Human responses to extreme altitudes

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Synopsis  It is a strange coincidence that the highest point on Earth is very close to the limit of human tolerance to hypoxia. The physiological changes that allow humans to reach these extreme altitudes involve enormous alterations of their normal state. It is useful to contrast this response with two others to high altitude. One is acclimatization that allows lowlanders to ascend to altitudes of up to 5000 m and remain there for an indefinite period. The other is evolutionary adaptation which allows highlanders to live continuously over generations at altitudes up to 5000 m. These two responses enable humans to survive for an indefinite period at high altitude. By contrast, the changes that allow ascent to extreme altitudes are not compatible with an extended stay because of a poorly-understood process called high-altitude deterioration. The most important physiological response to extreme altitude is extreme hyperventilation which, on the summit of Mt. Everest, drives the alveolar $\text{PCO}_2$ down to 7–8 mmHg. This is associated with a marked respiratory alkalosis with an arterial pH exceeding 7.7. Interestingly this alkalosis increases the oxygen affinity of hemoglobin, a response which the successful climber shares with many other animals in oxygen-deprived environments. The arterial $\text{PO}_2$ on the Everest summit is just over 1 liter.min$^{-1}$. Anaerobic metabolism as measured by blood lactate levels is paradoxically reduced at extreme altitudes.

Introduction

It is an extraordinary coincidence that the highest point on Earth is very close to the limit of human tolerance to hypoxia. In this setting of integrative and comparative biology it would be satisfying to find an evolutionary explanation for this, but of course none exists. Human beings rarely venture to altitudes above 6000 m and there is no survival advantage in being able to do so. There is no food or other commodity worth gathering at these altitudes and climbers do it “because it is there” (West, 1985, p. 155). Climbing Mt. Everest has always been seen as one of the ultimate human challenges.

In the context of human responses to altitude it is useful to consider three processes that are related but different (Table 1). The first is high-altitude acclimatization which refers to the physiological changes that occur in lowlanders (people who normally live near sea level) when they go to altitudes of up to about 5000 m to work or play. The second process is true evolutionary adaptation which has occurred in humans who have resided for many generations at high altitude (highlanders) especially in the South American Andes and the Tibetan plateau. The third process is the physiological changes that take place at extreme altitudes and these should be distinguished from the first two processes. Here there is adaptation in the sense that it is impossible to survive at high altitude without the changes, but these responses are accompanied by an inexorable deterioration in the body which makes long-term human survival above altitudes of about 6000 m impossible.

High-altitude acclimatization

The most important feature of acclimatization to altitudes up to about 5000 m is the increase in ventilation. This is brought about by hypoxic stimulation of arterial chemoreceptors and can be very vigorous. For example, lowlanders who go to an altitude of 5000 m and stay there for a period of weeks reduce their alveolar $\text{PCO}_2$ from its normal value of 40 mmHg to about 25 mmHg. The fall in $\text{PCO}_2$ occurs because for the same $\text{CO}_2$ production, the alveolar $\text{PCO}_2$ is inversely related to the alveolar ventilation. The physiological advantage of the hyperventilation is that it lessens the fall in alveolar $\text{PO}_2$, which would otherwise occur. For example, someone who moves rapidly to an altitude of 5000 m will develop an alveolar $\text{PO}_2$ as low as 39 mmHg but the ventilatory acclimatization that occurs over two weeks or so will raise it to about 48 mmHg. These are average values as reported by Rahn and Otis (1949) although there is considerable individual variation.
Another feature of acclimatization is polycythemia which is brought about by the release of erythropoietin, mainly from the kidney, in response to the low arterial PO2. This stimulates the bone marrow to produce more red blood cells. However this process is slow and does not reach its steady state value for several weeks. Newcomers to high altitude often have an increased red cell concentration in their blood within the first day or two but this is caused by a reduced plasma volume, not increased red cell production. At one time it was thought that the polycythemia was the most important feature of acclimatization but we now know that its value is much less than that of the hyperventilation.

Other features of acclimatization include changes of oxidative enzymes in cells, reduction of the intercapillary distance in some peripheral tissues such as skeletal muscle, and changes in the oxygen affinity of hemoglobin. With ascent to moderate altitudes the oxygen affinity of hemoglobin is reduced because of the increase in 2,3-diphosphoglycerate within the red cells. However this is a relatively small effect and at higher altitudes such as over 5000 m, the respiratory alkalosis caused by the reduced arterial PCO2 causes an increased oxygen affinity of hemoglobin.

**Evolutionary adaptation to high altitude**

Because this topic has been discussed by other speakers in this symposium, for example Cynthia Beall, little will be said about it here. However the point can be made that this adaptation is not the same as acclimatization although the two processes share many similarities. Indeed in the older literature no distinction was drawn between acclimatization of newcomers to high altitude and permanent residents of high altitude who have been there for many generations. We now know that there are some differences. For example, the incidence of sleep-disordered breathing is higher in acclimatized lowlanders than in adapted highlanders (Lahiri *et al*., 1983). In addition, genetically-adapted residents have babies of near-normal birthweight compared with acclimatized lowlanders (Moore, 2003) and some adapted populations, for example Tibetans, have less pulmonary hypertension (Groves *et al*., 1993). Again, well-adapted highlanders on the Tibetan plateau tend to have lower hemoglobin concentrations than well-acclimatized lowlanders at the same altitude (Beall, 2000).

Do the physiological changes of high-altitude acclimatization or evolutionary adaptation allow humans at high altitude to function as well as those at sea level? As long ago as 1925 Barcroft argued against this stating “All dwellers at high altitudes are persons of impaired physical and mental powers” (Barcroft, 1925). I believe that this observation has stood the test of time and can be explained by the fact that although the fall of tissue PO2 at high altitude is reduced to some extent by acclimatization and evolutionary adaptation, the PO2 values are still far below those of sea level dwellers.

**Physiological changes at extreme altitudes**

This is the main topic of the present paper. As indicated above the changes should be distinguished from those of either acclimatized lowlanders or evolutionarily-adapted highlanders. First the physiological alterations

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**Table 1** Comparison of acclimatization, evolutionary adaptation, and physiological responses to extreme altitude

<table>
<thead>
<tr>
<th>Condition</th>
<th>Altitude</th>
<th>Physiological features</th>
</tr>
</thead>
</table>
| Acclimatization to high altitude | up to 5000 m | Hyperventilation  
Nearly complete renal compensation of the respiratory alkalosis  
Polycythemia  
Increase in intracellular oxidative enzymes  
Reduced intercapillary diffusion distances in some tissues |
| Evolutionary Adaptation        | up to 5000 m | Hyperventilation although this is less in best-adapted people  
Complete renal compensation  
Polycythemia although this is less in the best-adapted  
Changes in intracellular enzymes |
| Physiological responses to extreme altitude | above 7000 m | Extreme hyperventilation  
Marked respiratory alkalosis  
Incomplete renal compensation  
Increased O2-affinity of hemoglobin as a result of the alkalosis  
Very low maximal O2 consumption  
Great reduction in anaerobic metabolism  
Relentless loss of weight and other evidence of progressive deterioration |
are much more marked. In addition although the dramatic physiological changes at extreme altitudes are successful in maintaining life, humans inevitably deteriorate at these altitudes. Thus while it can be argued that the physiological changes of acclimatization and evolutionary adaptation allow these two groups to function reasonably satisfactorily in the hypoxic environment of high altitudes, this is not the case with the changes that take place at extreme altitudes.

Field studies of human physiology at extreme altitudes

The most extensive field studies of physiology of extreme altitude were those carried out during the 1981 American Medical Research Expedition to Everest (AMREE) (West, 1984). This expedition was specifically designed to study lowlanders first at sea level, then at extreme altitudes including the summit of Mt. Everest, altitude 8848 m, and finally on return to sea level. Extensive measurements were made in two laboratories situated at altitudes of 5400 and 6300 m. Additional data were obtained at the highest camp, altitude 8050 m, also between this camp and the summit, and finally on the summit itself. No previous measurements had been made at altitudes above 7440 m except for a few alveolar gas samples at 7830 m (Gill et al., 1962). These last two studies were made during the 1960–1961 Himalayan Scientific and Mountaineering Expedition usually known as the Silver Hut expedition (Pugh, 1962). Other studies on that expedition included measurements of maximal oxygen uptake at an altitude of 7440 m (Pugh, 1964) and these remain the highest measurements of maximal oxygen consumption to the present day.

One of the main topics studied during AMREE was the increase in ventilation at extreme altitudes. It was already well-known that this hyperventilation which results from stimulation of the peripheral chemoreceptors by the low P\textsubscript{O\textsubscript{2}} in the arterial blood was extensive but we asked some new questions. The first was whether there was a relationship between the hypoxic ventilatory response (HVR) and tolerance to extreme altitude. To answer this members of the expedition were ranked by their hypoxic ventilatory response (HVR) measured at sea level, and curiously enough the climber with the highest response got to the summit first, the one with the second-highest response reached the summit second, and the one with the third-highest response was third. Of course this must be partly by chance but it suggested a relationship between the HVR and performance at extreme altitude. This was even more pronounced in the members of the expedition who were unfortunately born with a low HVR and generally did not tolerate high altitude well. The conclusion was that there was a relationship between hypoxic ventilatory response and tolerance to extreme altitude (Schoene et al., 1984) and this has subsequently been confirmed by others (Masuyama et al., 1986) although there is not universal agreement on the topic.

A major objective was to determine the degree of hyperventilation at the highest altitude of all, the Everest summit. To do this we exploited the inverse relationship between alveolar ventilation and the P\textsubscript{CO\textsubscript{2}}. Alveolar gas samples were taken by Chris Pizzo, M.D. while he was sitting on the summit using a specially-designed alveolar gas sampler. The samples were subsequently analyzed at UCSD and the alveolar P\textsubscript{CO\textsubscript{2}} values are shown in Figure 1. Here the alveolar P\textsubscript{CO\textsubscript{2}} is plotted against barometric pressure which falls as altitude increases, and the triangles are the means of values found at three altitudes on AMREE while the circles show data from previous expeditions. Note the roughly linear decrease in alveolar P\textsubscript{CO\textsubscript{2}} as barometric pressure falls and that on the summit the P\textsubscript{CO\textsubscript{2}} has the extraordinarily low value of 7–8 mmHg. This indicates an enormous degree of hyperventilation given that the sea level value is 40 mmHg. In fact, the alveolar ventilation increased some 5–6-fold.

Additional information was obtained when the alveolar P\textsubscript{O\textsubscript{2}} and P\textsubscript{CO\textsubscript{2}} were plotted on an oxygen-carbon dioxide diagram as shown in Figure 2. The closed circles show data collated by Rahn and Otis (1949) and the triangles are the means at the three barometric pressures of Figure 1. Sea level is at top right and
the summit of Mt. Everest is at bottom left. Note that as the altitude increased both the alveolar $P_{O_2}$ and $P_{CO_2}$ fell. The $P_{O_2}$ falls because of the decreasing $P_{O_2}$ in the air around the climber. The $P_{CO_2}$ falls because of the increasing hyperventilation. Once a particular altitude has been exceeded (about 7000 m), there is no further change in the alveolar $P_{O_2}$. Instead it is defended at a level of about 35 mmHg or, in other words the alveolar $P_{O_2}$ is insulated from the falling $P_{O_2}$ around the climber. This can only be brought about by the continuing increase in ventilation as the climber ascends. Now we see why the hypoxic ventilatory response is so important. Not everybody is able to mount the degree of hyperventilation to drive the alveolar $P_{CO_2}$ down to 7–8 mmHg, and with a low hypoxic ventilatory response this would not be possible.

We were not able to take arterial blood on the Everest summit because of the extremely hostile conditions there. However the arterial $P_{O_2}$ was calculated using the Bohr integration to determine the change in the capillary $P_{O_2}$ as blood is loaded in the lung. This showed that the end-capillary value was about 28–30 mmHg and that it was lower than the alveolar value. This was presumably because of diffusion limitation under these extraordinary conditions (West et al., 1983b).

The acid-base status of the climber was of great interest because of the extremely low alveolar $P_{CO_2}$. When the $P_{CO_2}$ was combined with the base excess values measured in venous blood on two climbers the morning after their summit ascent, the Henderson-Hasselbalch equation gave an arterial pH of between 7.7 and 7.8, an extraordinary degree of respiratory alkalosis (Winslow et al., 1984). Table 2 shows the best information from field studies to date on the alveolar gas and arterial blood values for a climber on the summit of Mt. Everest.

The extraordinary respiratory alkalosis has some fascinating implications. A pH above 7.7 markedly increases the oxygen affinity of hemoglobin and it is interesting that mammals that live at high altitude generally have an increased oxygen affinity and therefore a left-shifted oxygen dissociation curve. For example, Hall (1937) showed that the vicuña and llama at high altitude in the South American Andes have markedly left-shifted oxygen dissociation curves compared with a range of mammals that live at sea level. Furthermore as Table 3 shows, a large number of strategies have been developed throughout the animal kingdom to increase the oxygen affinity of hemoglobin for animals in oxygen-deprived environments. A well-known example for many physiologists is the high oxygen affinity of the human fetus because of the presence of fetal hemoglobin which has an in vivo $P_{50}$ of about 20 mmHg in contrast to the value of 27 mmHg in the adult. The low $P_{50}$ of fetal hemoglobin is attributable to its reduced binding with diphosphoglycerate. It is very remarkable that the climber at extreme altitude is able to increase the oxygen affinity of his hemoglobin by a completely different mechanism, namely extreme respiratory alkalosis.

At the start of planning for the expedition one of the intriguing puzzles was whether it was possible to climb Mt. Everest without supplementary oxygen because available data relating maximal $O_2$ consumption ($V_{O_2,max}$) to barometric pressure suggested that on the Everest summit there was insufficient oxygen for any external work. However the question was dramatically answered by Messner and Habeler in 1978 when

![Fig. 2 Oxygen-carbon dioxide diagram showing the changes in alveolar $P_{O_2}$ and $P_{CO_2}$ from sea level (top right) to the Everest summit (bottom left). Note that above a certain altitude (about 7000 m) there is no further fall in the $P_{O_2}$. Instead it is defended at a level of about 35 mmHg. Modified from West et al. (1983b).](https://academic.oup.com/icb/article-abstract/46/1/25/661337)

### Table 2 Alveolar gas and arterial blood values on the summit of Mt. Everest

<table>
<thead>
<tr>
<th>Altitude meters</th>
<th>Barometric pressure (mmHg)</th>
<th>Inspired $P_{O_2}$ (mmHg)</th>
<th>Alveolar $P_{O_2}$ (mmHg)</th>
<th>Arterial $P_{O_2}$ (mmHg)</th>
<th>$P_{CO_2}$ (mmHg)</th>
<th>pH (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8848 (summit)</td>
<td>253</td>
<td>43</td>
<td>35</td>
<td>28</td>
<td>7.5</td>
<td>&gt;7.7</td>
</tr>
<tr>
<td>Sea level</td>
<td>760</td>
<td>149</td>
<td>100</td>
<td>95</td>
<td>40</td>
<td>7.40</td>
</tr>
</tbody>
</table>
they made their historic ascent without supplementary oxygen. One of our major goals therefore was to obtain measurements $\dot{V}O_{2\text{max}}$ at the highest possible altitude. Figure 3 shows $\dot{V}O_{2\text{max}}$ plotted against the inspired PO$_2$, and it can be seen that as the altitude increased and the PO$_2$ fell, $\dot{V}O_{2\text{max}}$ rapidly decreased. On the Everest summit the value was just over 1 liter.min$^{-1}$ which is a miserably low value for $\dot{V}O_{2\text{max}}$ being equivalent to that of someone walking slowly on the level. However it is just sufficient to explain how Messner and Habeler were able to reach the summit without supplementary oxygen. In fact their accounts indicate that the last 100 meters of vertical height took over an hour to climb and this rate is consistent with the measurements of maximal oxygen consumption. In fact their accounts indicate that the last 100 meters of vertical height took over an hour to climb and this rate is consistent with the measurements of maximal oxygen consumption. In fact their accounts indicate that the last 100 meters of vertical height took over an hour to climb and this rate is consistent with

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Subject/Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different sequence in globin chain</td>
<td>Human fetus, bar-headed goose, toad-fish</td>
</tr>
<tr>
<td>Decrease in 2,3 DPG</td>
<td>Fetus of dog, horse, pig</td>
</tr>
<tr>
<td>Decrease in ATP</td>
<td>Trout, eel</td>
</tr>
<tr>
<td>Different Hb, small Bohr effect</td>
<td>Tadpole</td>
</tr>
<tr>
<td>Mutant Hb (Andrew - Minneapolis)</td>
<td>Family in Minnesota</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>Climber at extreme altitude</td>
</tr>
</tbody>
</table>

Table 3 Strategies for increasing oxygen affinity of hemoglobin in hypoxia

Many other measurements were made on the expedition but there is only space to discuss two of them here. Particularly interesting information was obtained from neuropsychological measurements made before, during and after the expedition. Since it is well-known that the central nervous system is very vulnerable to hypoxia, it was not surprising that impairment of neuropsychological function could be demonstrated at very high altitudes, for example in the Camp 2 laboratory at 6300 m. But the most provocative results were obtained when measurements made after the expedition were compared with those made before. It was found that two of the neuropsychological measurements remained abnormal. One was a test of short-term memory although this returned to normal after twelve months. On the other hand, a test of manipulative ability carried out using a finger-tapping test remained abnormal in a number of the expedition members for a longer period of time. The conclusion was that it is not possible to spend time at these enormous altitudes and have the central nervous system escape completely unscathed.

Some measurements were also made at an altitude of 6300 m of the increase in blood lactate concentration accompanying maximal exercise (West et al., 1983a). The results showed a resting blood lactate concentration of 1.7 mM which rose to only 3.0 mM after maximal exercise. This very small rise contrasts with the very large increase in blood lactate concentration during maximal exercise in severe acute hypoxia where the value may rise to 12 mM or even more. The fact that acclimatized subjects at high altitude have a small increase in blood lactate concentration during maximal exercise in spite of the extreme tissue hypoxia was reported by Edwards as long ago as 1936 during the international high-altitude expedition to Chile (Edwards, 1936). The phenomenon is known as the lactate paradox and has been studied extensively by Cerretelli and colleagues (1982). Figure 4 shows some of the data and it is remarkable that extrapolation of the line relating maximal blood lactate to altitude suggests that above an altitude of about 7000 m, there will be no rise in blood lactate at all during maximal exercise! Although several explanations have been offered for these low lactate values none is completely satisfactory as yet.

Studies using low-pressure chambers

A frequently asked question is why do field studies, for example on Mt. Everest, to study human adaptation to extreme altitude when the low pressure conditions can be simulated in an altitude chamber. At least two extensive studies have been carried out in this way

![Graph of maximal O2 uptake vs. inspired PO2](image_url)
but while they have certainly added to our knowledge of how humans respond to high altitude, for some as yet unexplained reasons they have not been able to accurately reproduce the physiological adaptations to extreme altitude.

Operation Everest II

In this ambitious experiment 8 subjects ranging in age from 21 to 29 years spent 40 days and 40 nights in an elaborate low-pressure chamber facility at the U.S. Army Research Institute of Environmental Medicine in Natick, Massachusetts (Houston et al., 1987). This sophisticated facility had a large room which contained bunks, an eating area and a stationary bicycle, a smaller study chamber that was used for invasive procedures such as cardiac catheterization, while between these two was an airlock that was provided with toilet and washing facilities. Barometric pressure, oxygen concentration, temperature, relative humidity were monitored around the clock, and although it is sometimes suggested that chamber experiments such as this is less expensive than a field expedition the opposite is almost certainly true. The experimental plan was to gradually decompress the subjects over a period of about 35 days followed by excursions to the “summit” where the inspired P$_{O_2}$ was 43 mmHg. This P$_{O_2}$ was chosen based on the AMREE data which showed a summit barometric pressure of 253 mmHg (West et al., 1983). Not all the subjects were able to tolerate the highest altitudes but nevertheless very valuable information was obtained.

Some of the most interesting observations were on the pulmonary circulation. Cardiac catheterization was performed using a Swan-Ganz catheter at barometric pressures of 760, 347, 282 and 240 mmHg. During the last measurement the oxygen concentration in the chamber was 22% so that the inspired P$_{O_2}$ was 43 mmHg which was the appropriate value for the “summit.” It was found that there was a marked increase in mean pulmonary arterial pressure at rest from sea level where the value was 15 ± 0.9 mmHg to 34 ± 3 mmHg at a barometric pressure of 282 mmHg (Groves et al., 1987). This increase in pressure was accompanied by an increase in pulmonary vascular resistance from 1.2 to 4.3 mmHg.l$^{-1}$.min$^{-1}$. With maximal exercise the increase in mean pulmonary artery pressure with altitude was even more striking, rising from 33 ± 1 mmHg at sea level to 54 ± 2 mmHg at a barometric pressure of 282 mmHg (Fig. 5). Interestingly, the pulmonary artery wedge pressure as a measure of pulmonary venous pressure did not alter with altitude.

Cardiac output was measured and it was shown that the relationship between this and oxygen consumption remained essentially unchanged confirming earlier results obtained on the Silver Hut expedition of 1960–1961 (Pugh, 1964). However heart rate increased and stroke volume decreased at a given work level as previously reported by others. An important new finding was that when the subjects breathed 100% oxygen at the high altitudes, there was no significant fall in pulmonary vascular resistance in spite an increase in cardiac output. Since a rise in cardiac output normally results in a decrease in pulmonary vascular resistance, the result indicates a substantial degree of irreversibility of the increased pulmonary vascular resistance during oxygen breathing which implies structural changes in the blood vessels due to remodeling. An unexpected result was the preservation of cardiac function at extreme altitude (Reeves et al., 1987; Suarez et al., 1987). It was possible to measure ventricular ejection fraction by two dimensional echocardiography and it was found that this was preserved at a barometric pressure of 252 mmHg; indeed if anything it was actually improved. This fascinating finding emphasizes the critical difference between the effects of hypoxemia and ischemia on the normal myocardium.

Equally important results were found in the studies of pulmonary gas exchange. Arterial blood was
sampled at sea level and barometric pressures of 428, 347, 282 and 240 mmHg (Sutton et al., 1988) (Table 4).

At sea level the arterial P\textsubscript{O\textsubscript{2}} at rest had a mean value of 99 mmHg and this fell to 87 mmHg at the highest level of exercise (Table 4). As the altitude increased the arterial P\textsubscript{O\textsubscript{2}} decreased both at rest and for each given work level. On the “summit” where the inspired P\textsubscript{O\textsubscript{2}} was 43 mmHg, the arterial P\textsubscript{O\textsubscript{2}} was 30 mmHg at rest and this decreased to 28 mmHg at the maximal work rate of 120 watts. Note that this is in good agreement with the calculated arterial P\textsubscript{O\textsubscript{2}} on AMREE when the inspired P\textsubscript{O\textsubscript{2}} was 43 mmHg (Table 2).

An analysis of the causes of the hypoxemia was made by performing the multiple inert gas infusion technique at sea level and at barometric pressures of 429, 347, 282 and 240 mmHg (Wagner et al., 1987). This allowed assessment of the relative contributions of diffusion limitation and ventilation-perfusion inequality to the hypoxemia. It was found that diffusion limitation of oxygen across the blood-gas barrier occurred at oxygen uptakes greater than 3 l.min\textsuperscript{-1} at sea level, and at less than 1 l.min\textsuperscript{-1} on the “summit.” This is another demonstration of the vulnerability of the normal lung to diffusion limitation of oxygen uptake at very high altitude, especially on exercise, as referred to in discussing the AMREE results. Evidence of increasing ventilation-perfusion inequality from rest to exercise was found at all altitudes, but least on the “summit” presumably because the work rate there was relatively low. A study of the correlation between the degree of ventilation-perfusion inequality and variables in the pulmonary circulation including cardiac output, pulmonary artery pressure and pulmonary arterial wedge pressure suggested that at least part of the inequality was caused by interstitial pulmonary edema.

Skeletal muscle was studied by taking needle biopsies of the vastus lateralis muscle at barometric pressures of 380 and 282 mmHg (Green et al., 1989a,b). Measurements of muscle area were also obtained from computer tomography scans of the thighs and upper arms. It was found that muscle area decreased significantly by about 14% during the simulated ascent. The reasons were clarified by measurements on the

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**Fig. 5** Mean pulmonary artery pressure (PAM) minus mean pulmonary artery wedge pressure (PAWM) plotted against cardiac output at various barometric pressures (P\textsubscript{B}) during Operation Everest II. From Groves et al. (1987).

**Table 4** Barometric pressures, equivalent altitudes, and arterial blood gases during rest and maximal exercise on Operation Everest II.

<table>
<thead>
<tr>
<th>Barometric Pressure (mmHg)</th>
<th>Inspired PO\textsubscript{2} (mmHg)</th>
<th>Altitude on Mt. Everest (m)</th>
<th>\text{rest} P\textsubscript{O\textsubscript{2}} (mmHg)</th>
<th>P\textsubscript{CO\textsubscript{2}} (mmHg)</th>
<th>pH</th>
<th>\text{max exercise} P\textsubscript{O\textsubscript{2}} (mmHg)</th>
<th>P\textsubscript{CO\textsubscript{2}} (mmHg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>760</td>
<td>149</td>
<td>0</td>
<td>99</td>
<td>34</td>
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<td>87</td>
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<td>4825</td>
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<td>25</td>
<td>7.46</td>
<td>42</td>
<td>20</td>
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<td>347</td>
<td>63</td>
<td>6482</td>
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<td>7.44</td>
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<td>282</td>
<td>49</td>
<td>8043</td>
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<td>13</td>
<td>7.53</td>
<td>33</td>
<td>11</td>
<td>7.49</td>
</tr>
<tr>
<td>253*</td>
<td>43</td>
<td>8848</td>
<td>30</td>
<td>11</td>
<td>7.56</td>
<td>28</td>
<td>10</td>
<td>7.52</td>
</tr>
</tbody>
</table>

*From Sutton et al. (1988) and Houston et al. (1987).

**Actual chamber pressure was 240 mmHg but because of oxygen contamination of the chamber air, the oxygen concentration was 22%. Therefore the inspired P\textsubscript{O\textsubscript{2}} was 43 mmHg corresponding to a barometric pressure of 253 mmHg for 21% oxygen.**

§From West (1996).
biopsies which showed a significant 25% decrease in the cross-sectional area of type I fibers, and a 26% decrease in type II fibers. This accounted for an increase in capillary density though this was nonsignificant.

The biopsies also allowed studies of muscle enzymes and these showed that several that were representative of the citric acid cycle were unchanged. However at the lowest barometric pressure of 282 mmHg where biopsies were made, there was significant reductions in succinic dehydrogenase, citrate synthetase, and hexokinase compared with measurements made on returning to sea level.

Biochemical measurements on the biopsies showed a significant reduction in muscle lactate concentrations at barometric pressures of 380 and 282 mmHg. This is consistent with the observation of low blood lactate concentrations after exhaustive exercise at extreme altitude in acclimatized subjects referred to earlier.

The studies described above on the pulmonary circulation by cardiac catheterization, pulmonary gas exchange by arterial puncture and the sophisticated multiple inert gas elimination technique and skeletal muscle by needle biopsy emphasize the very sophisticated and invasive nature of the studies that can be done in a low-pressure chamber. Nevertheless there are some disadvantages in simulating an ascent to extreme altitude in this way. For some unexplained reason the subjects never acclimatize as well as they do on a mountain. The instigator of Operation Everest II, Charles Houston, clearly recognized this when he wrote “Why, in such a pampered state, did they [the subjects of OEl] not acclimatize better? Was ascent too fast, time at altitude to short? Are the stresses of a mountain a help rather than a hindrance in acclimatization? Perhaps the extreme work of climbing, or the bitter cold, or the anxiety and tension all enhance acclimatization more than we anticipated. We don’t know.” (Houston, 1988–1989, p. 100). The lack of acclimatization was seen in various measurements including a higher alveolar $P_{CO_2}$ and lower alveolar $P_{O_2}$ at extreme altitude, a correspondingly smaller increase in arterial pH, higher blood lactate values compared with other measurements at similar altitudes in acclimatized climbers, and the fact that maximal exercise ventilations increased with altitude right up to the “summit” which is contrary to the experience of AMREE and the Silver Hut expedition. Thus while this extensive chamber study gave very valuable information in the areas of the physiology of the pulmonary circulation, pulmonary gas exchange and skeletal muscle changes, for some unexplained reason it did not accurately simulate changes in the field.

**Operation Everest III**

Other simulated climbs of Mt. Everest have been made in low-pressure chambers. One of the most important was that carried out by Richalet et al. (1999) in 1997 at the COMEX facility in Toulouse, France. Eight volunteers preacclimatized in the Vallot Observatory (4350 m) and then spent a total of 31 days in the low-pressure chamber ultimately reaching a barometric pressure of 253 mmHg. Arterial blood gas values were similar to those of Operation Everest II with a “summit” arterial $P_{O_2}$ of 31 mmHg, $P_{CO_2}$ of 12 mmHg and pH of 7.58. The higher $P_{CO_2}$ than on AMREE for both of these chamber studies is consistent with a lesser degree of acclimatization. Body weight fell on an average by 5.4 kg again indicating that the physiological changes allow survival rather than successful long-term adaptation. Many other measurements were made including confirmation of the marked pulmonary hypertension and the preserved left ventricular contractility (Boussuges et al., 2000). However an interesting finding was transient neurological disorders possibly caused by gas emboli and also marked changes in mood in some subjects.

**Recent field studies**

Few field studies on physiology of extreme altitude have been done since the 1980s. One exception was the British 40th Anniversary Everest Expedition which took place in 1993 when measurements of alveolar $P_{O_2}$ and arterial oxygen saturation were made on 9 subjects as they climbed from 3500 m to 8000 m on the south side of Everest. The alveolar $P_{O_2}$ was measured with a fuel cell analyzer and the oxygen saturation values came from pulse oximetry. Four climbers reached an altitude 8000 m and one was successful in getting to the summit. The values for alveolar $P_{O_2}$ agreed well with the AMREE data, being 38 mmHg at an altitude of 8000 m compared with the mean value on AMREE of 37 mmHg for the same altitude. Again, the arterial oxygen saturation measured by pulse oximetry at 8000 m was 70% while that calculated from the AMREE blood and alveolar gas measurements was 71% (Winslow et al., 1984). It is interesting that the arterial oxygen saturation is maintained at a relatively high value, and this can be explained by the extraordinary respiratory alkalosis (Table 2).

**Deterioration at extreme altitude**

As indicated earlier extreme altitudes are associated with a progressive deterioration of the body that precludes permanent residence. The precise altitude...
at which this occurs is unclear but certainly it was certainly evident during the Silver Hut expedition when some 8 physiologists spent several months at an altitude of 5800 m. Having said this caretakers at the Aucanquilcha mine in north Chile have spent as long as two years at an altitude of 5950 m (West, 1986) but these were Bolivians and perhaps there is a difference between lowlanders and highlanders in this respect. Also the caretakers did make weekly excursions to the lower altitude of 4200 m to play football!

The causes of deterioration at extreme altitude are poorly understood but presumably are related to the extreme hypoxia. The most striking feature is a relentless loss of weight. For example on the Silver Hut expedition the rate of weight loss was between 0.5 and 1.5 kg.wk\(^{-1}\) with total weight losses ranging from 6.4 to 9 kg (Pugh, 1962). The cause of this weight loss is not entirely clear although certainly appetite is reduced at high altitude. There was an abundance of food at the Silver Hut although these were the early days of freeze-dried food which was not as palatable as it is today. The mean weight loss during Operation Everest II was 7.4 kg half of which was muscle (Rose et al., 1988). During that experiment calorie intake was meticulously measured and it was concluded that the weight loss was mainly due to anorexia with the weight loss falling proportionally to calorie intake. Body weight also decreased by an average 5.4 kg during Operation Everest III and again this was attributed to a negative caloric balance (Richalet et al., 1999). Other unpleasant features of being at extreme altitude include mood changes, insomnia and severe breathlessness accompanying even minor physical activities.

An interesting feature of the Silver Hut expedition was that it was possible to go down to the Base Camp at an altitude of 4650 m in one day and this usually resulted in a rapid gain in weight. In fact a striking feature of extreme altitudes is how quickly general well-being increases with only a moderate decrease in altitude.

Although anorexia is probably the dominant cause of the weight loss, there is some evidence of intestinal malabsorption. Some members of the Silver Hut expedition noted fatty stools as in steatorrhea and on AMREE there was evidence of reductions of both fat and xylose absorption (Boyer and Blume, 1984). Milledge had earlier obtained evidence of impaired xylose absorption in patients who were hypoxic (Milledge, 1972), and Dinmore et al. (1994) found impaired xylose absorption at high altitude. Westerterp and colleagues (1994) also reported malabsorption at an altitude of 6542 m.

### Conclusion

In conclusion human beings who are successful in ascending to extreme altitudes show extraordinary physiological changes in response to the uniquely low inspired \(P_{O_2}\). These responses allow the climber to survive this extremely hostile environment and return to tell the tale. The responses include an enormous increase in ventilation which maintains the alveolar \(P_{O_2}\) at a value of about 35 mmHg but in the process drives the alveolar \(P_{CO_2}\) down to 7–8 mmHg. Interestingly the consequent respiratory alkalosis increases the oxygen affinity of hemoglobin, a features that the successful climber shares with many animals that live in oxygen-deprived environments. The increased affinity assists the loading of oxygen in the pulmonary capillary. Nevertheless the \(V_{O_2max}\) is extremely low at about 1 l.min\(^{-1}\). Paradoxically anaerobic metabolism is also greatly reduced at extreme altitudes.

However these dramatic changes are not compatible with long-term survival. For example, even at the comparatively modest altitude of 5800 m during the Silver Hut expedition, there was a relentless loss of weight over some 3–4 months. Thus the physiological responses in response to extreme altitudes should be thought of in terms of survival rather than successful long-term adaptation to the environment. Finally it is worth noting again the extraordinary coincidence that the highest point on Earth subjects humans to a degree of oxygen deprivation that appears to be very close to the limit for survival.

### Acknowledgments

The work was supported by NIH grant RO1 HL 60698.

### References


