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Caudwell Xtreme Everest Expedition

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Abstract

Grocott, Michael P. W., Daniel S. Martin, Mark H. Wilson, Kay Mitchell, Sundeep Dhillon, Monty G. Mythen, Hugh E. Montgomery, and Denny Z. H. Levett. Caudwell Xtreme Everest Expedition. *High Alt. Med. Biol.* 11:133–137, 2010.—The Caudwell Xtreme Everest (CXE) expedition involved the detailed study of 222 subjects ascending to 5300 m or higher during the first half of 2007. Following baseline measurements at sea level, 198 trekker-subjects trekked to Everest Base Camp (EBC) following an identical ascent profile. An additional group of 24 investigator-subjects followed a similar ascent to EBC and remained there for the duration of the expedition, with a subgroup of 14 collecting data higher on Everest. This article focuses on published data obtained by the investigator-subjects at extreme altitude (>5500 m). Unique measurements of peak oxygen consumption, middle cerebral artery diameter and blood velocity, and microcirculatory blood flow were made on the South Col (7950 m). Unique arterial blood gas values were obtained from 4 subjects at 8400 m during descent from the summit of Everest. Arterial blood gas and microcirculatory blood flow data are discussed in detail.

Introduction

The Caudwell Xtreme Everest (CXE) Expedition took place during the spring and early summer of 2007 (Grocott et al., 2007). Consequently, much of the scientific output of this large and complicated study remains to be published (as of February 2010). This review has three aims: (1) to briefly summarize the research aims, design, and conduct of CXE, (2) to highlight unique characteristics of CXE, and (3) to review the currently published scientific output of the expedition, focusing on data obtained at extreme altitude (>5500 m).

Research Aims

The aim of Silver Hut was to understand the physiological consequences of prolonged exposure to ambient hypoxia (West, 2001). The American Medical Research Expedition to Everest (AMREE) team set out to make unique measurements of physiology at extreme altitude (West, 1982). Operation Everest II and III (OE II and III) provided detailed, often invasive, physiological measurements in a chamber environment (Houston et al., 1987; Richalet et al., 1999). These studies have given us a clear and elegant description of adaptation (acclimatization) to prolonged severe ambient hypoxia.

CXE was based on the premise that healthy humans exposed to ambient hypoxia at altitude provide a useful model for understanding responses to hypoxia (adaption and maladaption) in critically ill patients (Grocott, Montegomery and Vercueil, 2007). Central aims of CXE were, therefore, to describe interindividual differences in acclimatization phenotype (hypoxic adaptation) and to identify genotype–phenotype associations. Important design elements included the large study size compared with previous high altitude expeditions ($n = 222$), comprehensive phenotype description, and matched-subject ascent profiles. The infrastructure necessary to achieve these goals also provided an opportunity to make unique measurements at extreme altitude in smaller groups of subjects.

Design and Conduct

CXE was a longitudinal, healthy volunteer study involving two distinct subject groups, totaling 222 subjects, ascending to Everest Base Camp (EBC) or higher during the first 6 months of 2007. All subjects were initially studied at sea level in London (75 m), and they then followed an identical ascent route to EBC. Trekker-subjects completed this trek in 11 days from Kathmandu, whereas investigator subjects took 13 days from Kathmandu (Fig. 1). One hundred and ninety eight trekker-subjects and 24 investigator-subjects commenced the trek; 190 trekker-subjects and 24 investigator-subjects reached EBC. The trekkers returned to Kathmandu following EBC testing, and

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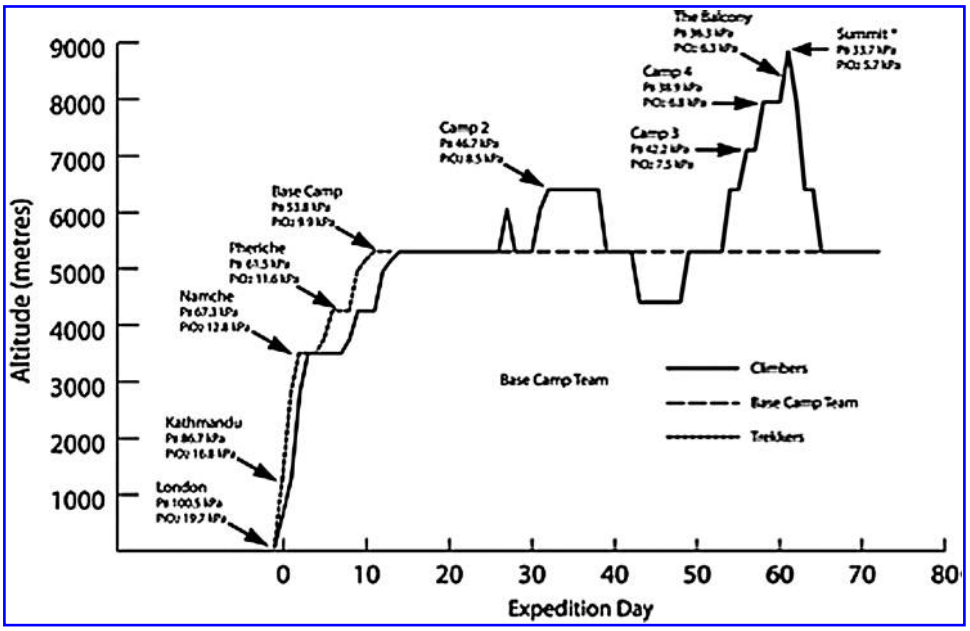

FIG. 1. CXE trekker and investigator ascent profiles.

the investigator-
subjects remained at EBC for the duration of the expedition, with a subgroup of 14 collecting data higher on Everest. Importantly, although trekker and investigator data may be compared, it will not be combined, owing to the different ascent profiles and altitude- exposure histories of the two groups (all investigators had previous exposure to extreme altitude; most trekkers had limited previous high altitude exposure).

To describe interindividual phenotypic variation in the process of acclimatization, simple physiological variables were obtained from all subjects daily during the ascent (e.g., heart rate, blood pressure, pulse oximetry). At the field laboratories, breath-by-breath expired gas analysis and skeletal muscle and brain near-infrared spectroscopy (NIRS) values were obtained at rest and during exercise; plasma samples were taken for inflammatory markers, nitric oxide metabolites, and markers of organ injury; and a neurological test battery including pupillometry, saccadometry, retinal photographs, and comprehensive neuropsychometric assessment was recorded. Subgroups of investigator-subjects underwent a variety of more invasive tests at sea level and EBC, including arterial cannulation for cardiac output measurement and skeletal muscle biopsies for morphological, biochemical, and proteomic analysis.

Unique Characteristics of CXE

Unique characteristics of CXE included the large subject cohort following an identical ascent profile (to explore interindividual variability), the magnitude of field research infrastructure, and the novel extreme-altitude goals. Large trekker cohorts have previously been used as subject groups for studies at high altitude by other groups, notably Medex <www.medex.org.uk/> (Woods et al., 2002) in 1994 in the

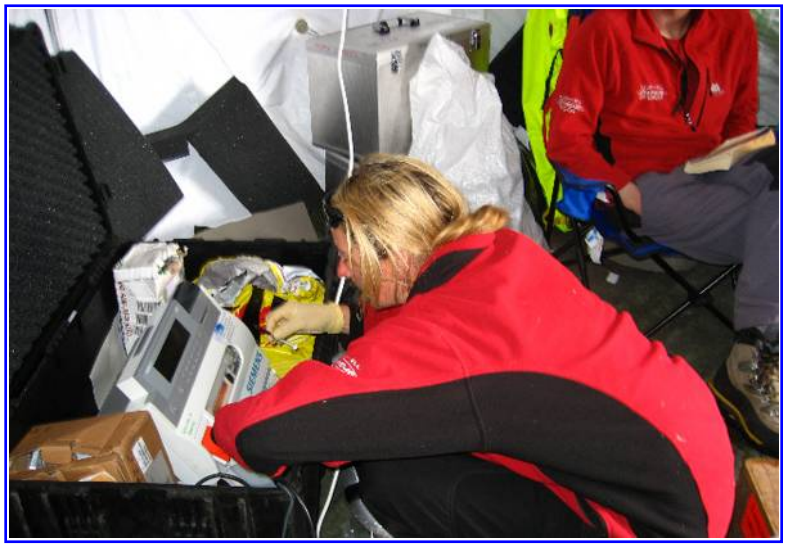

FIG. 2. Measurement of arterial blood gases using a bench-top blood gas analyzer at Camp 2 (6400 m) in the Western Cwm.

FIG. 3. The Balcony on the SE ridge of Everest, the location of arterial blood gas sampling at 8400 m. Note Sherpa with vacuum flask containing iced-water slurry for transport of blood samples to bench-top blood gas analyzer at Camp 2 (6400 m), May 2007.

Everest region and 1998 trekking to Kanchenjunga Base Camp. However, ascent profiles were not consistent between trekker groups within the same study. By ensuring that our trekker groups followed the same trek route to EBC, with the same rate of ascent, we have a high degree of confidence that observed intraindividual differences represent signal (true physiological differences) rather than noise (variations in exposure to environmental hypoxia). The size of the CXE cohort ($n = 198$) provides the statistical power to detect differences in phenotypic response by somatic genotype (prospective gene–environment interaction study) (Grocott and Montgomery, 2008).

The CXE team established an infrastructure of fully staffed field laboratories in Kathmandu (1300 m), Namche Bazaar (3500 m), Pheriche (4250 m), and at EBC (5300 m). Further laboratories were established at 6400 m in the Western Cwm and at 7950 m on the South Col. These laboratories were physically located in Sherpa lodges below EBC and in dedicated field shelters (EBC and Western Cwm Camp 2) or in high altitude tents (South Col) above EBC. All laboratories below the South Col were supplied with 240-V AC electricity and blood sample collection and processing facilities, in addition to the physiological measurement capabilities.

The novel extreme-altitude research goals were based in part on unanswered questions outstanding from previous field and chamber studies and in part on the availability of technological innovations that allowed us to make measurements that were previously impossible in this environment. The measurement of arterial blood gases in climbers at or near the summit of Everest falls into the first category (Grocott et al., 2009). The use of two-dimensional color flow and pulse wave Doppler to determine middle cerebral artery diameter and blood velocity on the South Col falls into the latter category.

In this context, CXE followed a similar approach to that used by the 1981 AMREE (West, 1982). However there are differences between the AMREE and CXE approaches. First, as all CXE investigators were climbers, we did not have separate investigator and climbing teams above EBC. Second, our highest fixed laboratory was on the South Col, whereas on AMREE the highest fixed laboratory was in the Western Cwm. In common with AMREE, we chose the safest route (SE Ridge) with the highest success rate (Huey and Salisbury, 2003). We used supplemental oxygen while climbing (2 L/min) and sleeping (0.5 L/ min) from Camp 3 (7100 m).

Published Data from Extreme Altitude

A minority of the research conducted on the 2007 CXE has reached publication in peer-reviewed journals. Published data (as of early February 2010) from the investigator-subjects at extreme altitude are presented below.

Arterial oxygen partial pressure and content

Arterial blood gas values and hemoglobin measurements were obtained after a minimum of 20 min of rest without supplemental oxygen. A bench-top blood gas analyzer was used for blood gas analyses (Fig. 2) and a handheld photometric device was used for hemoglobin measurement. Samples requiring transport to the laboratory were carried in ice-water slurry in a vacuum flask for no more than 2 h prior to analysis. Data from 10 investigator-subjects demonstrated that mean oxygen content was maintained at or above sea-level values up to 7100 m in well-acclimatized subjects (Grocott et al., 2009). Samples obtained at 8400 m (Fig. 3) (barometric pressure 272 mmHg) from 4 climbers descending following a successful summit attempt showed a mean Pao_2 of 24.6 mmHg (3.28 kPa) and a mean $Paco_2$ of 13.3 mmHg (1.77 kPa) while breathing ambient air. Individual subject values for Pao_2, $Paco_2$, pH, and alveolar–arterial oxygen difference are presented in Table 1. The lowest Pao_2 recorded in a subject who was apparently functioning completely normally was 19.1 mmHg (2.55 kPa). This is the lowest reported value in a human. Of note, the mean arterial lactate concentration was 2.2 mmol/L,

Table 1. Individual Values for Arterial Pa_{O_2}, Pa_{CO_2}, and pH in 4 CXE Subjects at 8400 m on Everest

	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH	PA_{O_2} (mmHg)	Alveolar–arterial oxygen difference (mmHg)
Subject 1	29.5	12.3	7.55	32.4	2.89
Subject 2	19.1	15.7	7.45	26.9	7.81
Subject 3	21.0	15.0	7.52	27.4	6.44
Subject 4	28.7	10.3	7.60	33.2	4.51

suggesting that anaerobic metabolism was not contributing substantially to resting energy production.

The mean calculated alveolar–arterial oxygen difference was 5.4 mmHg (0.72 kPa). We speculated that this unexpectedly high alveolar–arterial oxygen difference might result from either subclinical high altitude pulmonary edema or functional limitation in pulmonary diffusion. Blood gas values obtained from rested subjects at a similar barometric pressure in a prolonged hypobaric chamber study (OE II) exhibited an alveolar–arterial oxygen difference of 1.5 mmHg (0.2 kPa) (Sutton et al., 1988). This suggests that functional limitation in pulmonary diffusion was insignificant at rest. Therefore, we propose that the most likely cause of the increased alveolar–arterial oxygen difference in our data was subclinical pulmonary edema resulting from prolonged exertion during the ascent to the summit and subsequent descent prior to the arterial blood sampling.

Previous studies had estimated blood gas values at the summit of Everest from alveolar samples (AMREE) (West et al., 1983) or by measurement at comparable barometric pressure in a hypobaric chamber (OE II and III) (Sutton et al., 1988; Richalet et al., 1999). A comparison of extreme altitude (or equivalent chamber pressure) arterial Pa_{O_2}, Pa_{CO_2}, and pH estimates and measurements from AMREE, OE II, OE III, and CXE is presented in Table 2. The CXE Pa_{O_2} values are the only direct field measurements at this altitude, and 2 of the 4 subjects exhibited Pa_{O_2} values substantially lower than the OE I and II measurements or the AMREE estimate. Both of these two subjects had a calculated alveolar–arterial oxygen difference greater than 5 mmHg (0.67 kPa) and may have had subclinical pulmonary edema (see above). Of note, these individuals (subjects 2 and 3) also had higher resting Pa_{CO_2} values than the other two subjects. This suggests a weaker hypoxic ventilatory response (HVR), which may in turn have resulted in a greater fall in Pa_{O_2} with exercise and consequently a greater susceptibility to pulmonary edema. The CXE Pa_{CO_2} and pH values are consistent with the OE II and OE III measurements, as well as with the AMREE Camp 6 estimates. The AMREE summit estimates of Pa_{CO_2} and pH values are outliers (lower Pa_{CO_2} and higher pH) among these data. This might be explained by the acknowledged high HVR of the subject involved (Schoene et al., 1984) or by the time interval between removal of supplementary oxygen and measurement (>10 min for AMREE and >20 min for CXE) (Grocott et al., 2009; West et al., 1983).

Distribution of blood flow

Using sidestream dark-field imaging (SDF), we have previously reported, for the first time, abnormalities of the microcirculatory flow index (MFI, a measure of blood flow in vessels <50 μm in diameter) in the sublingual blood vessels of climbers at extreme altitude (Martin et al., 2009). On CXE, 24 subjects had sublingual MFI and vessel density measurements recorded at altitudes up to 7950 m (Martin et al., 2010). MFI was consistently reduced in small (<25 μm and medium-sized (26 to 50 μm) vessels following ascent to altitude, with the greatest reduction seen at EBC at the end of the expedition (at which point vessel density was also altered). The change in MFI measured at EBC at the end of the expedition was greater in climbers who had ascended high on the mountain than in investigators who had stayed at EBC. Grid crossings (an index of vessel density) were increased at all altitudes. Administration of supplemental oxygen at 7950 m resulted in a further reduction in MFI and increases in grid crossings. Interestingly, neither changes in MFI nor vessel density were correlated with peripheral oxygen saturations, heart rate, diastolic blood pressure, or rate–pressure product (Martin et al., 2010). Although the implications of these unique observations remain uncertain, it may be that microcirculatory dysfunction contributes to the functional limitation (e.g., reduced maximum oxygen consumption and cognitive impairment) observed at high altitude.

Unpublished Data from Extreme Altitude

Oxygen consumption. Oxygen consumption from breath-by-breath expired gas analysis was measured at 6400 and at 7950 m, the highest altitude on the surface of Earth at which oxygen consumption has been measured.

Neurological function. A comprehensive battery of neuropsychometric tests was undertaken at 6400 and 7950 m.

Cerebral blood flow. Novel observations of changes in the middle cerebral artery velocity and diameter, measured using two-dimensional color flow and pulse wave Doppler, were made at 6400 and 7950 m.

Table 2. Comparison of Arterial Pa_{O_2}, Pa_{CO_2}, and pH Estimates and Measurements at 8400 m and above from AMREE, OE II, OE III, and CXE

	P_B (mmHg)	P_{IO_2} (mmHg)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH
AMREE,Camp 6, 8400 m	267	46	*No estimate*	*12.9*	*7.58*
AMREE,summit, 8848 m	253	43	*28*	*7.5*	*7.75*
OE II, "summit"	253	43	30	12	7.56
OE III (Comex),"summit"	253	43	30.6	11.9	7.58
CXE,Balcony, 8400 m	272	47	24.6	13.3	7.53

P_B, barometric pressure; P_I, moist inspired air. Figures in italics are estimates (not direct measurements) of arterial values. The level of precision for quoted estimates and measurements is taken from the original reports.

Conclusions

CXE was completed safely and effectively. More than 90% of planned testing was completed. Twelve investigators ascended to the South Col (7950 m) and 8 reached the summit (8848 m) without significant adverse consequence. Early published results derive predominantly from the investigator groups and focus on extreme-altitude measurements, including arterial blood gas values and microcirculatory blood flow. Future publications exploring the physiological and genetic determinants of interindividual variability in acclimatization may provide target biomarkers for research aimed at improving the care of critically ill patients.

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Disclosures

The authors have no conflicts of interest or financial ties to disclose.

Appendix 1: Membership of the Caudwell Xtreme Everest Research Group

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