Extreme physiology, How much can the human body take?

Doctors at altitude

Monty Mythen MBBS, FRCA, MD
Smiths Medical Professor of Anaesthesia and Critical Care,
University College London, UK
National Clinical Lead,
Enhanced Recovery Partnership Programme
Department of Health (UK)
m.mythen@ucl.ac.uk

On behalf of The Caudwell Extreme Everest Research Team

Introduction: Caudwell Xtreme Everest was an observational cohort study of variation in human adaptation to progressive environmental hypobaric hypoxia conducted between England and Nepal in 2007.

Objectives: To describe the spectrum of adaptive responses in humans exposed to graded environmental hypobaric hypoxia and identify factors (physiological and genetic) associated with inter-individual variation in these responses. To explore the utility of this approach as a model for disease states where hypoxaemia (and/or cellular hypoxia) is a key feature (cause or consequence) of the disease and thereby improve understanding, and develop novel therapies in such conditions.

Design: Observational cohort study of progressive incremental exposure to environmental hypobaric hypoxia.

Setting: University human physiology laboratory in London, UK (75m) and 7 field laboratories in Nepal at 1300m, 3500m, 4250m, 5300m, 4250m, 6400m, 7950m and 8,400 (just below the summit of Mount Everest) .

Participants: 198 healthy volunteers and 24 investigators trekking to Everest Base Camp (5300m). A subgroup of 14 investigators studied at altitudes up to 8400m on Everest. The completion rate for planned testing was more than 99% in the investigator group and more than 95% in the trekkers overall.

Main outcome measures: Exercise capacity (VO_2 max and lactate (anaerobic) threshold) and exercise efficiency (ΔVO_2:ΔWork relationship), brain and muscle NIRS (at rest and during exercise), plasma inflammatory markers and nitrate metabolites, allele frequencies of known or suspected hypoxia responsive genes, spirometry, neurocognitive testing, pupilometry. In nested subgroups: microcirculatory imaging (SDF), muscle biopsies with proteomics and transcriptomics, continuous cardiac output measurement, arterial blood gas measurement, trans-cranial Doppler during exercise, gastrointestinal tonometry, thromboelastography and ocular saccadometry.

Results: Of 198 healthy volunteers leaving Kathmandu, 190 reached Everest Base Camp (5300m). All 24 investigators reached basecamp. Unique measurements were safely performed at extreme altitude, including the highest measurements of exercise capacity, cerebral blood flow and microvascular blood flow at 7950m and arterial blood gas measurement at 8400m. In four femoral arterial samples taken at 8400 m (27,559 ft), at which altitude the barometric pressure was 36.3 kPa, the mean PaO2 in subjects breathing ambient air was 3.28 kPa (24.6 mm Hg), with a range of 2.55 to 3.93 kPa (19.1 to 29.5 mm Hg). The mean PaCO2 was 1.77 kPa (13.3 mm Hg), with a range of 1.37 to 2.09 kPa (10.3 to 15.7 mm Hg) (ref below: Grocott et al. *N Engl J Med.* 2009*).*

Conclusions: This study demonstrates the feasibility and safety of conducting a large, controlled, healthy volunteer cohort study of human adaptation to hypoxia in this difficult environment. Systematic measurements of a large set of variables were achieved with high fidelity in 222 subjects at altitudes up to 5300 metres. The resulting dataset is a unique resource for the study of genotype:phenotype interactions in relation to hypoxic adaptation.

References

Cerretelli, P. 1976. Limiting factors to oxygen transport on Mount Everest. *Journal of applied physiology* 40, no. 5: 658-667.

Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE; Caudwell Xtreme Everest Research Group. 2009. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med.* no. 8;360(2):140-9.

Grocott, M, and H Montgomery. 2008. Genetophysiology: using genetic strategies to explore hypoxic adaptation. *High Alt Med Biol* 9, no. 2: 123-129.

Grocott, M, H Montgomery, and A Vercueil. 2007. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. *Crit Care* 11, no. 1: 203.

Grocott M, Richardson A, Montgomery H, Mythen M. 2007. Caudwell Xtreme Everest: a field study of human adaptation to hypoxia. *Crit Care*, no. 11(4):151.

Houston, CS. 1997. Operation Everest one and two. Studies of acclimatization to simulated high altitude. *Respiration* 64, no. 6: 398-406.

Houston, CS, JR Sutton, A Cymerman, and JT Reeves. 1987. Operation Everest II: man at extreme altitude. *J Appl Physiol* 63, no. 2: 877-882.

Marshall, R. P. 2002. Angiotensin Converting Enzyme Insertion/Deletion Polymorphism Is Associated with Susceptibility and Outcome in Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine* 166, no. 5: 646-650.

Martin DS, Levett DZ, Mythen M, Grocott MP; Caudwell Xtreme Everest Research Group. 2009. Changes in skeletal muscle oxygenation during exercise measured by near-infrared spectroscopy on ascent to altitude. *Crit Care*. No. 13 Suppl 5:S7.

Montgomery, HE, R Marshall, H Hemingway, S Myerson, P Clarkson, C Dollery, M Hayward, DE Holliman, M Jubb, M World, EL Thomas, AE Brynes, N Saeed, M Barnard, JD Bell, K Prasad, M Rayson, PJ Talmud, and SE Humphries. 1998. Human gene for physical performance. *Nature* 393(6682), no. 6682: 221-222.

Poli-de-Figueiredo, LF, AG Garrido, N Nakagawa, and P Sannomiya. 2008. Experimental models of sepsis and their clinical relevance. *Shock* 30 Suppl 1, 53-59.

Pugh, LG, MB Gill, S Lahiri, JS Milledge, MP Ward, and West JB. 1964. Muscular exercise at great altitudes. *J Appl Physiol* 19, 431-440.

Richalet, JP, P Robach, S Jarrot, JC Schneider, NP Mason, E Cauchy, JP Herry, A Bienvenu, B Gardette, and C Gortan. 1999. Operation Everest III (COMEX '97). Effects of prolonged and progressive hypoxia on humans during a simulated ascent to 8,848 M in a hypobaric chamber. *Adv Exp Med Biol* 474, 297-317.

West, JB, SJ Boyer, DJ Graber, PH Hackett, KH Maret, JS Milledge, RM Jr Peters, CJ Pizzo, M Samaja, FH Sarnquist, and al. et. 1983. Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 55, no. 3: 688-698.