Research on Mount Everest: Exploring Adaptation to Hypoxia to Benefit the Critically Ill Patient

JM van der Kaaij1,2, DS Martin1, MG Mythen1, MP Grocott1,4

1 Centre for Altitude Space and Extreme Environment Medicine University College London (UCL), Institute of Child Health, London, United Kingdom
2 Department of Anaesthesiology, VU Medical Centre, Amsterdam, The Netherlands
3 Smiths Medical Professor of Anaesthesia and Critical Care, Portex Unit, UCL Institute of Child Health, London, United Kingdom
4 Critical Care Research Unit, Southampton University Hospitals NHS Trust, Southampton, United Kingdom

Abstract - Critically ill patients often suffer from hypoxaemia to which the response of the human body is far from understood. As this category of patients form a heterogenous group, they are difficult to study. In contrast to animal and cellular models, a new paradigm was suggested by the University College London (UCL) Centre for Altitude Space and Extreme Environment (CASE) Medicine, involving exposure of healthy volunteers to environmental hypobaric hypoxia in a controlled manner. This is based on the assumption that ascent to high altitude will trigger adaptive processes similar to the ones occurring in critically ill patients suffering from hypoxaemia, thereby obtaining better understanding of adaptive and maladaptive processes caused by hypoxaemia in a clinical context. In the spring of 2007 the medical research expedition Caudwell Xtreme Everest (CXE) took place on the slopes of Mount Everest in Nepal. Twenty-four investigator subjects (from a total of 60 investigators) and 198 volunteer subjects were studied over a period of three months. Specific hypotheses about oxygen delivery, oxygen consumption and metabolic efficiency were tested. Inter-individual responses to environmentally induced hypoxaemia were described and beneficial phenotypes and genotypes sought. In this article an explanation of this approach to hypoxia research along with an overview of the CXE expedition are presented. The results available to date are described in detail. Ultimately, the aim is to translate the knowledge obtained into further interventional research and practice in the clinical setting in the hope of improving the care of patients in whom hypoxaemia is a fundamental problem.

Keywords - hypobaric hypoxia, hypoxia adaptation pathways, microcirculation, cellular metabolism, critically ill, translational research

Introduction

In critically ill patients, regardless of their underlying pathology, hypoxaemia (reduced arterial oxygenation) is common and may be caused by a variety of underlying pathologies [1]. Hypoxaemia, regardless of its cause, can result in tissue hypoxia (reduced cellular and mitochondrial oxygen availability). Hypoxia may generate a stimulus for cellular dysfunction, particularly when combined with systemic inflammation [2]. Our understanding of the human response to hypoxaemia is far from complete and difficulties that arise from studying the heterogeneous group of patients that populate intensive care units contribute to this. Animal and cellular models have been proposed to help elucidate mechanisms that may explain adaptation to oxygen deprivation but these approaches also have significant limitations [3-6].

Healthy individuals ascending to high altitude are exposed to a decline in the atmospheric partial pressure of oxygen (hypobaric hypoxia), which results in a reduction of inspired, alveolar and arterial partial pressures of oxygen. The physiological responses to this ‘insult’ are likely to be similar to responses evoked in hypoxaemic patients [7,8]. It is therefore hypothesized that a better understanding will be obtained of the processes that occur when patients succumb to sub-acute hypoxaemia as a result of disease, by studying the effects of hypobaric hypoxia in healthy volunteers [1]. This conceptual framework inspired a team of scientific and medical investigators to organise a research expedition in the spring of 2007 to Mount Everest in Nepal, the summit of which is the highest point on the surface of the Earth (8848m). The project was called Caudwell Xtreme Everest (CXE) and was organised by the University College of London (UCL) Centre for Altitude Space and Extreme Environment (CASE) Medicine.

During a three month stay at altitude, the team studied a total of 222 subjects as they walked to the base camp of Mount Everest (5300m) and went on to perform investigations in a sub-group of this cohort (‘climbers’) to a maximum altitude of 8400m on the mountain. The aim was to study individual physiological responses to sustained hypobaric hypoxia, measuring specific variables and relating them to genetic variations.

The ultimate and novel goal was that lessons learnt on the mountain would drive translational research in the clinical setting and directly benefit patients; in a sense bringing knowledge ‘from mountainside to bedside’ [1,7]. This review discusses the objectives and conduct of the expedition along with some of the results of studies published to date and their possible implications and relevance for practice in intensive care.

Correspondence

JM van der Kaaij
E-mail: JM.vanderKaaij@vumc.nl
Why is the mountain a good laboratory?
In the past a number of studies have been performed in hypoxic environments both at altitude in the field and in hypobaric chambers [9-14]. The Operation Everest series of studies had a duration of about six weeks with four to eight subjects. They were performed in the controlled environment of a decompression chamber to exclude ‘mountain’ factors such as cold, inadequacies in intake of food and fluids, exhaustion, and anxiety [13]. Their aim was to understand better the adaptation of humans to environmental hypoxia by examining changes in the oxygen transport system. Stresses found in a mountainous environment were taken away by providing ambient temperature control, availability of excellent and ample food, access to communication devices such as radio and telephone, and exercise facilities. Despite the constitution of this ‘hypobaric paradise’ the subjects experienced similar symptoms to those found in subjects participating in research in a true mountainous environment: sore throat and cough, sleep disturbance, decreased mental and physical activities [13]. Furthermore, comparable values to those measured in field studies were found for many variables, such as maximum oxygen uptake and weight loss [13], suggesting that the ‘mountain stress factors’ are not significant confounding factors for studies conducted in the field. Moreover, chamber studies are very resource intensive due to the requirement for continuous medical and technical cover. Additional problems for large chamber studies are the limited availability of hypoxic chamber facilities, the risk of decompression sickness in investigators [15,16] and the difficulties of recruitment of volunteers to spend prolonged periods in close confinement. Of note, the environmental conditions within the tents and shelters where experiments were conducted during CXE, showed substantially less variation than ambient conditions, and were similar to many laboratory environments [17].

Hypotheses of cxe
The CXE expedition set out to address two primary hypotheses [18,19]. The first hypothesis was that factors other than those related to global oxygen transport (cardiac output, ventilation, and

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<tr>
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<tr>
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<tr>
<td>A-a oxygen difference (kPa)*</td>
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<tr>
<td>Haemoglobin (mmol/liter)§</td>
<td>12.54</td>
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* PaCO2 denotes partial pressure of arterial carbon dioxide, PAO2 partial pressure of alveolar oxygen, PaO2 partial pressure of arterial oxygen, and SaO2 calculated arterial oxygen saturation.
† To convert the values for PaO2, PaCO2, PAO2, and the alveolar-arterial oxygen difference to kilopascals, multiply by 0.1333.
‡ These values were calculated with the use of the algorithms currently approved by the Clinical Laboratory Standards Institute [37].
§ The values obtained for haemoglobin are the mean values of measurements obtained at 5300 m (17,388 ft) 9 days before and 8 days after the arterial blood sampling.
¶ The respiratory exchange ratio was measured at an elevation of 7950m while the subject was resting.
|| No measured respiratory exchange ratio was available for this subject; the value was derived from the mean values for the other three subjects.
** PAO2 was calculated with the use of the full alveolar gas equation.

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haemoglobin concentration) would in part explain the observed inter-individual differences in performance at altitude. This was based on studies that have previously demonstrated that at altitude, maximum oxygen uptake (VO₂ max), a measure of maximum exercise capacity, remains reduced compared to sea level values despite adequate acclimatization, reflected by normalization of arterial oxygen content (CaO₂) [20-22]. Furthermore, exercise capacity at high altitude differs markedly between individuals and these differences cannot be explained by simple measures of oxygen flux, or by specific differentiating physiological features at sea level [23]. These other factors that were investigated included alterations in the microcirculation that might limit oxygen delivery within the tissues [24] and a down-regulation of cellular metabolism [25,26].

The second hypothesis was that genotype differences would explain a substantial proportion of inter-individual variation in environmentally induced phenotypes. In lowlanders ascending to altitude, as well as in critically ill patients, insertion variants of the angiotensin converting enzyme (ACE) gene have been associated with better performance and improved outcome respectively [27-31]. Furthermore, the assumption is that large populations could only have lived for generations in an extreme environment of hypobaric hypoxia by evolving towards a beneficially adapted genotype (and phenotype) [32]. We therefore explored whether the genotypes associated with beneficial phenotypes in healthy lowland subjects exposed to hypoxia for days and weeks ('rapid responders' to hypobaric hypoxia) could reveal underlying adaptive mechanisms [33].

Methodology of the studies

Design

We approached the hypotheses with a number of core and supporting studies, together forming the foundation of this longitudinal observational cohort study. A total of 222 healthy subjects were studied prospectively whilst being exposed in a progressive and controlled manner to environmental hypobaric hypoxia, during a trek from Lukla (2800m) to Everest Base Camp (EBC, 5300m) in Nepal, in the spring of 2007.

A small parallel study (up to 3900m), the Smith Medical Young Everest Study, acquired unique observational data on a group of nine children between six and thirteen years of age. Results of these observations and its implications are described in detail elsewhere [34]. Approval for all studies was gained from the UCL Committee on the Ethics of Non-NHS Human Research and was accompanied by a comprehensive risk management plan.

Subjects

The study participants were divided in two distinctive groups, ‘trekkers’ and ‘investigators’. Recruitment of trekkers was from the general public who expressed an interest in participating in

![Fig 2-A. Setting up the laboratory in Camp 2, in the Western Cwm of Everest (6400m)](image)
The expedition, following public advertisements. This trekker group comprised 198 subjects of which 73 were female. The investigator group was composed of 24 subjects who were selected from the total of 60 investigators involved in the planning and conduct of the project in the field. The investigators were further divided into two cohorts: ‘base camp team’ (n=10, 4 females) who remained at Everest Base Camp (EBC) (5300m ± 500m), and ‘climbers’ (n=14, 2 females) who ascended to various heights on Mount Everest, with the maximum at 8848m. Selection criteria as well as baseline characteristics of the study population are described elsewhere [17]. The set-up was as such that the prolonged stay at high altitude of the investigators would also enable follow-up of adaptation to more chronic hypoxia.

**Ascent profile**

All subjects were tested in London (sea level, 75m) prior to departure to Nepal. Ascent profiles differed between trekkers and investigators but within their respective groups, ascent profiles were identical throughout (figure 1) [35]. The duration of ascent for the trekkers was one to three days slower than the number of days usually scheduled by many commercial operators. It was deliberately designed as such to minimise the incidence of altitude related illness in the subjects and to enable as many of them as possible to complete the trek and provide a full dataset. Once testing at EBC was completed the trekkers descended back to Lukla whilst the base camp staff investigators remained at EBC (± 500m) and climber-investigators ascended and descended the mountain until the end of the expedition.

**Logistics**

The size of the expedition together with the remoteness of the research locations also presented a substantial logistic challenge. In total 26,000 kg of equipment was shipped to Kathmandu (Nepal) from where over a half million individual items needed to be transported to the various field laboratories. This was achieved by a dedicated logistics team working in partnership with a trekking/mountaineering company. The roles of over 40 Sherpas were invaluable. In the years building up to the CXE 2007, extensive validation of laboratory equipment was done in environmental chambers. A pilot expedition to the Alps (in 2006) and two successful expeditions to the summit of Cho Oyu (8201m) (in 2005 and 2006) were undertaken to ensure investigators and equipment would operate adequately at these high altitudes.

**Fig 2-B.** Measuring oxygen consumption via breath-by-breath gas analysis in a member of the climbing team in the laboratory at 7950m (South Col)

**Fig 3.** Member of the climbing team ‘dressed’ with an arterial line and nasogastric tube awaiting his lactate threshold cardio-pulmonary exercise test and gastric tonometry
Studies
A total of ten different studies were designated as ‘core’ and all subjects participated in these unless exclusion criteria were met [17]. The studies could be divided into eight topics:

- oxygen transport and metabolic efficiency (breath-by-breath analysis during cardiopulmonary exercise at set workloads to obtain insight in oxygen economics with increasing levels of hypobaric hypoxia);
- maximum exercise capacity combined with assessment of leg muscle and brain satiuation during cardiopulmonary exercise;
- measurement of systemic saturations;
- measurement of inflammatory biomarkers and markers of tissue injury and oxidative stress, and nitric oxide metabolites, where the aim was to identify biomarkers associated with beneficial and maladaptive responses to the exposure to hypobaric hypoxia, and to explore the interaction between hypoxaemia and inflammation;
- neurocognitive functioning (neuropsychometric tests assessing changes in skills as cognition, memory, attention and fine motor skills, following exposure to longer-term environmental hypoxia. In addition Trans-Cranial Doppler (TCD) measurements, pupillometry, saccadometry and retinal photography, as well cerebral tissue oxygenation (NIRS) were collected in order to correlate with the functional measures of cognition);
- lung function;
- genetophysiology. Blood samples from all subjects taken in London provided the genetic material for analysis of specific candidate genes, genes known or believed to be involved in the response to hypoxia [33]. These will be correlated with the observed phenotypes in their response to exposure to hypobaric hypoxia;
- symptom diary. This included a daily assessment of symptoms and simple physiological variables as well as a short exercise challenge.

Studies were conducted at sea level (75m) and thereafter during the trek sequentially in Kathmandu (1300m), Namche Bazaar (3500m), Pheriche (4250m), and Everest Base Camp (5300m). The climbing team was also studied at Camp 2, in the Western Cwm of Everest (6400m) (figure 2-A) and at the South Col (7950m). The studies were conducted at sea level (75m) and thereafter during the trek sequentially in Kathmandu (1300m), Namche Bazaar (3500m), Pheriche (4250m), and Everest Base Camp (5300m). The climbing team was also studied at Camp 2, in the Western Cwm of Everest (6400m) (figure 2-A) and at the South Col (7950m) (figure 2-B) and at the Balcony (8400m). Laboratory characteristics are described elsewhere [17]. Subgroups of both groups of subjects participated in additional studies that, by the nature of the research question, were not performed in every single laboratory. These studies included description of the sublingual microcirculation, gastric tonometry (figure 3), brain magnetic resonance imaging (at sea level before and after the trek) as well as vascular changes (Doppler ultrasound), cardiac function (electrocardiography and echo), smell, oxygen transport at extreme altitude (arterial blood gases), and mitochondrial functioning (muscle biopsies).

Summarized results so far
To our knowledge, this is the largest group of subjects that has been studied in such detail at altitude. Although trekkers and investigators followed the same route and were submitted to the same set of core studies, data from these groups can be compared but not combined – due to the highly-selected nature of the investigator group. Published data so far are mainly from the investigators group and from the preparatory Cho Oyu expeditions, due to the vast amount of data obtained from the trekkers. Developments in technology allowed the use of novel devices for measurements and imaging of physiological and pathophysiological changes at altitude and provided a first validation of the use of some of these devices at altitude. Testing, trekking, and climbing goals were achieved in a safe and controlled manner.

Arterial blood gases and oxygen content
Direct field measurements of the arterial partial pressure of oxygen (PaO2) were made and CaO2 calculated in 10 climbers breathing ambient air at different altitudes up to a maximum of 8400m, in order to define the limits of tolerance to hypoxia [36]. Arterial blood samples were obtained at 75m (London), 5300m (EBC), 6400m (Camp 2), 7100m (Camp 3), and because of adverse weather conditions at 8400m (the Balcony) instead of the summit (8848m). All subjects were taken off supplemental oxygen (breathing ambient air) for at least 20 minutes prior to blood sampling. In the four subjects tested at 8400m, the mean arterial blood gas measurements and calculated values for pulmonary gas exchange were as shown in Table 1. Up to an altitude of 7100m, the mean arterial oxygen was comparable to what was measured at sea levels (197.1 ml/L). At 8400m the mean CaO2 was decreased to 145.8 ml/L and showed marked inter-individual variability (range 89.7-190.7 ml/L). The variability could be explained by inter-individual variation in the briskness of their hypoxic ventilatory response and depression, which physiologically occur following acute exposure and re-exposure to hypobaric hypoxia. Upon heavy exercise the alveolar-arterial oxygen difference (Aa-DO2) increases as sea level [38]. Wagner et al. not only confirmed this observation but also showed that resting Aa-DO2 levels decrease with falling PaO2 [39]. Furthermore, he showed that the measured and predicted Aa-DO2 levels differed with increasing levels of exercise and with increase in altitude [39]. Based on both theory and empirical data [40], we expected the Aa-DO2 in the climbers to be around 0.27kPa. However, the mean calculated Aa-DO2 was 0.72 kPa (range 0.39-1.04 kPa). This higher gradient may have been the result of subclinical pulmonary oedema or inhomogenous pulmonary vasoconstriction affecting ventilation perfusion matching [41,42], thereby contributing to the low measured PaO2. The finding that none of the subjects were severely hyperlactatemic despite the chronic hypoxaemia is consistent with findings in resting subjects at a simulated altitude of 8848m [20]. This supports the idea that cellular adaptation to chronic hypoxaemia may tend towards a more efficient use of oxygen preventing anaerobic cellular metabolism, rather than relying on anaerobic metabolism.

Microcirculatory blood flow at high attitude
The first direct visualisation of the sublingual microcirculation was made in 12 healthy volunteers ascending the 8201m high mountain Cho Oyu in 2006 [43]. Recordings were acquired using sidestream dark-field (SDF) imaging by a hand-held microscope emitting green light from its tip at a wavelength of 548nm to illuminate the sublingual mucosa [24, 44]. This pilot study established
the use of the SDF camera in this environment in visualising the microcirculation and obtaining quantitative data. On Everest, further images were obtained in the investigators group up to an altitude of 7950m [45]. Based on the findings in the pilot study [44] it was hypothesized that hypobaric hypoxia would reduce the blood flow within the sublingual microcirculation and increase the capillary vessel density. From the base camp staff (EBC) subjects (n=10) images were obtained at 75m, 3500m, on arrival at 5300m (5300m-a) and 54 days later at 5300m (5300m-b). The climbers (n=14) were studied at these same altitudes and furthermore at 6400m and 7950m. At this latter altitude, supplemental oxygen was administered to the subjects prior to and during imaging. From the images of all subjects at every study point, a microcirculatory flow index (MFI) (no flow / intermittent flow / slow flow / continuous or normal flow) could be calculated. Compared with sea level, the median MFI was significantly reduced at all altitudes, both in small (< 25 μm diameter) and medium-sized (26-50 μm diameter) vessels. MFI in these vessels after prolonged stay at altitude was significantly lower than on arrival at 5300m. Mean vessel density increased significantly at all altitudes with no further change during prolonged stay. The climbers compared to the EBC-subjects showed a significantly lower MFI in small and medium-sized vessels. Supplemental oxygen at 7950m tended to further reduce median MFI, and increase vessel density, but inter-individual variability was seen. Peripheral oxygen saturation (SpO₂), taken at every altitude during image-acquisition, did not correlate with any microcirculatory measurement, nor did the haematocrit. Although the used technique has its limitations [45], the described findings support previous work on this imaging modality [44].

The interpretation of the results, however, is not straightforward. A possible explanation for the increase in vessel density could be recruitment of ‘resting’ vessels in the microvascular network initiated by hypoxaemia, leading to a reduction of the intercapillary distance, slowing of blood flow, and shortening of tissue transit time [45]. Increase in vessel density could also follow neovascularisation, promoted by increased levels of vascular endothelial growth factors [45,46]. Exploring these and alternative underlying mechanisms is required to understand the microcirculatory response to chronic hypoxaemia at altitude and in critically ill patients, and warrants further investigations.

Tissue oxygenation
Near infra red spectroscopy (NIRS) is a non-invasive technique for continuous monitoring of tissue and cerebral microcirculatory oxygenation by reflecting the venous haemoglobin oxygen status [47]. We used this technique to observe changes in tissue oxygen saturation (StO₂) in the vastus lateralis muscle during incremental cardiopulmonary exercise testing, as the capacity to exercise is governed by the equilibrium of oxygen supply and utilisation [48]. Good quality data were obtained at sea level, on arrival and before departure from EBC 5300m from 16 of the 24 investigators (figure 4 and 5). The ‘base camp team’ subjects, who were exposed to a constant level of hypobaric hypoxia during prolonged stay at EBC, showed a more rapid decrease in muscle oxygenation towards the end of the two months. In comparison, a slower rate and smaller magnitude of desaturation was seen in the ‘climbers’ subjects. This may be explained by a higher haemoglobin level in the ‘climbers’.

Figure 4. Graph representing a Near-Infrared Spectroscopy (NIRS) plot, taken at sea level (75m). [A], start of unloaded cycling; [B], start of loaded cycling; [C], maximum oxygen consumption.

Figure 5. Graph representing a Near-Infrared Spectroscopy (NIRS) plot (of the same subject as represented in Figure 4) at altitude, obtained after 54 days at Everest Base Camp (5300m). [A], start of unloaded cycling; [B], start of loaded cycling; [C], maximum oxygen consumption.
due to exposure to a more severe level of hypobaric hypoxia (higher altitude) with corresponding increase in CaO₂. Alternatively they may be protected by mechanisms following the process of hypoxic preconditioning, secondary to periods of exposure to more severe hypobaric hypoxia. These mechanisms could involve changes in the microcirculatory blood flow to the skeletal muscle, influences on the affinity of oxygen to haemoglobin or its ability to diffuse within the muscle; all processes taking place at the distal end of the oxygen cascade, the peripheral circulation [48].

Skeletal muscle energetics

31P magnetic resonance spectroscopy (31P-MRS) and magnetic resonance imaging (MRI) were used to assess the metabolic response in skeletal muscle to hypobaric hypoxia [49]. A total of seven trekkers and seven climbers (of whom four summited the 8848m high Mount Everest) were studied prior to departure to Nepal. A protocol of a series of plantar flexion exercises and recovery was followed whilst the subject was in the bore of the magnetic resonance system. Muscle morphology and energetics measurements were taken following each exercise or recovery bout. All trekkers were restested within 48 hours after returning from Everest Base Camp (5300m) to sea level. All climbers ascended to at least 7950 m (South Col). Five of them were restested within seven days following their return to sea level. Pre-trek, a significant difference was seen in muscle cytosolic inorganic phosphate (P), the climbers having a higher concentration. Furthermore, the climbers had better pre-trek mitochondrial function than the trekkers, supported by significantly shorter phosphocreatinine recovery half-times (PCrᵣ₁/₂) in the climbers. Whether this is a result of self-selected beneficial phenotype (experienced climbers knowing to respond well to exposure to high altitude versus altitude-naive trekkers), stable modifications in phenotype following altitude exposure, unusually persistent conventional physiological adaptations caused by repeated hypoxia exposure, a combination of these suggestions or other underlying mechanisms is unknown and warrants further investigation [49]. The effect of altitude exposure to muscle morphology and energetics was similar in both groups: post-trek, resting cytosolic [P] was raised significantly to pre-trek and a loss of 4% calf muscle cross sectional area was found significant. With unchanged PCrᵣ₁/₂ this finding showed a reduction of the muscle aerobic capacity. Nevertheless, that did not affect the muscle function as exercises could be completed in a similar way post-trek to pre-trek. Furthermore, exercising skeletal muscle high energy phosphate metabolites remained unchanged. The underlying mechanisms for the total of findings require further specifically targeted experiments.

Cardiac function and energy metabolism

It is thought that hypoxia from impaired oxygen delivery to the heart as a result of coronary atherosclerosis, activates hypoxic signalling pathways, thereby mediating diastolic dysfunction [50]. We therefore hypothesized that hypobaric hypoxia may cause changes in cardiac high energy metabolism resulting in cardiac dysfunction [51]. In 14 trekkers cardiac energy metabolism (expressed by the phosphocreatinine/ATP ratio) and measurements of cardiac mass, volumes, and function were assessed using 31P magnetic resonance spectroscopy (31P-MRS) and echocardiography and magnetic resonance (MR) imaging respectively. Measurements were taken at sea level within three weeks prior to departure for Nepal, then within 48 hours after return from the trek to Everest Base Camp (5300m) and again six months later. Post-trek compared to pre-trek, a significant reduction was seen in left ventricular mass, both left and right ventricular stroke volumes, and peak left ventricular filling rates (assessed during diastole and mitral inflow, expressed as the ratio between the passive filling of the ventricle (Early wave) and the active filling with atrial systole (Atrial wave), the E/A ratio. Furthermore, PCr/ATP ratio was found to be decreased by 18%. All observed abnormalities reversed to pre-trek measurements at the six months interval. The findings of reduced myocardial energetics are similar to observations in patients with limited oxygen delivery from coronary disease [52], native high altitude-acclimatized Sherpas [53], and animals [54]. They suggest that a reduction in cardiac high energy levels may be a universal response to periods of prolonged reduced oxygen availability [51]. The underlying cellular mechanisms are unknown and require further investigation to understand its implications for cardiac metabolism and function in order to advance our understanding of hypoxia-related disease.

Discussion: the journey from mountainside to bedside

The CXE Research Group had a mission: “to conduct research into hypoxia and human performance at extreme altitude aimed at improving the care of the critically ill and other patients where hypoxia is a fundamental problem” (www.xtreme-everest.co.uk). Studying healthy volunteers has the advantage of observations not being influenced by specific disease or medical intervention components as would be the case in a study population of patients, especially the heterogeneous group that critically ill patients form. The identical ascent profiles followed in each cohort meant that any physiological differences detected between individuals were likely to be a result of variability in adaptation to hypoxia, rather than differential hypoxic exposure. The large quantity of data obtained during the CXE expedition from 222 subjects being gradually exposed to hypobaric hypoxia, gives significant statistical power to explore inter-individual variation in adaptation to hypoxia. The obtained physiological variables from all subjects at different altitudes, in combination with analysis of biomarkers, and transcriptomic and proteomic analysis of cellular material derived from muscle biopsies, should provide insight into functional changes in cellular and mitochondrial oxygen use in response to hypobaric hypoxia. Moreover, it may disclose novel mechanisms controlling cellular function in hypobaric hypoxia and in disease. Eventually we hope to be able to distinguish ‘rapid responsive’ phenotypes from ‘slow responders’. A decrease in the partial pressures of oxygen within the human body, evokes a response in transcription of genes involved. A series of mechanisms evolve in an increase in levels of Hypoxia-Induced Transcription (HIF) factor [33,55]. Heterodimers HIF-1 and HIF-2 αβ are very likely to play a role in the acclimization changes following exposure to hypoxia, as they activate the transcription of target genes involved in responses to changes in oxygen levels [55]. Furthermore, in mice it has been demonstrated that partial deficiency of HIF-1 α impairs the physiological response
to both continuous and intermittent hypoxia [55]. Differently said, target sequences on genes will vary between genes, thereby not eliciting the same amount of expression between each individual upon exposure to hypoxia [33]. Analysis of genetic material and comparison between the two phenotypes is likely to reveal variations in allelic frequencies, resulting in changes in gene products as well as original candidate genes [33] to which treatment could ultimately be targeted. Separately, the pathophysiologic insights deriving from this model of field study will require validation by applying them to the clinical setting. Use of the numerous technical devices could be of value in this. In the future, critically ill patients might be assigned to ‘good adaptor’ or ‘bad adaptor’ genotypes and alternative treatments administered. Target blood gas values might be redefined and permissive hypoxaemia evaluated in these ‘good adaptor’ patients. Furthermore, the fraction of administrated oxygen to patients suffering from chronic hypoxaemia might become ‘genotype-directed’ as too high a concentration of oxygen might worsen already maladaptive response processes [45].

The preliminary results of the CXE expedition will drive new research in healthy volunteers, in the hypobaric hypoxic environment and in patients in the clinical environment. The results so far have generated new hypotheses and the possibility of future interventions. Last summer, UCL CASE Medicine embarked upon a new three-week project, Xtreme Alps 2010 to the Capanna Regina Margherita (4554m), where the focus was on an interventional study along with novel observational studies. Ultimately, the hope is that this approach will contribute to a better understanding of the pathophysiologic processes involved in adaptation to hypoxaemia and thereby improve care and outcome for the critically ill patients where this is a problem.

Conclusion

CXE demonstrated that it was possible to safely conduct a longitudinal observational cohort study of a large group of subjects in a natural hypobaric environment. By using this model, the CASE Medicine team hope to obtain better insights into the different components of hypoxia adaptation pathways and to define genes associated with a good response to a hypoxic insult. Ultimately the goal is to translate this knowledge to the clinical setting, bringing it from mountainside to bedside, so that critically ill and other patients suffering from hypoxia will benefit from specific targeted therapies.

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