FORM 1 – OUTLINE RESEARCH PROPOSAL

Principal Investigator[1]

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Collaborators[2]

1. Dr Julien V. Brugniaux PhD, Senior Lecturer in Health and Exercise Sciences (Bailey Lab)
2. Luke Liddle, MPhil student, Clinical Physiology (Bailey Lab)
3. Naomi Dodds, 3rd year medical student (Bailey Lab)
4. Kate N. Thomas, PhD student, School of Physical Education, Sport and Exercise Sciences/Department of Surgery, Dunedin School of Medicine, University of Otago, Dunedin 9054, New Zealand

Research title[3]

Cerebrovascular benefits of remote ischaemic preconditioning during ascent to high-altitude; implications for acute mountain sickness?

Lay summary[4]

Mountaineers sometimes experience splitting headaches when climbing to high-altitude, known as acute mountain sickness (AMS). We think this is because they simply can't get enough oxygen to their brain thanks to the lack of a molecule known as nitric oxide (NO) in the blood which helps increase blood flow. We think we can reduce AMS by asking them to perform special training that involves decreasing and then increasing blood flow to their legs using special "cuffs". We think this will help free-up more NO to get more blood and oxygen to their brains so that they'll feel way better.

Scientific proposal[5]

Background: Emerging evidence suggests that the ability to acclimatise to high-altitude is in part dependent on the delicate interplay between free radical stress and antioxidant defence. Excessive free radical formation can cause structural membrane damage, deplete NO bioavailability and increase susceptibility to AMS. Alternatively, at physiological, albeit undefined concentrations, free radicals are involved in the adaptive response to hypoxia (1). Novel strategies are therefore required to harness the beneficial aspects of free radical formation in an attempt to optimise acclimatisation. Remote ischaemic preconditioning (RIPC) may represent one such approach since it describes how transient non-lethal ischaemia-reperfusion of remote tissue can protect the brain against future free radical-mediated injury. However, its benefits have not previously been explored at high-altitude.

Aim: Determine for the first time if RIPC alters cerebrovascular acclimatisation.

Hypothesis: RIPC will result in free radical-mediated improvements in vascular endothelial function subsequent to increased vascular NO bioavailability that will extend to the cerebrovasculature enhancing cerebral perfusion and oxygenation thereby preventing AMS.

Methods: ***Design.*** Measurements will be performed at sea-level and upon arrival at basecamp (~4,800m) both at rest and during a maximal exercise challenge. ***Participants.*** Twenty four healthy men/women will be randomly assigned in a single-blind manner to either a RIPC (n = 12) or SHAM (n = 12) intervention. They will be asked to perform either 4 cycles of 5-min (5 min recovery) of 220 mmHg (RIPC) or 20 mmHg (SHAM) bilateral occlusion of the lower limbs to be performed in the morning and evening every day during their ascent to basecamp. ***Measurements.*** *Venous biomarkers* of free radicals (electron paramagnetic resonance spectroscopy), antioxidants (HPLC) and NO metabolites (ozone-based chemiluminescence). *Flow-mediated endothelium-dependent vasodilatation* of the brachial artery and *cerebral blood flow* through select arteries (Duplex/transcranial Doppler ultrasound). The latter will also permit assessment of complementary measures of cerebral haemodynamic function notably dynamic cerebral autoregulation (transfer function analysis), cerebrovascular reactivity to carbon dioxide and orthostatic tolerance. *Clinical symptoms* of AMS, cephalagia and neurocognitive function (clinically-validated questionnaires). *Exercise test* for the determination of maximal oxygen uptake (offline Douglas bag method).

Reference: 1. **Bailey DM, Rimoldi SF, Rexhaj E, Pratali L, Salmon CS, Villena M, McEneny J, Young IS, Nicod P, Allemann Y, Scherrer U, and Sartori C**. Oxidative-nitrosative stress and systemic vascular function in highlanders with and without exaggerated hypoxemia. *Chest* 143: 444-451, 2013.

Research requirements[6]

I. Hardware supplied by Bailey Lab:

Neurovascular:

Portable transcranial Doppler + probes + headsets (2kg)

Finometer Pro for measurement of arterial (non-invasive) blood pressure (5 kg)

Heart-rate monitors (Polar) + chest belts (negligible)

ECG module + powerlab for data assimilation (2kg)

Capnograph + mouthpiece + sampling line (0.5 kg)

Portable pulse oximeters (negligible)

Laptop (1kg)

Hardware for neurocognitive battery (pegboards etc, 0.5kg)

Cardiovascular:

Portable Duplex ultrasound + probe + holder (2kg)

Metabolic:

All hardware for processing of bloods (pipettes *etc*).

Mini-mountain centrifuge (2kg)

Cryopak (5kg unprimed and free of samples)

Hardware kindly requested:

1. Portable cycle ergometer (if not feasible, box-stepper + metronome)
2. Off-line oxygen uptake analysis (Douglas bags, Servomex analysers, Tissot spirometer *etc*)
3. An additional cryopak would be ideal if possible

II. Consumables supplied by Bailey Lab:

All chemicals, re-agents, buffers and blood sampling-related consumables will be provided (5kg).

Consumables kindly requested:

Access to liquid nitrogen for transport of bloods back to UK

Predicted mass of all hardware/consumables = ~20kg

[1]Title, full name, current post, department, institution, contact postal address, email address, telephone (including country and area code)
[2]If known. Title, full name, department, institution.
[3]Max 20 words
[4]Project summary in simple English. Max 100 words.
[5]Background; Aims and hypothesis; Methods. Max one side of A4 plus reference list
[6]Equipment; Consumables; Required Personnel; Max one side of A4

- Formatting
  - Please type information into table above and expand table as necessary
  - Min 12 point, min 1.5 line spacing, 2cm margins, times new roman, reference format as per Journal of Applied Physiology guidelines,
- Submission
  - Email one pdf file to j.h.macdonald@bangor.ac.uk
  - You may submit as many proposals as you wish
  - Closing date: 01.09.13, 1200, Greenwich Mean Time
  - You will receive confirmation of submission within five working days
- Queries
  - Contact Medical Expeditions Manaslu 2015 Research Lead
    - Jamie Macdonald PhD, Extremes Research Group, Bangor University
    - Email: j.h.macdonald@bangor.ac.uk
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