Caudwell Xtreme Everest

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The study of human physiology perturbed by exposure to extreme environments has been proposed as a useful approach for obtaining novel data to improve our understanding of both physiology and pathophysiology. Parallels between physiological patterns of response at altitude and in critically ill patients have been suggested. Genetic associations with beneficial adaptation or outcome are common to both contexts. Caudwell Xtreme Everest, a study of adult human physiological responses to progressive environmental hypoxia, was designed to provide data to improve understanding of responses to hypoxia in critical illness. A smaller parallel study described responses to more moderate altitude in children (Smith's Medical Young Everest Study). The strengths and weaknesses of these studies will be discussed along with a summary of the data collected.

The Caudwell Xtreme Everest (CXE) research project was designed to explore human adaptation to hypobaric hypoxia in order to improve understanding of responses to hypoxemia and cellular hypoxia in critically ill patients.[1] A large cohort of healthy volunteers was studied before and during exposure to progressive environmental hypoxia. The aim of the study is to explore variation between individuals in the pattern of response to hypoxia and to identify factors that contribute to this variation. Specific hypotheses relating to tissue and cellular oxygen handling and genotype-phenotype interactions are being explored. The ultimate goal is the development of new treatments and approaches in the care of the critically ill resulting in improved patient outcomes. The Smiths Medical Young Everest Study (SMYES) is a smaller parallel study of children ascending to more moderate altitude and provides novel data in a neglected study group. This article/lecture will explain the underlying concepts behind this approach to exploring human physiology and outline the form and scope of the CXE and SMYES projects.

EXTREME ENVIRONMENT PHYSIOLOGY

CXE developed from the general premise that human physiological and pathophysiological responses to extreme environments can provide novel data that may lead to improved understanding of clinical problems. The hope is that knowledge obtained in this way might lead to the development of new therapeutic strategies resulting in improved patient outcomes. In the context of human physiology and medicine, an extreme environment may be defined as any environment where humans require either physiological adaptation or technological innovation in order to survive.[2] Simple physiological stress does not define an extreme environment; there must be a risk of illness or death in some, if not all, exposed individuals in order to justify the requirement for adaptation or innovation. Although some would propose that the psychological and sociological characteristics of an environment should be incorporated in this definition, this can result in difficulty in distinguishing the simply unpleasant from the potentially dangerous (where survival may be at stake).

This approach of studying healthy humans in extreme environments is justified if three conditions are met: the data produced should be shown to be valuable; the data is obtained more efficiently using an extreme environmental study or cannot be obtained in any other way; and the risk of the environment is acceptable to the subjects. The last of these conditions is made explicit by written informed consent that clearly includes discussion of any environmental risks of the study. Clinical benefit is most readily apparent when a new finding leads directly to a change in practice (e.g., novel therapeutic agent or management strategy) resulting in improved outcomes for patients. Benefit may also be obtained by observations or empirical findings leading to developments in understanding of pathophysiology that contribute more generally to future clinical developments.

ADAPTATION TO HIGH ALTITUDE AS A MODEL FOR CRITICAL ILLNESS: THE CXE HYPOTHESES

The role of hypoxia in critical illness and the possible relationship between responses to hypoxia at high altitude and critical illness have been explored elsewhere.[3] Cellular hypoxia may be both cause and consequence of a variety of conditions common in critically ill patients. Few if any critically ill patients do not have marked cellular hypoxia in at least one organ system. Hypoxia may trigger inflammatory pathways, and inflammation may in turn lead to localized or more generalized hypoxia. Adaptive responses to hypoxemia at altitude in part reflect patterns of response in critical illness. Oxygen consumption and flux (delivery) is commonly increased in the acute phase of critical illness and following the trauma of major surgery; the response to acute hypoxemia during early exposure to altitude is to increase oxygen flux (elevation of cardiac output and hemoglobin). At this stage, augmenting oxygen delivery by increasing blood flow or oxygen content may improve outcome in critically ill and post-surgical patients. Conversely, in established critical illness the reverse is true: oxygen consumption tends to fall and deliberately increasing oxygen delivery has no benefit or may even cause harm. A similar pattern pertains in well-acclimatized individuals where limitation of oxygen consumption seems to be an important feature of the adaptive process. Furthermore, allelic variants of ubiquitously expressed genes (Angiotensin Converting Enzyme) associated with improved outcomes in several critical illnesses (e.g., ARDS) are also associated with improved performance at extreme altitude.

A paradox at the center of altitude physiology is that variations in performance at altitude are not explained by either sea level performance or resting oxygen delivery at altitude (product of cardiac output and oxygen content). Furthermore, relative differences in physiological variables thought to be responsible for "acclimatization" (e.g., ventilation, cardiac output, and hemoglobin) do not explain differences in observed performance. Changes in tissue or cellular oxygen handling might provide an explanation for this puzzling situation. Possible mechanisms may include alterations in microcirculatory flow leading to impaired cellular oxygen delivery, limitation of oxygen diffusion within the tissues, and variation in relative cellular metabolic efficiency (modification of the relationship between oxygen consumption and work). If cellular metabolic efficiency does change in some subjects, and the underlying mechanisms can be identified, then the implications would be significant. A therapy capable of altering the relative efficiency of cellular oxygen use might allow less aggressive targeting of oxygen delivery in some critically ill patients. This in turn has the potential to reduce the known adverse effects associated with some of the strategies to improve oxygen availability at a cellular level (mechanical ventilation, high-inspired oxygen levels, blood transfusion) and potentially improve patient outcomes.

CXE set out to test the hypotheses that alterations in performance at high altitude might be explained by changes in microcirculation blood flow (and hence local oxygen delivery) or by alterations in cellular "metabolic efficiency," the ratio between work output and oxygen consumed. We also set out to explore the hypothesis that inter-individual variation in observed adaptive changes would be related to variation in the frequencies of alleles of candidate genes. Specific candidate genes will include those implicated in mediating changes in "metabolic efficiency," known hypoxia sensitive genes, and genes known to be unregulated during fetal life. The possibility that physiological pathways identified as beneficial or maladaptive in fetal life, may be associated with similar effects in adults exposed to conditions of profound hypoxia/hypoxemia is particularly intriguing. Recent advances in the understanding and investigation of fetal gene expression may give new life to Sir Joseph Barcroft's oft quoted analogy of "Everest *in utero*".[4]

Clearly the study of healthy individuals exposed to hypoxia at high altitude has limitations as a model for critical illness. However, alternatives may have equivalent or greater limitations and studies in critically ill patients are fraught with difficulty. Patients with critical illness are a heterogeneous population. They have a variety of presenting complaints, preexisting illness, and subsequent patterns of organ failures and are receive a variety of treatments. One consequence of this heterogeneity is that separating out the specific effects of an individual variable can be very difficult: the signal to noise ratio is very low. The limitations of animal models have been highlighted by the repeated failure of antisepsis treatments that have shown no benefit in humans despite promising results from studies in animals. Cellular and molecular studies are an important component of patient, volunteer, and animal studies, but on their own are no substitutes for exploring integrated physiology at a whole organism level. Increasingly, complex computer models have huge potential, but the validity of current models is still uncertain and they rely on iterative process with regular "reality checks" from human data. Studies in hypobaric chambers are a possible alternative to field studies at high altitude but have several disadvantages. Prolonged chambers studies are expensive, not least due to the requirement for continuous medical and technical staffing and capacity is limited (CXE involved more than 11 person years of subject exposure to hypobaric hypoxia). Finally, recruitment of more than 200 healthy volunteers for research during a trek in the Himalaya is feasible; it is doubtful whether the same could be achieved for a 2-week chamber exposure.

THE CAUDWELL XTREME EVEREST STUDY

CXE is the largest human high-altitude experiment ever conducted and builds on work conducted during previous high altitude[5] and chamber studies.[6] The strengths of CXE are the large number of subjects studied and the unique data collected near to the summit of Everest. During the first 6 months of 2007, more than 200 healthy volunteers were studied at sea level in London and at four field laboratories at increasing altitudes up to 5300 meters (Everest Base Camp) in Nepal. Fifteen climbing investigators went through the same tests and then ascended high on the mountain to make novel measurements up to and above 8000 meters. More than 60 investigators were involved in data collection. The strengths of CXE recruited many more subjects and many more subjects and conducted.

The core studies were designed to map out changes in exercise capacity and exercise efficiency during progressive exposure and adaptation to the hypoxic environment. Oxygen consumption was measured using Cardiopulmonary Exercise Testing (breath-by-breath respiratory gas analysis) while pedaling a cycle ergometer. Subjects were exercised to exhaustion to explore exercise capacity (anaerobic threshold and maximum oxygen consumption) while exercise efficiency was investigated using a steady-state protocol. During exhaustive exercise cerebral and muscle tissue oxygenation were monitored using Near-Infrared Spectroscopy. Subjects filled in a daily symptom diary and recorded simple physiological variables (including oxygen saturations) before and after a standardized exercise challenge (CXE Step Test). Additional studies on all subjects included spirometry, and a detailed neurological assessment ranged from simple pupillary responses to a complex neurocognitive battery lasting up to 45 minutes.

Subgroups of the base-camp and climbing investigators were studied in more depth. ECG, echocardiography, transcranial Doppler recording of the middle cerebral artery and real-time imaging of the microcirculation provided valuable data. Invasive techniques including intra-arterial cannulation, muscle biopsy, and gastrointestinal tonometry allowed more precise description of adaptive changes. Arterial access allowed continuous monitoring of cardiac output and blood pressure during exercise as well as serial sampling of biological markers. Muscle biopsies will allow us to explore the transcriptome and proteome in order to explore whether observed variations in allelic frequencies result in changes in gene products. Conversely, the availability of tissue to explore patterns of transcription and expression may allow identification of novel candidate genes to explore the relationship between observed phenotype and allelic variation.

Although complex imaging techniques are impractical in remote environments, several studies involved Magnetic Resonance Imaging (MRI) before and after the altitude exposure. These studies explored both structural predisposition to hypoxia related pathology and, in the climbers, subtle changes associated with prolonged significant hypoxemia. In addition, a small group underwent functional MRI studies and these should contribute substantially to our understanding of the metabolic changes induced by prolonged exposure to hypoxia.

Higher on the mountain, arterial blood gases were obtained at 8400 meters while descending from the summit and a novel semi-closed breathing system was evaluated above 6000 meters.

The SMYES study followed 9 children of 6 years and older as they ascended to nearly 4000 meters in the foothills of Everest. The children were already traveling to the region with their parents who were involved in the CXE study and the opportunity was taken to obtain some simple observational data. Measurements included oxygen saturations, end-tidal CO_2, spirometry, sleep studies, and symptom scoring. These data are among the first available in this group of subjects and provide a stepping stone to future studies as well as demonstrating the feasibility of safely studying children in this environment.

CONCLUSION

The output of these studies so far is a huge amount of novel data. Data entry on the main study database was completed in December 2007, and the dataset is currently being validated and quality controlled. Exercise test analysis and data management will be completed by June 2008. The first of a planned series of primary publications are currently in peer review. The investigators hope that as the data is analyzed and the hypotheses confirmed or refuted, that a new phase of translational clinical studies in critical care and high-risk major surgery will be driven by the novel results.

ACKNOWLEDGMENTS

Caudwell Xtreme Everest (CXE) is a research project coordinated by the Centre for Altitude, Space and Extreme Environment Medicine, University College London, UK. The aim of CXE is to conduct research into hypoxia and human performance at high altitude in order to improve understanding of hypoxia in critical illness. Membership, roles and responsibilities of the CXE Research Group can be found at www.caudwell-xtreme-everest.co.uk/team. The research was funded from a variety of sources, none of which are public. The entrepreneur John Caudwell, whose name the expedition carries, donated £500 000 specifically to support the research. BOC Medical, now part of Linde Gas Therapeutics, generously supported the research early on and continues to do so. Lilly Critical Care, The London Clinic (a private hospital), Smiths Medical, Deltex Medical and The Rolex Foundation have also donated money to support the research and logistics. All monies were given as unrestricted grants. Specific research grants were awarded by the Association of

Anesthetists of Great Britain and Ireland, and the UK Intensive Care Foundation. The CXE volunteers who trekked to Everest basecamp also kindly donated to support the research.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES **1**