EXPOSITION TO EXTREME ENVIRONMENTAL HYPOXIA AND ITS EFFECT ON THE INFLAMMATORY AND CARDIOPULMONAR RESPONSE: BIOLOGICAL, GENETIC AND CLINICAL IMPACT.

Acronym: SHERPA

Principal Investigator:

[1]José Manuel Soria, PhD

Co-Investigators:

[2]Oriol Sibila, PhD., MD; [3]Marc Abuli, MD; [4]Emma Roca, BSc; [4]Lexa Nescolarde, PhD; [5]Enrique Roche, PhD ; [3]Antoni Bayés-Genís, PhD., MD; [6]Eduardo Garrido, PhD., MD; [7]Daniel Brotons, PhD, MD; [8]Yogesh Subedi. MD; [9]Sanjeeb Bhandari, MD

Investigator affiliation:

[1]Unit of Genomic of Complex Diseases. Research Institute Sant Pau (IIB-Sant Pau). Universitat Autonoma de Barcelona (UAB). Barcelona. Spain
[2]Neumology Department. Hospital de la Santa Creu i Sant Pau. Universitat Autonoma de Barcelona (UAB). Barcelona. Spain
[3]Cardiology Department. Hospital Germans Trias i Pujol. Badalona. Spain
[4]Center for Biomedical Engineering Research, Universitat Politècnica de Catalunya (UPC), Barcelona. Spain
[5]Universidad de Elche. Elche. Spain
[6]Physiology Department. Universitat de Barcelona (UB). Barcelona. Spain
[7]Consell Català de l'Esport, Generalitat de Catalunya. Barcelona. Spain
[8]Subedi's affiliation
[9]Bhandari's affiliation

Investigation Sites:

Samyak Diagnostic Lab. Kathmandu. Nepal; Everest Base Camp, Khumbu Valley, Nepal

1. INTRODUCTION

Thank you for your interest in participating in this project. You are being invited to take part in this research study because you comply one of these requirements:

1.- a healthy volunteer who participate in the trekking to Everest Base Camp (EBC) with Ferran Latorre's expedition that to be held in April 2017.

2.- a healthy volunteer climber at EBC who has the purpose to reach at least 7,500 m altitude between April-May 2017.

3.- a healthy Nepalese volunteer who has been born and raised at high altitude (elevation greater than 3600m), and who has the purpose to reach at least 7,500 m altitude between April-May 2017).

In all three cases, you are free from known cardiovascular and lung disease.

By participating in this study, your data will help us to substantially improve our understanding of biological adaptation to acute and chronic reductions in the level of oxygen in the blood (called hypoxia). The findings are clinically relevant and relates to chronic respiratory and cardiovascular disease, such as sleep apnea, chronic obstructive pulmonary disease, and congestive heart failure. Please read this information sheet carefully before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you of any kind and we thank you for considering our request.

2 YOUR PARTICIPATION IS VOLUNTARY

Taking part in the study is voluntary (your choice). If you do not want to take part, or if you agree to take part and then change your decision later, this is not a problem. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. If you wish to participate, you will be asked to sign this form. If you decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision. Furthermore, you will not lose the benefit of any medical care to which you are entitled or are presently receiving after such a decision.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THE STUDY?

The research team includes co- investigators from Spain (Hospital de la Santa Creu i Sant Pau belong to Autonomous University of Barcelona and Hospital Germans Trias I Pujol belong to University of Barcelona), and Nepal (). The work is, in part, supported by the Hospital de la Santa Creu i Sant Pau Research program.

4. BACKGROUND

Many respiratory and cardiovascular diseases involve exposure to low levels of oxygen (hypoxia), high blood pressure in the lung, and difficulty in breathing. Some examples of these diseases include sleep apnea, chronic obstructive pulmonary disease, and congestive heart failure. Sleep apnea, in particular, is independently associated with an increased risk for stroke, high blood pressure, and heart attack. Ascent to high altitude provides an excellent way to examine physiological adaptation to acute and chronic hypoxia. Because of the time necessary to study any chronic adaptation (e.g., several weeks of exposure), the profound limitations on quality of life, and related expense, studying the effects of high altitude at sea level using rooms that change pressure or gas content is not feasible. Moreover, to study biological *adaptation* to the chronic environmental stress of living at high altitude necessitates a long period of study and, ideally, comparison between sea-level natives and humans native to high altitude.

5 WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to compare gene expression, lung and heart function in sea-level natives (Trekkers and Climbers) and humans native to high altitude (Sherpas). The main aims for our research studies are stated below:

Physiology:
- To study the cardiopulmonary response to hypoxia and height (peripheral blood and saliva) and to evaluate the appearance of pulmonary pathology.
- Measure markers of oxidative imbalance, of inflammatory damage, the global and localized BIA, hydration and activation/damage parameters muscle and markers of heart and muscle damage.

Genetics:
- Quantify the expression of the whole genome to identify the mechanisms involved in adaptation to altitude and hypoxia (moderate and severe).
- Correlate the levels of gene expression with all the parameters studied in the project.

6 WHO CAN PARTICIPATE IN THE STUDY?

Healthy human volunteers who are western trekkers or climbers and high-altitude natives can participate in this study if they are between the ages of 18 and 50 years, and have no history of heart, lung, or brain disease.

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

You will not be permitted to participate in this study if you are obese or have history of hear, lung, or brain disease. The investigators will directly assess such exclusion criteria during your initial laboratory visit.

8 WHAT DOES THE STUDY INVOLVE?

The studies will be conducted in Kathmandu, and at the Everest Base Camp, Khumbu Valley, Nepal, at the base of Mt Everest (barometric pressure 412 ± 1 mmHg).

1 Overview of the Study

Participation in these studies will involve one visit to a laboratory in Kathmandu for Trekkers, one visit to Everest Base Camp for Trekkers and two visits to Everest Base Camp for Climbers and high-altitude natives (Sherpas).
During the first part of this visit, we will ensure you meet the necessary criteria for participation and will involve medical history, pulmonary function testing (spirometry), ultrasound measurements of your heart and arteries. Following this, if you met the necessary criteria for participation, your blood volume, and your resting physiological parameters (heart rate, blood pressure, ventilation) will be assessed. We will perform the same protocol en the second visit
Each testing session will last around 1 hour. The specific details of each of the measurements that will be performed are detailed below under 'procedures of the study'.

1. **Studying the cardiac function, lung vascular function and bioimpedancy in the three groups of participants: Trekkers, Climbers and High altitude natives.**

Total study time: 1 hours

a) Venous blood samples:

While you are lying down we will collect a small (5ml) sample of blood from a vein in your arm. This is a quick and painless procedure although you may experience a skin prick that may cause discomfort.

b) Breathing and Cardiovascular Measurements:

During all procedures we will record breathing, heart, and blood pressure parameters. To do this you will breathe through a facemask, will wear electrodes on your chest, and will wear pressure cuffs on your finger and upper arm. All of these procedures are non-invasive and you will not feel pain.

c) Echocardiography and Exercise Test

Ultrasound will be used to measure the function of your heart and lungs. A smooth probe will be placed on your chest and you will be asked to breathe normally and to hold your breath for periods of a few seconds. Then exercise test compares the function of your heart at rest. You will be carefully supervised at all times during this test and may stop at any time you feel uncomfortable.

d) bioimpedancy:

The whole-body bioimpedance measurements will be obtain at 50 kHz with a phase-sensitive bioimpedance analyser model BIA-101 Anniversary (AKERN-Srl, http://www.akern.com, Florence, Italy) which injects a constant sinusoidal alternating current of 245 µARMS. The measurement will be doing in tetra-polar whole-body (gold standard) configuration [Lukaski et al., 1986], to assess the hydration and nutritional state. For these non-invasive measurements will be use adhesive contact Ag/AgCl electrodes (BIATRODES/0ELB, AKERN-Srl). The subjects will be keep in supine position during 10 min for made measurement.

e) Espirometry:

An spirometry test will be used to measure your lung capacity. While you are sitting, you will breathe into a mouthpiece that is connected to an spirometer (Datospir Micro,

SibelMed SA, Barcelona, Spain) . The spirometer records the amount and the rate of air that you breathe in and out over a period of time (20-30 seconds).

f) Oxygen Saturation:
Oxygen saturation will be measured using a portable pulse oximeter (H100-B1, Asmedic, Barcelona, Spain). The pulse oximeter is a diagnostic tool that enables the indirect measurement of the percentage of oxygenated haemoglobin in a patient's capillary blood. It is connected to one in your finger, and measurement is done in less than 10 seconds.

9. WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECTS OF PARTICIPATING?

You are asked to report any unusual symptoms during each of the tests. You can stop any test at any time if you are feeling uncomfortable. Every effort will be made to conduct the tests in such a way to minimize discomfort and risk. Female participants in this study must avoid pregnancy. Failure to do so may result in potential harm to your fetus. You should discuss these issues (of not being or becoming pregnant during the course of the study) with your study doctors, and find an acceptable solution that will address this matter. However, the following risks should be considered:

Blood measurement: There are few, if any, complications for those participating in this test. A small amount of pain may be associated with routine blood withdrawal from a vein. It is possible that some individuals may experience lightheadedness, fainting, and/or nausea from the blood collections. You may experience localized bruising and swelling at or near the puncture site. You may also experience petechiae (small, non raised red spots on skin) where the tourniquet was applied. Occasionally, some individuals are allergic to the antiseptic used in skin preparation, the glue used in adhesive bandages, or latex. In this case, an alternate antiseptic, paper tape, and non-latex gloves will be used. Qualified technicians will be present for all the testing sessions to reduce discomfort and monitor your condition.
Laboratoy work will be done at Samyak Diagnostic PVT. LTD, Nepal. First ISO:1589:2012 Accreditated Laboratory.

Bioimpedancy:

The use of non-invasives bioimpedance measurements in whole-body configuration at 50 kHz, for nutritional assessment was validate by US Department of Health & Human Service. National Institut of Health: (https://consensus.nih.gov/1994/1994bioelectricimpedancebodyta015html.htm) and published in: National Institutes of Health. Bioelectrical impedance analysis in body composition measurement. NIH Technical Assessment Statement 1994. Am J Clin Nutr 1996; 64(Suppl): 524S–532S.

Spirometry: You will breath through a mouthpiece, and no harms associated to spirometry test are expected. You may expect cough and transient sickness after a forced breath.

Oxygen Saturation: No harms associated to oxygen saturation, determined using a pulse oximeter in a finger.

A physician (either Drs Sibila, Abuli or Subedhi) will be on-site during all experimental sessions should any complications arise. However, complications are very unlikely given the rigorous screening you will first undertake prior to admission to the study.

It must be noted that individual responses to the experimental procedures exist and you are encouraged to report any unusual sensations or symptoms to the investigator. You are permitted to end testing at any time for any reason.

10. WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

You will not directly benefit from this study; however, you will gain information regarding the structure and function of your heart and lungs at rest. We hope that the information learned from this study can be used in the future to benefit people suffering from chronic respiratory or cardiovascular disease.

11. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information [and/or samples] collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data [and/or samples] will not be able to be withdrawn for example where the data [and/or sample] is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data [and/or samples], please let your study doctor know. If your participation in this study includes enrolling in any optional studies, or long-term follow-up, you will be asked whether you wish to withdraw from these as well.

The study investigators may decide to discontinue the study at any time, or withdraw you from the study at any time, if they feel that it is in your best interests.

12. AFTER THE STUDY IS FINISHED

The tests performed in this study are not intended to be diagnostic and are not performed under diagnostic conditions. We will provide a copy of your results should you wish to discuss them with your physician.

13. WHAT WILL THE STUDY COST ME?

Participating in this study will not cost you anything. Any and all costs incurred during your participation will be paid for by the expedition.

14. WILL I BE PAID?

To cover any loss of earnings and/or daily expenses, we will provide you with $100 USD for your time.

15. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your rights to privacy are legally protected by law that require safeguards to ensure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the investigators and the Hospital de la Santa Creu i Sant Pau Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Any study related data or samples, sent outside of Nepal will be sent only to Spain and will be destroyed after use.

Disclosure of Race/Ethnicity

Studies involving humans now routinely collect information on race and ethnic origin as well as other characteristics of individuals because these characteristics may influence how people respond to different medications. Providing information on your race or ethnic origin is voluntary.

17. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Dr. Oriol Sibila or Dr..

18. SUBJECT CONSENT TO PARTICIPATE IN:

EXPOSITION TO EXTREME ENVIRONMENTAL HYPOXIA AND ITS EFFECT ON THE INFLAMMATORY AND CARDIOPULMONAR RESPONSE: BIOLOGICAL, GENETIC AND CLINICAL IMPACT.

Acronym: SHERPA

In signing this form you are consenting to participate in this research project and acknowledge you have been told you will receive a signed and dated copy of this form. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else.

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me

2 SIGNATURES

Printed name of subject

Signature Date

Printed name of witness Signature Date

Printed name of principal investigator/Designated representative

Signature Date Signature Date