquart
3 Vrije Universiteit Brussel, Department of Movement and Sport Sciences, Pleinlaan 8, 1050 Brussels

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1.5 Laboratory Manager (Investigator)

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1.6 Monitoring of the study

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1.7 Privacy

All data obtained from study participants will be coded and not passed on to other people. Personal data and personal details are stored in paper form in a locked filing cabinet. The head of the research laboratory and at the same time the head of the study has access here, and the administration of the documents also falls within his area of responsibility.

All digital data is encrypted and encoded. No conclusions can be drawn about individuals. The digital data is stored on internal computers, archived and not released to outsiders.

Employees involved in data processing have no insight into the personal data and the coding of it.

1.8 Other committees or institutes involved

The study is being conducted in the research laboratory at the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden, Weststrasse 8, 7302 Landquart, Switzerland.

The test products and measuring equipment are all located in this room and therefore all measurements can be carried out at the same location. The room offers enough space.

At present, no further studies with this arrangement are taking place in this experimental laboratory. During this period, no studies will take place in our laboratory.

No other institutes and committees are involved in this study or in the approval or monitoring of the study.

SUPSI

2 ETHNIC & REGULATORY ASPECTS

2.1 Study Registration

The implementation of the present study is the responsibility of the Cantonal Ethics Committee Zurich. An application for admission is submitted. Any further conditions of the responsible ethics committee must be implemented in the study protocol.

When the study protocol is submitted to the Cantonal Ethics Committee in Zurich, the study is also registered with the Swiss Coordination Office for Research on Human Subjects. In addition, the study will be registered in a WHO-recognized primary registry (clinicaltrials.gov).

2.2 Categorization of the study

The study is categorized as another clinical trial of risk category A (ClinO, Art. 20). The subjects are taken to terrestrial and simulated altitudes. Neither tissue samples nor other invasive methods are performed. The simulated height is carried out with a CE certified device according to the instructions for use.

2.3 Competent Ethics Committee (CEC)

Human research in the Canton of Graubünden falls under the remit of the Cantonal Ethics Commission Zurich. Changes to the study protocol are not permitted without the prior consent of the CEC, except for the immediate elimination of obvious hazards to the participants. According to chap. 2.10 to the CEC.

An early termination or interruption of the study must be reported to the CEC within 15 days, and the regular end within 90 days. The final report must be submitted within one year of the end of the programme. Corrections are to be reported in accordance with Chapter 2.10.

2.4 Competent Authorities (CA)

The present study falls under the remit of the Cantonal Ethics Committee Zurich. Obligations and deadlines can be found in the previous point.

2.5 Ethical Leadership of the Study

The study will be conducted in accordance with this protocol and the current version of the Helsinki Declaration, the ICH-GCP, the European Medical Device Directive 93/42/EEC and the ISO standard 14155 and ISO 14971 (where applicable), as well as the Swiss Human Research Ordinance and thus Swiss law.

The CEC receives an annual report and is informed about the course of studies.

2.6 Conflict

There is no financial conflict of interest on the part of the sponsor/investigator, nor is there a corresponding relationship of dependency.

2.7 Patient information and informed consent

The examiners will explain to each participant individually the nature of the study, its content, intent and objective. This includes the protocol flow, approximate time duration, possible risks and benefits. The participant is informed that participation is voluntary and can be withdrawn from the study at any time, without personal consequences of any kind. The participant will be informed about data protection, the handling of personal data and their access.

Each participant receives written subject information and the declaration of consent with the detailed study description and all necessary information to be able to decide whether to participate in the study. The participant will also be given sufficient time to read this written information and to ask questions to the responsible examiners.

The subject information and the informed consent form are submitted to the CEC, where they must be reviewed and approved.

The signed declaration of consent must be submitted before the start of the study process. The participant should read them before signing and check their contents. The responsible examiner then also signs the declaration of consent. Finally, the participant receives a copy of the declaration of consent. The signed declaration of consent is kept in the original as a study document in a locked filing cabinet.

2.8 Confidentiality & Privacy

The examiners ensure that the privacy of the participants is maintained. In particular, data protection and confidentiality are guaranteed, and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal details, are kept in the original as a study document in a locked filing cabinet.

The digital data is encrypted and treated confidentially, and access to the personal data is denied to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers.

Direct access to the personal data is allowed only to the head of the research laboratory (study leader), as well as authorized persons of the CEC.

2.9 Early termination of the study

The sponsor or the principal investigator or physician present may discontinue the study early if/if:

- ethical concerns
- insufficient number of subjects
- the safety of the participants cannot be guaranteed
- Findings from clinical practice make it pointless to continue the study
- early evidence or harm of the experimental intervention has been proven
- the health of the subjects is at risk

2.10 Adjustments to the protocol

Adjustments and changes to the current study are only permissible after review by the CEC.

Short-term changes to the protocol prior to an audit by the CEC may be made to ensure the rights and safety of participants. However, such adjustments must be documented and reported to the CEC as

soon as possible.

Significant changes are only permissible after a review of the CEC. Any other changes must be notified to the CEC as soon as possible and listed in the annual report.

SUPSI

3 BACKGROUND AND RATIONALE

3.1 Background and justification

Research has consistently shown that exposure to extreme environments (i.e., hot, cold, altitude) can impair cognitive function (Taylor et al., 2015). For logistical reasons and to better control the (climatic) conditions in which the subjects are tested, most of these tests are carried out in laboratories. By testing under such controlled conditions, researchers can remove any co-founding factors and isolate the cause of stress, allowing them to better understand the mechanisms by which impairment can occur. However, when exposed to such "real world" environments, they often experience a number of other additional stressors at the same time, which can also affect their performance. Surprisingly, however, little attention has been paid to the study of these additional stressors in combination (Tipton, 2012).

The best example of multiple stressors that occur in combination is when climbing to high altitudes. Although the percentage of oxygen remains constant at different altitudes (20.93%), the air pressure decreases exponentially as the altitude increases. As a result, the oxygen partial pressure in the arterial blood and tissues is reduced (hypoxia), which leads to a deterioration in both physical and cognitive performance. However, in addition to the stressful effects of hypoxia, other stressors, such as temperature and fatigue, can also be added, which are known to significantly affect human functions (McMorris et al., 2017).
The reduced oxygen level in the blood during exposure at high altitude causes breathing disorders during sleep. Consequently, sleep at altitude is characterized by a reduction in total sleep, sleep efficiency, and sleep quality (de Aquino Lemos et al., 2012).

While both hypoxia and sleep deprivation are reported to have negative effects on cognitive performance at rest, this may not be true when a person is exercising or moving. It is known that cognitive performance improves with normoxia with light moderate exercise (Chang et al., 2012). In addition, there is growing evidence that exercise can even cancel out the negative effects of hypoxia on cognitive performance (Ando et al., 2013; Komiyama et al., 2017). Another point that gives rise to further research in the field of hypoxia is the sensation of pain. It has already been shown in previous studies that the sensation of pain differs between normoxic and hypoxic situations (Noel-Jorand et al., 1996). To the knowledge of the authors, however, there are only limited studies that compare these parameters in a laboratory condition with the reactions in the real world. In addition, various patient groups also suffer from lung dysfunction (such as COPD) and are therefore at least partially under hypoxic conditions. With this study, we can contribute to understanding the psychophysiological reactions under hypoxia.

Aim of the study

The aim of this study is to evaluate and compare the psychophysiological changes during terrestrial and simulated altitude. These changes will be investigated after a 5-minute step-up task and after a 5-minute cold water immersion of the hand in a) a normobaric, normoxic situation, b) normobaric, hypoxic situation and c) hypoxic, hypobaric situation.

3.2 Medical product and indication

Simulated altitude training is quickly becoming the most promising development in the world in terms of athletic performance and peak fitness.
With the Cloud 9, a simulated altitude of 2700 m and 3530 m above sea level can be achieved. This corresponds to an oxygen partial pressure of 15.0% and 13.5% respectively. The Cloud 9 altitude training device is designed for all levels of sports (including athletes) who want to improve their performance. The Cloud 9 is a solid, certified product that complies with the European Directives on

Electromagnetic Compatibility, Machinery Directive, Air Pressure Equipment and Low Voltage Equipment (89/336/EEC, 91/368/CEE, 93/68/CEE, 97/23/EC, EN61010-1).

Cloud 9 mapping: https://chasingtargets.eu/altitude-tent-rental-service/

3.3 Preclinical evidence

Studies under hypoxic conditions have already been carried out in the medical field with a wide variety of pathologies, such as obesity under stress(Girard, Malatesta, & Millet, 2017; Park, Jung, Kim, & Lim, 2019) but also with seniors (Pramsohler et al., 2017). Hypoxic conditions can lead to psychological changes in addition to physiological changes (Taylor et al., 2015). Chronic stays at altitude can further lead to a physiological change (Smith et al., 2014)
It is known that cognitive and physical performance improves with normoxia with light moderate exercise (Chang et al., 2012). In addition, there is growing evidence that exercise can even cancel out the negative effects of hypoxia on cognitive performance (Ando et al., 2013; Komiyama et al., 2017).

SUPSI

3.4 Current clinical evidence

According to the authors' knowledge, there are currently hardly any clinical studies that contrast the psychophysiological effects of terrestrial altitude with simulated altitude.

3.5 Medical product: method of application in the study

During the normobaric, hypoxic situation, an altitude of 3530 m above sea level is simulated, which corresponds to an oxygen partial pressure of 13.5%. This situation is realized by a mask system, with the help of Cloud 9.

https://trainingwithaltitude.co.uk/product/altitude-mask/

3.6 Peers

The intervention group is also the control group, as a crossover design is used.

Randomization

Randomization takes place according to the situation (normobar & normoxic vs. normobar & hypoxic). The situation you find yourself in first is decided by drawing lots.

3.7 Risk / Benefits

Possible risks in the situation of terrestrial and simulated altitude are the appearance of headaches, impaired consciousness, disorientation and nausea. In addition, a doctor is present during the measurements. Subjects who may be at risk are recorded by the screening procedure and the health questionnaire and are not included in the study. However, the risk is to be classified as minor, as studies are already being conducted with obese patients and seniors under hypoxic conditions, which has not led to any complications. Participants do not derive direct benefits from participating in the study. More information on securing the test subjects can be found in chap. 8.1.1.Justification

SUPSI

for the choice of population

This series of studies is being conducted with healthy adults to minimize the health risk. The psychophysiological reactions of the body to terrestrial and simulated altitude training are assumed to be probable in this test subject population.

The test subjects are comprehensively informed about the course of the study and possible risks before they are accepted to participate in the study. You will also receive the information in written form and have the opportunity to ask questions if anything is unclear. The declaration of consent explains to them what their rights and obligations are when participating. In addition, they are informed that they may withdraw from participation at any time without giving reasons, without incurring any disadvantages as a result.

SUPSI

4 STUDY OBJECTIVES

4.1 General objectives

The aim of this study is to evaluate and compare the psychophysiological changes during terrestrial and simulated altitude. These changes will be investigated after a 5-minute step-up task and after a 5-minute cold water immersion of the hand in a) a normobaric, normoxic situation, b) normobaric, hypoxic situation and c) hypoxic, hypobaric situation.

4.2 Primary objectives

The primary goal is to compare and evaluate the physiological effects of terrestrial altitude and simulated altitude. For this purpose, the following parameters are measured:

Objective parameters:

- Perfusion of the skin microcirculation (flux)
- Blood oxygen saturation (%)
- Oxygen saturation of the muscles (%)
- Oxygen saturation of the brain (%)
- Heart rate (b/min)
- Blood pressure (mm/Hg)
- Skin temperature (°C)
- Lactate (mmol/l)
- Creatine kinase (U/L)
- Balance test (° & m/sec)

Subjective parameters:

- Pain sensation (N)

The primary goal is to compare and evaluate the psychological effects of terrestrial altitude and simulated altitude. For this purpose, the following parameters are measured:

Subjective parameters:

- Sleep Disorder Questionnaire
- Lake Louis Altitude Sickness Questionnaire
- Dyspnea questionnaire
- State of mind questionnaire
- Stanford Sleepiness Questionnaire
- Automated, cognitive test battery

4.3 Secondary Objectives

The secondary goal is to compare and evaluate thermal comfort and temperature perception according to terrestrial altitude and simulated altitude. For this purpose, the following parameters are measured:

-

Subjective parameters:

- Thermal comfort
- Temperature sensation

4.4 Other safety aspects (long-term)

No more risks than those discussed so far are to be expected in this study.

5 STUDENT OUTCOMES

5.1 Primary outcomes

Perfusion of skin microcirculation

The perfusion of the skin microcirculation is visualized using the Laser Speckle Contrast Imager (moorFLPI 2, moor instruments, www.moor.co.uk). The "moorFLPI-2 Full-Field Laser Perfusion Imager" measures blood flow measured in flow rates (arbitrary units) of the skin's microcirculation. The laser is intended for clinical and physiological research. The fabric is illuminated with a divergent infrared laser beam. The laser measures down to a depth of 1mm, so it mainly detects the superficial blood flow, speed and concentration of red blood cells. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Oxygen saturation of the muscles and brain

The oxygen saturation of the muscles and brain is measured non-invasively with a deep tissue oxygenation monitor (moorVMS-NIRS, moor instruments, www.moor.co.uk). For this purpose, adhesive electrodes are attached over the muscle and forehead. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Figure: Measurement of oxygen saturation of the brain and muscles

Oxygen saturation of the blood

The oxygen saturation of the blood is measured with a portable pulse oximeter with finger clip probe

(Nonin 7500, Nonin medical B.V., Plymouth, USA). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

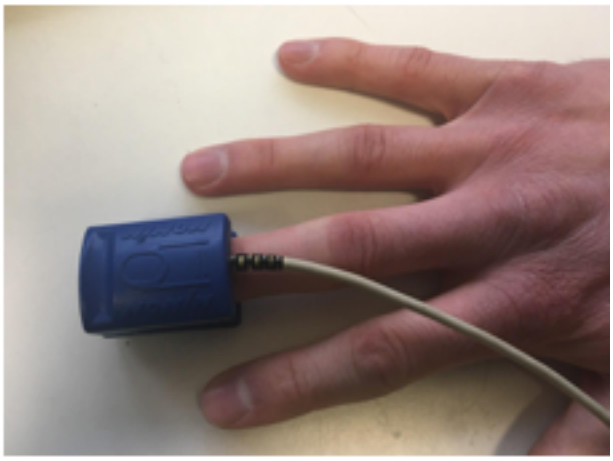

Figure: Measurement of the oxygen content of the blood

Blood pressure and heart rate

The heart rate is measured with a heart rate belt and an additional 2-point ECG (Actiheart, Camntech Ltd., Cambridge, UK). Blood pressure is measured by means of an electronically automated upper arm blood pressure monitor (Boso-Medicus uno). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Skin temperature

Skin temperature is measured via the iButton system (www.ibuttonlink.com). The self-adhesive sensors transmit the information about the skin temperature wirelessly to a computer. Furthermore, the skin temperature is recorded by means of a thermal imaging camera (FLIR). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Lactate and creatine kinase

The lactate and creatine kinase measurement are carried out by capillary blood measurement (Accutrend, Roche Diagnostic, Rotkreuz, Switzerland & Reflotron, Roche Diagnostic, Rotkreuz, Switzerland). The affected area is disinfected and a superficial wound is pierced to take capillary blood. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Balance measurement

The fluctuations of the hull are recorded and evaluated with the Sway Star™ System (www.b2i.info). The Sway Star™ is a measuring instrument that contains gyroscopes. It is attached to a belt that is placed around the patient's waist. The data is evaluated with the associated Sway Star ™software and transferred to the data sheet. This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand.

Figure: Measuring balance with the Sway StarTM

Pain sensation

The pain threshold is measured using a pain pressure algometer (NOD, www.to-nod.com). As soon as the patient reports pain, this measurement is stopped. This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand.

Psychological measurements

The psychological measurements (sleep disorder, altitude sickness, dyspnea, state of mind, drowsiness) are evaluated on the basis of written questionnaires.

The cognitive test battery consists of 8 tasks (ANAM, US Department of Defence, Vista Life Sciences, USA), which are carried out on a laptop computer.

These measurements are carried out after the baseline measurement and after the cold water bath immersion of the hand.

5.2 Secondary outcomes

Thermal comfort and temperature perception

This parameter is measured using a scale. The test subjects indicate their subjective temperature perception on a 9-point scale from -4 (very cold) to +4 (very hot). They then rate the thermal comfort between 0 (pleasant) and 4 (extremely unpleasant) on a 5-point scale. These measurements are carried out after the baseline measurement and after the cold water bath immersion of the hand.

5.3 Security considerations

No further results are recorded that would serve safety.

Discontinuation of the experiment is the responsibility of the examiner with regard to the subject's subjective feelings and expressions.

If a test subject does not feel well during the application according to his or her subjective assessments, he or she can discontinue the experiment and withdraw participation in the study without any disadvantages. A doctor is also present to ensure the safety of the test subjects.

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6 STUDIENDESIGN

Study design and justification

Randomized, clinical, crossover study

This is a category A intervention study (ClinO, Art. 20), whereby the intervention involves testing a tested product on healthy volunteers. The group size is N = 24. The intervention product (Cloud 9) is a solid, certified product that complies with the European Directives on Electromagnetic Compatibility, Machinery Directive, Air Pressure Equipment and Low Voltage Equipment (89/336/EEC, 91/368/CEE, 93/68/CEE, 97/23/EC, EN61010-1.

6.1 Method for minimizing influencing factors

6.1.1 Randomization

The situation (normobar & normoxic vs normobar & hypoxic) will be randomized. The randomization procedure is carried out by lottery.

6.1.2 Blinding

Blinding the test subjects is not possible with regard to the situation.

It is not possible to blind the data collectors.

However, blinding the statistician can be guaranteed, who has no access to the personal data of the test persons and is not present during the data collection.

6.1.3 Other Methods

No other methods are used.

6.2 Procedure for unblinding (code break)

There is no provision for the statistician to be blinded.

6.3 Procedure for unblinding (code break)

Blinding (coding) of study participants is only permitted if an unforeseen incident or medical problems occur during or after the completion of study participation in a subject, which may be attributable to participation in the study.

For incidents (AE) that occur during or shortly after the simulated altitude (within the first 24 hours) and can potentially be attributed to the intervention, the principal investigator may, at his or her discretion, immediately waive the blinding of the study participant and the investigators present to ensure adequate treatment of the study participant.

In the case of incidents (AE) that occur longer than 24 hours after the simulated altitude, clarification with a doctor is mandatory and a doctor's certificate is required for the lifting of blindness. Data may then also be passed on to the attending physician with the consent of the study participant concerned. This approach is justified because no life-threatening incidents are to be expected due to the intervention used here.

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7 STUDENT POPULATION

7.1 Inclusion Criteria

Inclusion Criteria

- Healthy, adult aged 18 to 50 years
- No cardiovascular diseases and/or interventions
- no surgical interventions on the cardiovascular system.
- No current injuries and/or pain conditions
- Regular and sufficient sleep
- No terrestrial altitude of 1000 m exceeded in the last month (including flights)
- Not exposed to any form of hypoxia in the last month
- Signed consent form

Exclusion criteria

- Age over 50 years
- Current injuries of any kind and/or pain conditions
- Acute and/or chronic pain conditions
- Known general diseases (e.g. diabetes mellitus)
- Fear of hypoxia
- Fear of heights or sensitivity to terrestrial altitude
- Regular intake of medication (including self-purchased medication), with the exception of anticonception drugs
- Cardiovascular disease or abnormalities
- Abnormalities of blood analysis or ECG
- Mental illnesses
- Pregnancy / breastfeeding
- Cognitive / linguistic inability to understand the study information or the study action.

7.2 Recruitment and Screening

Recruitment

It is advertised on the websites (homepage & Facebook) of "Thim van der Laan" and "SUPSI". In addition, information posters will be hung up in the school building. The exact texts have been prepared according to the checklist of the Cantonal Ethics Commission Zurich.

As advertisements (text visible):

- Homepage of the Physioschule Thim van der Laan: www.physioschule.ch and SUPSI: www.supsi.ch
- Facebook page of the Thim van der Laan Physiotherapy School: https://www.facebook.com/physioschule and SUPSI: https://www.facebook.com/supsi.physiotherapie/

Screening

During the first contact, the potential participants are informed about the course and risks of the study, as well as the conditions for and the amount of compensation explained. A checklist for contacting them

by telephone serves as a basis.

During the first telephone contact, a questionnaire is filled out by the study management to determine the suitability as a study participant.

The checklist for the initial determination of suitability during the initial telephone contact can be found in the attachments. The advertisements and health questionnaires are also in the inserts.

7.3 Allocation of situations

The situation assignment (normobar & normoxic vs. normobar & hypoxic) is done concealed by means of a lot in a sealed envelope, which is drawn under the supervision of the study leader. This lot shows whether the subject first goes through the normobaric & normoxic situation or the normobar & hypoxic situation.

7.4 Discontinuation of study participation

If a participant withdraws from the study, the lot of the allocation is returned to the pot in a new envelope and a new participant is sought.

All data collected to date will be evaluated as far as possible and included in the data analysis (in accordance with Art. 9 ClinO). After evaluation, the data is irreversibly anonymized.

The conditions for the termination of the experiment were described in chap. 5.4.

There is no disadvantage for the participants if they discontinue their participation in the study.

8 STUDY INTERVENTION

8.1 Medical Device ID

8.1.1 Intervention product

The intervention product is a certified product. With the Cloud 9, a simulated altitude of 2700 m and 3530 m above sea level can be achieved. This corresponds to an oxygen partial pressure of 15.0% and 13.5%, respectively. The Cloud 9 altitude training device is intended for everyone (even amateurs) who wants to increase their performance. The Cloud 9 is a solid, certified product that complies with the European Directives on Electromagnetic Compatibility, Machinery Directive, Air Pressure Equipment and Low Voltage Equipment (89/336/EEC, 91/368/CEE, 93/68/CEE, 97/23/EC, EN61010-1.

Securing the test subjects

Only subjects who have completed the health questionnaire without risk factors will be admitted to the study. In this way, risk factors are detected at an early stage and the subjects for the study are not recruited. In addition, a doctor is present during the measurements to ensure the safety of the test subjects.

8.1.2 Control intervention

The control group will be observed under normobaric and normoxic conditions.

8.1.3 Packaging, labeling and use

The Cloud 9 is a solid, certified product that complies with the European Directives on Electromagnetic Compatibility, Machinery Directive, Air Pressure Equipment and Low Voltage Equipment (89/336/EEC, 91/368/CEE, 93/68/CEE, 97/23/EC, EN61010-1.

8.1.4 Storage

The Cloud 9 can be stored both outside in the dry and inside a room. The equipment is located inside our laboratory for the duration of the measurements and is only accessible to laboratory staff. The room in which Cloud 9 is located is fully ventilated and has the following dimensions: 7m x 14m x 2.5m.

8.2 Administration of the experiment

Since no prescription drugs or invasive methods are used, the experiment is not discussed further in chapters 8.2-8.4 and only chapter 9 is referred to.

8.2.1 Experimental intervention

Simulated height: The test subjects are in the laboratory of our institution and are connected to Cloud 9 by means of a mask. The subjects are exposed to a simulated altitude of 3530 m above sea level under normobaric conditions. This intervention is used to determine the psychophysiological effect under normobaric and hypoxic conditions.

Terrestrial altitude: The subjects are at an SAC hut (Bergrestaurant Hohsaas: https://www.hohsaas-bergrestaurant.ch) in the canton of Valais at an altitude of 3200 m above sea level. By means of this

exposure, the psychophysiological effect under hypobaric and hypoxic conditions is determined. The test subjects spend a single night in this SAC hut and the measurements are repeated the next day.

8.2.2 Control intervention

Control: The test subjects are in our laboratory under normobar and normoxic conditions. This situation serves as a control intervention, which is contrasted with the simulated and terrestrial situation.

8.3 Dosage, application modification

In the simulated altitude situation, the recommendations in the Cloud 9 operating manual are followed.

8.4 Adherence to the study intervention

The test subjects are neither motivated nor unnecessarily distracted by the examiners or the study director with conversations. Communication is kept to a minimum, only study-related discussions are conducted in order not to influence the psychophysiological effects and to ensure homogeneity.

8.5 Follow-up treatment of eliminated participants

Data already collected from eliminated participants is stored anonymously in the filing cabinet provided for this purpose. As far as possible, the data will be included in the data analysis of the study.

There is no disadvantage for the participants if they discontinue their participation in the study and no further interventions are necessary for follow-up treatment.

If study participation was discontinued due to a reaction occurring during study participation, this will be logged and reported to the sponsor investigator (head of the research laboratory), study leader and supervisor of the study. If medical care is necessary, the report is forwarded to the business liability insurance of Thim van der Laan AG (Basler Versicherung) in order to ensure the appropriate follow-up treatment.

8.6 Preventive measurements

Through the telephone assessment and the health questionnaire, the intake of medication, injuries and operations, as well as known relevant diseases and allergies are asked. In addition, only young and healthy subjects who have already been at this altitude and had no signs of altitude sickness are examined. Pregnant women or nursing mothers are not allowed to participate in the study. Subjects who assure the study leader that they are not pregnant are allowed to participate in the study. In case of uncertainty, the potential test subjects are provided with a pregnancy test free of charge. The test subjects must then present a negative pregnancy test (given away free of charge by us). The test result is noted on the health questionnaire.

8.7 Accompaniments

No further side effects are expected from study participation. However, a doctor is present to detect unexpected side effects and react accordingly.

SUPSI

8.8 Liability

The experiments are taking place in the research laboratory of the "Physiotherapie Graubünden" in Landquart and in the Hohsaas mountain restaurant (canton of Valais). The liability for the transport is assumed by the business liability insurance of Thim van der Laan AG (Basler Versicherung).

8.9 Return of the medical device

Cloud 9 was purchased by the research department of the "University of Applied Sciences and Arts Southern Switzerland" and will remain in the research laboratory after the measurements have been completed.

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9 STUDY STRUCTURE & EVALUATION

9.1 Schedule Study Protocol

1. ***Subject Information & Informed Consent***
   30 min
2. ***Preparation of the subject***
   20 min
3. ***Running the Test Log (Sublogs)***

Test protocol: Time required – maximum 90 min		
Normobar hypoxic vs. hypobar hypoxic vs. normobar normoxic		
Simulated Height (Cloud 9)	Terrestrial Altitude	Control intervention
1.) Baseline measurements Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase Balance measurement Pain sensation Psychological measurements Thermal comfort & temperature perception *20 min* **2.) Step-up task** *5 min* **3.) Follow-up** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood	**1.) Baseline measurements** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase Balance measurement Pain sensation Psychological measurements Thermal comfort & temperature perception *20 min* **2.) Step-up task** *5 min* **3.) Follow-up** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate	**1.) Baseline measurements** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase Balance measurement Pain sensation Psychological measurements Thermal comfort & temperature perception *20 min* **2.) Step-up task** *5 min* **3.) Follow-up** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate

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Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase *10 min* **3.) Cold water immersion of the hand** *5 min* **4.) Follow-up** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase Balance measurement Pain sensation Psychological measurements Thermal comfort & temperature perception *40 min*	Skin temperature Lactate & Creatine Kinase *10 min* **3.) Cold water immersion of the hand** *5 min* **4.) Follow-up** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase Balance measurement Pain sensation Psychological measurements Thermal comfort & temperature perception *40 min*	Skin temperature Lactate & Creatine Kinase *10 min* **3.) Cold water immersion of the hand** *5 min* **4.) Follow-up** Perfusion Microcirculation Oxygen Saturation Muscle & Brain Oxygen saturation of blood Blood Pressure & Heart Rate Skin temperature Lactate & Creatine Kinase Balance measurement Pain sensation Psychological measurements Thermal comfort & temperature perception *40 min*

Test log	**Time exposure**	**Visits**
Declaration of Consent	30 min	Unique
Simulated Height	20 + 90 min = 110 min	Unique
Terrestrial Altitude	20 + 90 min = 110 min	Twice (incl. 1x overnight stay)
Control intervention	20 + 90 min = 110 min	Unique
TOTAL TIME COMMITMENT	470 min + 1 night	

Each test subject can expect a total time expenditure of 470 minutes excluding the journey to and from Valais and the overnight stay at the SAC mountain hut.

9.1.1 Measurement of primary results

The primary measurements of perfusion of skin microcirculation, oxygen saturation of the muscles, brain, musculature as well as the measurement of blood pressure & heart rate, skin temperature, lactate, creatine kinase, pain sensation and balance can be measured within 10 min.

SUPSI

The psychological measurements, which are carried out on the basis of questionnaires, can be carried out within 10 minutes.

9.1.2 Measurement of primary results

The primary measurements refer to the area of application, lumbar back area, right-sided or left-sided paravertebral depending on randomization.

Perfusion of skin microcirculation

The perfusion of the skin microcirculation is visualized using the Laser Speckle Contrast Imager (moorFLPI 2, moor instruments, www.moor.co.uk). This measurement is non-invasive. The "moorFLPI-2 Full-Field Laser Perfusion Imager" measures blood flow measured in flow rates (arbitrary units) of the skin's microcirculation. The laser is intended for clinical and physiological research. The fabric is illuminated with a divergent infrared laser beam. The laser measures down to a depth of 1mm, so it mainly detects the superficial blood flow, speed and concentration of red blood cells. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Oxygen saturation of the muscles and brain

The oxygen saturation of the muscles and brain is measured non-invasively with a deep tissue oxygenation monitor (moorVMS-NIRS, moor instruments, www.moor.co.uk). For this purpose, adhesive electrodes are attached over the muscle and forehead. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Oxygen saturation of the blood

The oxygen saturation of the blood is measured with a portable pulse oximeter with finger clip probe (Nonin 7500, Nonin medical B.V., Plymouth, USA). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Blood pressure and heart rate

The heart rate is measured with a heart rate belt and an additional 2-point ECG (Actiheart, Camntech Ltd., Cambridge, UK). Blood pressure is measured by means of an electronically automated upper arm blood pressure monitor (Boso-Medicus uno). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Skin temperature

Skin temperature is measured via the iButton system (www.ibuttonlink.com). The self-adhesive sensors transmit the information about the skin temperature wirelessly to a computer. Furthermore, the skin temperature is recorded by means of a thermal imaging camera (FLIR). This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Lactate and creatine kinase

The lactate and creatine kinase are carried out by capillary blood measurement (Accutrend, Roche Diagnostic, Rotkreuz, Switzerland & Reflotron, Roche Diagnostic, Rotkreuz, Switzerland). The affected area is disinfected and a superficial wound is pierced to take capillary blood. This measurement is measured during the baseline measurements, after the step-up task and up to 30 min after the cold water bath of the hand (5 min interval).

Balance measurement

The fluctuations of the hull are recorded and evaluated with the Sway Star™ System (www.b2i.info). The Sway Star™ is a measuring instrument that contains gyroscopes. It is attached to a belt that is placed around the patient's waist. The data is evaluated with the associated Sway Star ™software and transferred to the data sheet. This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand.

Pain sensation

The pain threshold is measured using a pain pressure algometer (NOD, www.to-nod.com). As soon as the patient reports pain, this measurement is stopped. This measurement is carried out after the baseline measurement and after the cold water bath immersion of the hand.

Psychological measurements

The psychological measurements (sleep disorder, altitude sickness, dyspnea, state of mind, drowsiness) are evaluated on the basis of written questionnaires.

The cognitive test battery consists of 8 tasks (ANAM, US Department of Defence, Vista Life Sciences, USA), which are carried out on a laptop computer.

These measurements are carried out after the baseline measurement and after the cold water bath immersion of the hand.

9.1.3 Measurement of secondary results

The secondary measurement of thermal comfort and temperature perception can be measured within 1 min.

Thermal comfort and temperature perception

This parameter is measured using a scale. The test subjects indicate their subjective temperature perception on a 9-point scale from -4 (very cold) to +4 (very hot). They then rate the thermal comfort between 0 (pleasant) and 4 (extremely unpleasant) on a 5-point scale. These measurements are carried out after the baseline measurement and after the cold water bath immersion of the hand.

9.1.4 Collection of further results

No further results will be collected.

9.1.5 Collection of safety parameters

Apart from the health questionnaire (including pregnancy test for female subjects), no safety parameters are collected.

9.1.5.1 Unfavorable events

In the event of an allergic reaction, the experiment is stopped immediately.

9.1.5.2 Laboratory parameters

-

9.1.5.3 Vital signs

-

9.1.6 Collection of data in case of early termination of studies

For the participants, there is no disadvantage in the event of an (arbitrary) discontinuation of study participation and no further interventions are necessary for follow-up treatment. The data collected to date will be evaluated as far as possible and included in the data analysis (in accordance with Art. 9 ClinO).

However, if study participation was discontinued due to a reaction occurring during study participation, this will be recorded and reported to the sponsor investigator (head of the research laboratory), study management and supervisor of the study. In the event of necessary medical treatment, the report is sent to the business liability insurance of Thim van der Laan AG (Basler Versicherung).

The following are recorded:

- Date and time of the incident
- Course of the incident
- Persons involved & witnesses
- Study ID (specified by the CEC)
- Personal data of the person concerned (if not previously recorded)

9.2 Procedure at each visit of the test subjects

9.2.1 Single measurement

The project involves multiple visits.

9.2.2 Multiple visits

After contact has been made by telephone and suitability has been determined by telephone, the subject information and the declaration of consent are submitted for inspection and reading. If the subject agrees with the study conditions and criteria, he or she registers to make an appointment for the 1st contact day.

The 1st contact day includes, in the order described, the; On-site explanations, signing the consent form, completing the health questionnaire and taking the pregnancy test for female subjects. If these points are passed positively, an appointment is made for the actual measurement day (2nd-5th contact day).

1. On-site explanation and completion of the health questionnaire, 1st contact day

The subjects will be comprehensively informed about the process and possible risks before they are confirmed to participate in the study. The declaration of consent explains to them what their rights and obligations are when participating and that they may withdraw from participation at any time without giving reasons, without incurring any disadvantages as a result. More detailed information can be found in chapter 2.7. In addition, a health questionnaire is filled out to identify any risks. An initial selection

process of suitable test persons takes place. If the health form has been completed and no risks have been identified, the test subjects are summoned to the 2nd day of contact.

2. Measurement, 2nd-5th day of contact

2.1 Preparation of the subject

The subject lies in his underwear on a treatment table for a period of 20 minutes. This is followed by the baseline measurement.

2.2 Intervention

The subject is then exposed to either the simulated altitude or the normobaric & normoxic situation. Afterwards, a step-up task of 5 minutes and a cold water bath immersion of the hand for 5 minutes is performed. In the terrestrial situation, the subject is measured at the time of arrival at the SAC Hut, as well as the following day after an overnight stay at the SAC Hut. The experimental procedure is therefore illustrated:

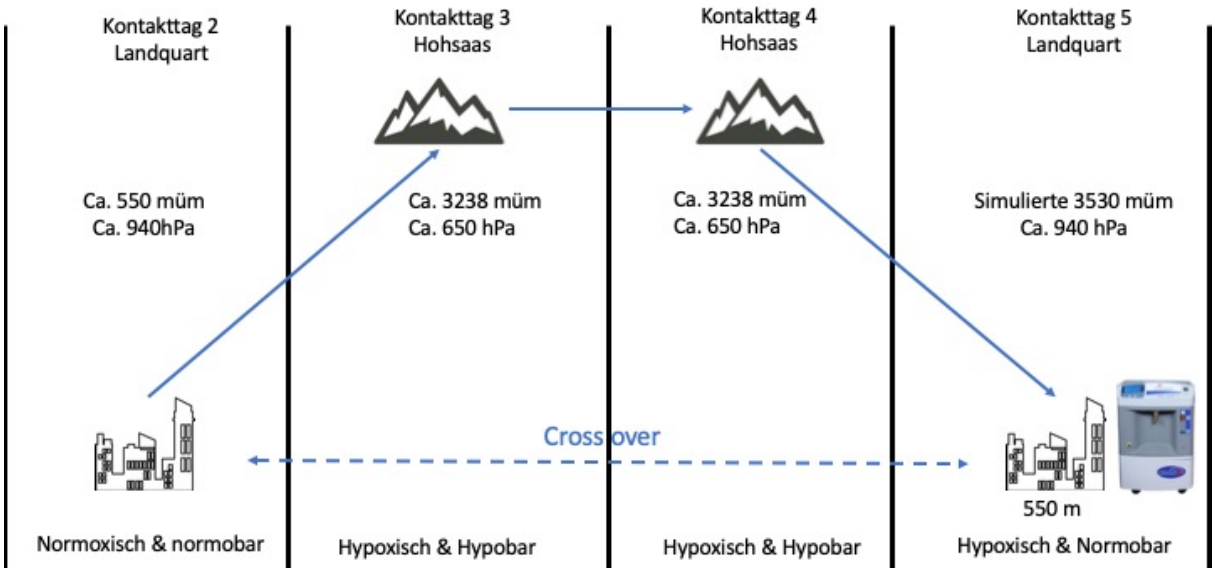

Illustration of the experimental process

2.3 Follow-up measurement

After the step-up task and after the cold water bath immersion of the hand, follow-up measurements are carried out.

After the step-up task, the perfusion of the microcirculation, the oxygen saturation of the muscles, the brain, the blood, the blood pressure and the heart rate, the skin temperature, the lactate and the creatine kinase are measured again once.

After cold water immersion, these parameters are measured again at intervals of 5 min up to 30 min after hand immersion. After these parameters have been collected, the balance measurement, the pain sensation as well as the psychological measurements and the thermal comfort and temperature

perception are measured again.

After this measurement day is completed, the test subjects either return to the laboratory and carry out the same test procedure in the mountain restaurant in Valais.

2.4 Conclusion and compensation

After the last follow-up measurement and after the subject has gone through all situations, the examination is over for the subject. He/she will receive the amount due to him/her according to the advertisement. The lump sum is 100 CHF. The gondola ride, the overnight stay, the travel costs to Valais and the meals in the SAC hut are covered by the University of Applied Sciences and Arts Southern Switzerland. The total compensation is not dependent on the completion of the study. The test subjects will be reimbursed for the costs in any case.

SUPSI

10 SAFETY

Other clinical trial with a medical device in the risk category Cat. ***A*** KlinV (Art. 20)

No medication will be administered to the subjects, nor will tissue samples be taken. No invasive methods are used.

No further security aspects are expected.

10.1 Drug study

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

-

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

-

10.1.3 Follow up of (Serious) Adverse Events

-

10.2 Medical Device Category C studies

-

10.2.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

-

10.2.2 Reporting of (Serious) Adverse Events and other safety related events

-

10.2.3 Follow up of (Serious) Adverse Events

-

10.3 Medical Device Category A studies

This project is carried out with a CE certified product. It is a study with 24 or fewer subjects. The study aims to gain fundamental knowledge in the field of altitude training. The study focuses on basic findings. The monitoring for quality assurance is carried out by Dr. Joseph Costello, who has gained numerous experiences and published studies in the field of extreme environmental conditions. In addition, a doctor is present during the measurements.

10.3.1 Definition and recording of safety-relevant events

An adverse event (ADVERSE EVENT) AE) is any unfortunate medical occurrence in a study subject who is exposed to a simulated or terrestrial altitude (as listed in Chapter 8.1.1) that is not necessarily causally related to the study process. An AE can therefore be any adverse and unintentional sign or symptom that can be related to the intervention product (according to Chapter 8.1.1).

According to swissethics.ch, a serious adverse event (SAE) is classified as any unfortunate medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization of the subject, results in a persistent or significant disability/inability, or is a congenital anomaly/birth defect. In our

study, an SAE is not to be expected due to the amount that is being investigated.

The equipment used in this study is used in accordance with the operating manual.

If the examination leads to a reaction described above, this is classified as a safety-relevant event by the study leader. For the affected study participant, the study is completed at this time, and the data already collected will be processed as described in chapters 7.4 and 9.1.6.

The subject-specific demographic data collection sheet (page 4) records:

- Date and time of the incident
- Course of the incident
- Persons involved & witnesses
- Study ID (specified by the CEC)
- Personal data of the person concerned (if not previously recorded)

10.3.2 Reporting of Safety related events

Pursuant to Art. 37, 43 paras, 1&2 and Art. 63 Clin V.

10.3.3 Notification of a security-relevant event

A safety-related event is logged and immediately reported to the sponsor investigator (head of the research laboratory), study management and supervisor of the study.

The CEC will be informed as soon as possible and appropriate changes will be made to the protocol of the study. Further explanations can be found in chapter 2.10. Safety and protective measures must be reported to the responsible CEC within two days.

The report continues to the business liability insurance (Basler Versicherung) of Thim van der Laan AG in Landquart.

11 STATISTICAL METHODS

11.1 Hypotheses & Factors

Psychophysiological changes under simulated and terrestrial altitude.

Perfusion of skin microcirculation

H0 The perfusion of the skin microcirculation does not change significantly at the simulated altitude compared to the terrestrial altitude.

H1 The perfusion of the skin microcirculation changes significantly in the simulated altitude compared to the terrestrial altitude.

Oxygen saturation of the muscles and brain

H0 The oxygen saturation of the muscles and the brain does not change significantly at the simulated altitude compared to the terrestrial altitude.

H1 The oxygen saturation of the muscles and the brain changes significantly in the simulated altitude compared to the terrestrial altitude.

Oxygen saturation of the blood

H0 The oxygen saturation of the blood does not change significantly in the simulated altitude compared to the terrestrial altitude.

H1 The oxygen saturation of the blood changes significantly in the simulated altitude compared to the terrestrial altitude.

Blood pressure and heart rate

H0 Blood pressure and heart rate do not change significantly at the simulated altitude compared to the terrestrial altitude.

H1 Blood pressure and heart rate change significantly at the simulated altitude compared to the terrestrial altitude.

Skin temperature

H0 The skin temperature does not change significantly at the simulated altitude compared to the terrestrial altitude.

H1 The skin temperature changes significantly at the simulated altitude compared to the terrestrial altitude.

Lactate and creatine kinase

H0 Lactate and creatine kinase do not change significantly at the simulated altitude compared to the terrestrial altitude.

H1 Lactate and creatine kinase change significantly in the simulated altitude compared to the terrestrial altitude.

Equilibrium

H0 The equilibrium does not change significantly at the simulated altitude compared to the

terrestrial altitude.

H1 The equilibrium changes significantly in the simulated altitude compared to the terrestrial altitude.

Pain sensation

H0 The sensation of pain does not change significantly in the simulated altitude compared to the terrestrial altitude.

H1 The sensation of pain changes significantly in the simulated altitude compared to the terrestrial altitude.

Sleep disorder

H0 The quality of sleep does not change significantly at the simulated altitude compared to the terrestrial altitude.

H1 The quality of sleep changes significantly in the simulated altitude compared to the terrestrial altitude.

Symptoms of altitude sickness

H0 The simulated altitude does not lead to any symptoms of altitude sickness compared to the terrestrial altitude.

H1 The simulated altitude leads to symptoms of altitude sickness compared to the terrestrial altitude.

Dyspnea

H0 The simulated altitude does not lead to dyspnea symptoms compared to the terrestrial altitude.

H1 The simulated altitude leads to dyspnea symptoms compared to the terrestrial altitude.

State of mind

H0 The simulated altitude does not lead to any changes in mood compared to the terrestrial altitude.

H1 The simulated altitude leads to changes in state of mind compared to the terrestrial altitude.

Sleepiness

H0 The simulated altitude does not lead to any drowsiness symptoms compared to the terrestrial altitude.

H1 The simulated altitude leads to drowsiness symptoms compared to the terrestrial altitude.

Cognition

H0 The simulated altitude does not lead to any cognitive changes compared to the terrestrial altitude.

SUPSI

H1 The simulated altitude leads to cognitive changes compared to the terrestrial altitude.

Thermal comfort and temperature perception

H0 The thermal comfort and the temperature perception do not change significantly in the simulated altitude compared to the terrestrial altitude.

H1 Thermal comfort and temperature perception change significantly in the simulated altitude compared to the terrestrial altitude.

A 2-factor analysis is carried out.

Factor 1: Situation (simulated altitude vs. terrestrial altitude)

Factor 2: Time (baseline, after step-up task, 0, 5, 10, 15, 20, 25, 30 min post-cold water immersion of the hand) or

Time (baseline, post-cold water immersion of the hand)

Explanations for the hypotheses:

It has already been established that hypobaric hypoxia can have a negative impact on postural stability in the antero-posterior plane, compared to normobaric hypoxia. This indicates that the change in pressure per se can play a more important role compared to hypoxia (Degache et al. 2012). However, it must also be mentioned that visual acuity (the view) can also influence postural stability. Movements that occur and are processed unconsciously can activate muscles that play a role in postural control (Brandt et al. 1986). This factor is kept as low as possible during the measurement during the stay in the SAC hut by the test subject looking at the wall (as in the laboratory) and not into the distance (through a window, for example).

Regarding oxygen saturation, measured with a pulse oximeter as in our study, the study by Savourey et al. 2003 and Self et al. 2011 showed that these values were lower in the hypobaric hypoxia situation compared to the simulated altitude. These differences were already evident after short-term exposure and comparable (simulated) altitude exposures to our study. For the cardiovascular differences, Faiss et al. 2013, Miyagawa et al. 2011 and Self et al. 2011 showed that heart rate and blood pressure increased after short-term exposure at terrestrial altitude, compared to the simulated altitude.

Based on these results for oxygen saturation, heart rate and blood pressure, it stands to reason that the inflammation and lactate levels in the terrestrial study group are higher after submaximal exercise compared to the values in the simulated altitude group. However, we would like to investigate this hypothesis in our experiment.

Altitude sickness symptoms, which are very often studied in this field of research, showed the following differences: The risk or development of altitude sickness seems to be greater at terrestrial altitude compared to simulated altitude (Loeppky et al. 2005, Miyagawa et al. 2011). The difference between terrestrial altitude and simulated altitude on sleep quality was also investigated. In both initial positions, oxygen transport is significantly suppressed during the sleep phase. However, the simulated height in this case is a continuous (during the sleep phase) situation (Berssenbrugge et al. 1983). Millet et al. (2012), on the other hand, described that the ventilation of the lungs, and consequently the CO2 content in the blood, are lower at the terrestrial altitude, compared to the simulated altitude. Poor sleep at terrestrial altitude could also have a negative effect on the daily state of mind as well as on drowsiness. Furthermore, the reduced oxygen saturation or the increased CO2 content in the arterial blood could

lead to a reduction in oxygen saturation in the muscles and brain (and reduced cognitive performance) in the terrestrial situation. However, it must be explicitly mentioned that a direct comparison can only be made here if the simulated and also the terrestrial altitude are carried out in the same amount of time.

Thermal comfort and temperature perception are largely dependent on the outside temperature. The room temperature in the SAC hut is therefore adapted as much as possible to the conditions of the laboratory in order to keep this disturbing factor as low as possible. However, the different temperature in the 2 scenarios could also have an impact on the perfusion of the skin's microcirculation. Furthermore, it was described that sympathetic tone is increased at terrestrial altitude compared to simulated altitude. Catecholamines, such as norepinephrine, also seem to be released more frequently at terrestrial altitudes (Mazzeo et al. 1994).

The result of Noel-Jorand et al. 1996 is interesting. These authors described that the sensation of pain is largely dependent on the hypoxia itself and not only on the difference in air pressure. The pain threshold has decreased in this study and sensory discrimination has increased below terrestrial altitude. Hypoxia and the resulting adaptation to the lack of oxygen itself seem to be the main reason for this (Noel-Jorand et al. 1996).

There are several mechanisms that could explain the different reactions of terrestrial and simulated altitude. It is obvious that the difference in air pressure and the duration of the hypoxic situation are the primary factors, which are different in these 2 scenarios. However, these different factors themselves provide information about psychophysiological effects and therefore provide the impetus for further discussions in this field of research. The different room temperatures could also have an influence on the reactions of the test subjects. In this point, we will try to keep the ambient temperature as similar as possible. We are aware that other factors such as contact with other people in the SAC hut, the view, etc. can influence the results. We will control these disruptive factors as best we can. However, it is also important to record these factors and bring them forward as discussion points in the study.

11.2 Sample size

The sample size in the literature varies. The planned number of 24 subjects is within the wide range and is expedient, time-wise and financially feasible for the study.

The G*Power analysis (V.3.1.) revealed (F-test, MANOVA:repeated measures, within-between interaction, effect size f(V) = 0.9, alpha err prob = 0.05, Power (1-beta err prob) = 0.6, number of groups = 3, number of measurements = 14) a required group of 23 participants.

11.3 Criteria for the statistical use of data in the case of incomplete data sets

Only data from subjects who have completed the entire protocol will be included in the study. This ensures that all data has been collected under the same conditions and thus remains homogeneous and comparable.

11.4 Scheduled analyses

11.4.1 Datasets and Data Population

Only datasets that can be used sensibly will be included in the study. Incomplete data sets that contain only part of the protocol are included in the analysis as far as possible. No new test subject is being sought to replace the missing data.

SUPSI

11.4.2 Primary Analysis

The statistical data analysis will be carried out by Prof. Dr. Tom Deliens after completion of the data collection of the entire project.

Repeated measures analysis of variance (MANOVA)

2 factors:

Factor 1: Situation (simulated altitude vs. terrestrial altitude)

Factor 2: Time (baseline, after step-up task, 0, 5, 10, 15, 20, 25, 30 min post-cold water immersion of the hand)

Repeated measures analysis of variance (MANOVA)

2 factors:

Factor 1: Situation (simulated altitude vs. terrestrial altitude)

Factor 2: Time (baseline, post-cold water immersion of the hand)

The significance level is set at $P < 0.05$, and the statistical data analysis is carried out with SPSS V. 23.

11.4.3 Secondary Analysis

Nonexistent.

11.4.4 Interim analyses

The data is processed after the project ends. No additional interim analyses are planned.

11.4.5 Security analyses

No security analyses are provided.

11.4.6 Deviations

Deviations from the planned statistical analysis are recorded and justified and reported to the CEC in the annual report.

11.5 Drop-outs and missing data

If a test subject does not complete the experiment, any data that has already been collected is destroyed and is not included in the final data analysis.

12 QUALITY ASSURANCE AND CONTROL

12.1 Data Archiving

12.1.1 Forms

Data protection and confidentiality are guaranteed and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal data and demographic and medical personal data are stored in the original as a study document in a locked filing cabinet. Only the head of the study (head of the research laboratory of the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden) has access (key possession) to this cabinet. The encryption of the identity of the test persons is not digitally recorded, i.e. surname, first name and date of birth are not digitally recorded in any way.

Direct access to the personal data will continue to be allowed only to authorized persons of the CEC.

12.1.2 Specification of forms

The data collected in writing is recorded in the form listed in the enclosures and is marked as study data. They are therefore subject to data protection and are stored in accordance with the information described in chapter 12.1.1.

12.1.3 Archiving of data

The data collected will be kept for 10 years. Data protection will continue to be guaranteed.

12.2 Data management

12.2.1 Data Management System

The raw data of the perfusion of the skin microcirculation (Laser Speckle Contrast Imager) are processed with the software "moorFLPI-2 full-field laser Perfusion Imager V1.1". The oxygen saturation of the muscles and the brain is processed with the software "moor VMS-PC v.4.2.". The i-buttons are read out with the i-Button MMT software. The data from the thermal imaging camera is processed with the "Flir Research IR max" software. The oxygen saturation values of the muscles and the brain are also processed with the software "moor VMS-PC v.4.2.". Lactate and creatine kinase are recorded with the reflotron (Roche Diagnostic, Rotkreuz, Switzerland) and transferred to a data sheet. The balance measurement is recorded and evaluated with the Sway Star™ System (www.b2i.info). Sleep disorder, Lake Louis altitude sickness, dyspnea, state of mind and drowsiness are recorded in writing with a questionnaire. Cognition is recorded digitally on a laptop and the score is stored there. The subjective perceptual parameters regarding thermal comfort and temperature perception are asked orally and the answers are handwritten on the raw data sheet. The pain sensation is transferred to a portable PC on a supplied software (www.to-nod.com).

12.2.2 Data security and backup

The digital data (laser speckle contrast imager, i-button, thermal imaging camera, oxygen saturation, pain sensation, balance, cognition) will be anonymized and treated confidentially, access to the personal data will not be allowed to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers. Access to the computers of the research laboratory at the "University of Applied Sciences and Arts Southern Switzerland" is only granted to the head of studies and the examiners (listed in Chapter 1), as well as

persons authorised by the CEC.

12.2.3 Analysis and archiving

After collection, the digital data is encrypted and stored on another external hard drive for further backup. This is stored in a locked filing cabinet to ensure data protection.

12.2.4 Validation of electronic data

Immediately after data collection, the quality of the data is checked and verified with the help of the visual representation.

12.3 Monitoring

The data collected can be viewed by authorised persons at any time (see Chapter 12.2.2)

The study is to be monitored by the following person:

Dr. Joseph Costello

University of Portsmouth
Department of Sport & Exercise Science
Spinnaker Building, Cambridge Road,
Portsmouth, Hampshire, P012ER

+44 239284 5366
joe.costello@port.ac.uk

12.4 Audits and inspections

A report on the current status of the study is given orally to the study supervisor (Dr. Joseph Costello) on a monthly basis. In addition, Dr. Costello will be present during the measurements. This also includes demonstrating and presenting results and statistical analyses.

An annual report on the course of the study will be submitted to the CEC. Authorized persons of the CEC can view the data forms as well as the digital data on the institute's own computers at any time.

Data protection is guaranteed at all times.

12.5 Confidentiality and data protection

The examiners ensure that the privacy of the participant is guaranteed. In particular, data protection and confidentiality are guaranteed and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal details, are kept in the original as a study document in a locked filing cabinet.

The digital data will be anonymized and treated confidentially, and access to the personal data will not be allowed to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers.

Direct access to the personal data is only allowed to authorized persons of the CEC.

12.6 Retention of biological material and health-related data

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SUPSI

13 PUBLICATION AND DISCLOSURE OF DATA

The examiners ensure that the privacy of the participant is maintained. In particular, the data protection and confidentiality of the data are guaranteed and no personal data is presented or published nor passed on to outsiders and unauthorized persons.

14 FUNDING AND SUPPORT

14.1 Financing

The study is funded by the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden. The auditors are employed by this institute and are remunerated for their work on this study in accordance with their employment contracts. No further support is needed.

SUPSI

15 INSURANCE

There is a public liability insurance policy with Basler Versicherung for Thim van der Laan AG in Landquart, where the study is being conducted.

SUPSI

16 REFERENCES

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17 APPENDIX

1. Subject information, informed consent and demographic data (health questionnaire)
2. Recruitment of test persons (advertisements)
3. Data Collection Questionnaire Measurements (Screening Test and Measurement Data Sheet)
4. Protocol Synopsis
5. Employee
6. CVs of all examiners