ORIGINAL ARTICLE

# Arterial Blood Gases and Oxygen Content in Climbers on Mount Everest

Michael P.W. Grocott, M.B., B.S., Daniel S. Martin, M.B., Ch.B., Denny Z.H. Levett, B.M., B.Ch., Roger McMorrow, M.B., B.Ch., Jeremy Windsor, M.B., Ch.B., and Hugh E. Montgomery, M.B., B.S., M.D., for the Caudwell Xtreme Everest Research Group*

## ABSTRACT

### BACKGROUND

The level of environmental hypobaric hypoxia that affects climbers at the summit of Mount Everest (8848 m [29,029 ft]) is close to the limit of tolerance by humans. We performed direct field measurements of arterial blood gases in climbers breathing ambient air on Mount Everest.

### METHODS

We obtained samples of arterial blood from 10 climbers during their ascent to and descent from the summit of Mount Everest. The partial pressures of arterial oxygen ($PaO_2$) and carbon dioxide ($PaCO_2$), pH, and hemoglobin and lactate concentrations were measured. The arterial oxygen saturation ($SaO_2$), bicarbonate concentration, base excess, and alveolar–arterial oxygen difference were calculated.

### RESULTS

$PaO_2$ fell with increasing altitude, whereas $SaO_2$ was relatively stable. The hemoglobin concentration increased such that the oxygen content of arterial blood was maintained at or above sea-level values until the climbers reached an elevation of 7100 m (23,294 ft). In four samples taken at 8400 m (27,559 ft) — at which altitude the barometric pressure was 272 mm Hg (36.3 kPa) — the mean $P_{A}O_2$ in subjects breathing ambient air was 24.6 mm Hg (3.28 kPa), with a range of 19.1 to 29.5 mm Hg (2.55 to 3.93 kPa). The mean $PaCO_2$ was 13.3 mm Hg (1.77 kPa), with a range of 10.3 to 15.7 mm Hg (1.37 to 2.09 kPa). At 8400 m, the mean arterial oxygen content was 26% lower than it was at 7100 m (145.8 ml per liter as compared with 197.1 ml per liter). The mean calculated alveolar–arterial oxygen difference was 5.4 mm Hg (0.72 kPa).

### CONCLUSIONS

The elevated alveolar–arterial oxygen difference that is seen in subjects who are in conditions of extreme hypoxia may represent a degree of subclinical high-altitude pulmonary edema or a functional limitation in pulmonary diffusion.

From the Centre for Altitude, Space, and Extreme Environment Medicine, University College London Institute of Human Health and Performance, London. Address reprint requests to Dr. Grocott at the Centre for Altitude, Space, and Extreme Environment Medicine, University College London Institute of Human Health and Performance, 1st Fl., Charterhouse Bldg., Archway Campus, Highgate Hill, London N19 5LW, United Kingdom, or at mike.grocott@ucl.ac.uk.

Drs. Grocott and Martin contributed equally to this article.

*The members of the Caudwell Xtreme Everest Research Group are listed in the Appendix.

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The partial pressure of atmospheric oxygen falls progressively as barometric pressure decreases with increasing altitude. Correspondingly, the ability to perform work (e.g., walking or climbing) diminishes with the decreased availability of atmospheric oxygen for aerobic respiration.[1,2] At the summit of Mount Everest (8848 m [29,029 ft]), the highest point on the earth's surface, the partial pressure of inspired oxygen ($PIO_2$) is believed to be very close to the limit that acclimatized humans can tolerate while maintaining functions such as ambulation and cognition.[3] Hillary and Tenzing used supplemental oxygen to achieve the first ascent of Everest in 1953. It was not until 25 years after their ascent that the first ascent of Everest without supplemental oxygen was made by Messner and Habeler.[4] Currently, less than 4% of persons who climb Everest do so without the use of supplemental oxygen (Salisbury R., Himalayan database: personal communication).

The only published measurements of the partial pressure of oxygen in arterial blood ($PaO_2$) at such a low barometric pressure were reported in two studies — Operation Everest II and Operation Everest III (Comex '97) — that were designed to simulate an ascent of Mount Everest by placing subjects in a hypobaric chamber.[5,6] The subjects in the two studies had a mean (±SD) resting $PaO_2$ of 30.3±2.1 mm Hg (4.04±0.28 kPa) and 30.6±1.4 mm Hg (4.08±0.19 kPa), respectively, at a barometric pressure equivalent to the summit of Mount Everest (253.0 mm Hg, or 33.73 kPa). Such profound hypoxemia was tolerable because the subjects had been gradually acclimatized to the simulated altitude over a period of 37 to 40 days. In 1981, the partial pressures of oxygen and carbon dioxide ($PaCO_2$) at end expiration were measured in a single person on Everest's summit after the person had been breathing without supplemental oxygen for approximately 10 minutes.[7] With the use of a classic Bohr integration, the $PaO_2$ for this climber was estimated to be 28 mm Hg (3.73 kPa).

We made direct field measurements of $PaO_2$ and arterial oxygen content ($CaO_2$) in climbers breathing ambient air at these extreme altitudes.

## METHODS

### STUDY PARTICIPANTS

We obtained approval for this study from the University College London Committee on the Ethics of Non-NHS Human Research. All participants gave written informed consent. The subjects in this study were 10 healthy climbers (9 men and 1 woman, ranging in age from 22 to 48 years), who were ascending Everest by its southeast ridge as part of a medical research expedition (Caudwell Xtreme Everest).[8,9]

All subjects had ascended higher than 6800 m (22,310 ft) without incident on previous expeditions, and all were well acclimatized, with no evidence of ill effects from high altitude or of other illnesses. Subjects who were ascending higher than 7950 m (26,083 ft) had all previously ascended higher than that altitude without incident.

### COLLECTION OF BLOOD SAMPLES

Arterial blood samples were obtained in London, at an altitude of 75 m (246 ft); at the Everest base camp, at an altitude of 5300 m (17,388 ft); in Camp 2, at an altitude of 6400 m (20,997 ft); in Camp 3, at an altitude of 7100 m (23,294 ft); and during the descent from the summit at a feature known as the Balcony, at an altitude of 8400 m (27,559 ft) (Fig. 1). The samples that were obtained in London and at the Everest base camp were obtained with the subject at rest, with the use of indwelling radial arterial cannulae that were placed as part of other study protocols; these samples were analyzed immediately. Samples obtained at an altitude higher than the Everest base camp were obtained from the right femoral artery, identified by digital palpation. Intraarterial placement of the needle (21-gauge) was confirmed by pulsatile filling of a heparinized 2-ml oiled glass syringe (Fisher Scientific). Syringes were immediately sealed with an airtight cap and placed in a plastic bag, which in turn was placed in an ice-water slurry inside an insulated vacuum flask. The flask was rapidly transported to a laboratory at Camp 2 in the Western Cwm; the length of time for this transfer to be completed was recorded. Barometric pressure was measured at the altitude at which the blood samples were taken, with the use of a handheld digital barometer (GPB 2300, Greisinger Electronic). Arterial samples were obtained by two investigators, both of whom had extensive experience with cannulation of the femoral artery and blood sampling.

### SUPPLEMENTAL OXYGEN

Supplemental oxygen was used only at or above Camp 3 (7100 m), with the following flow rates: 2 to 3 liters per minute while the subject was

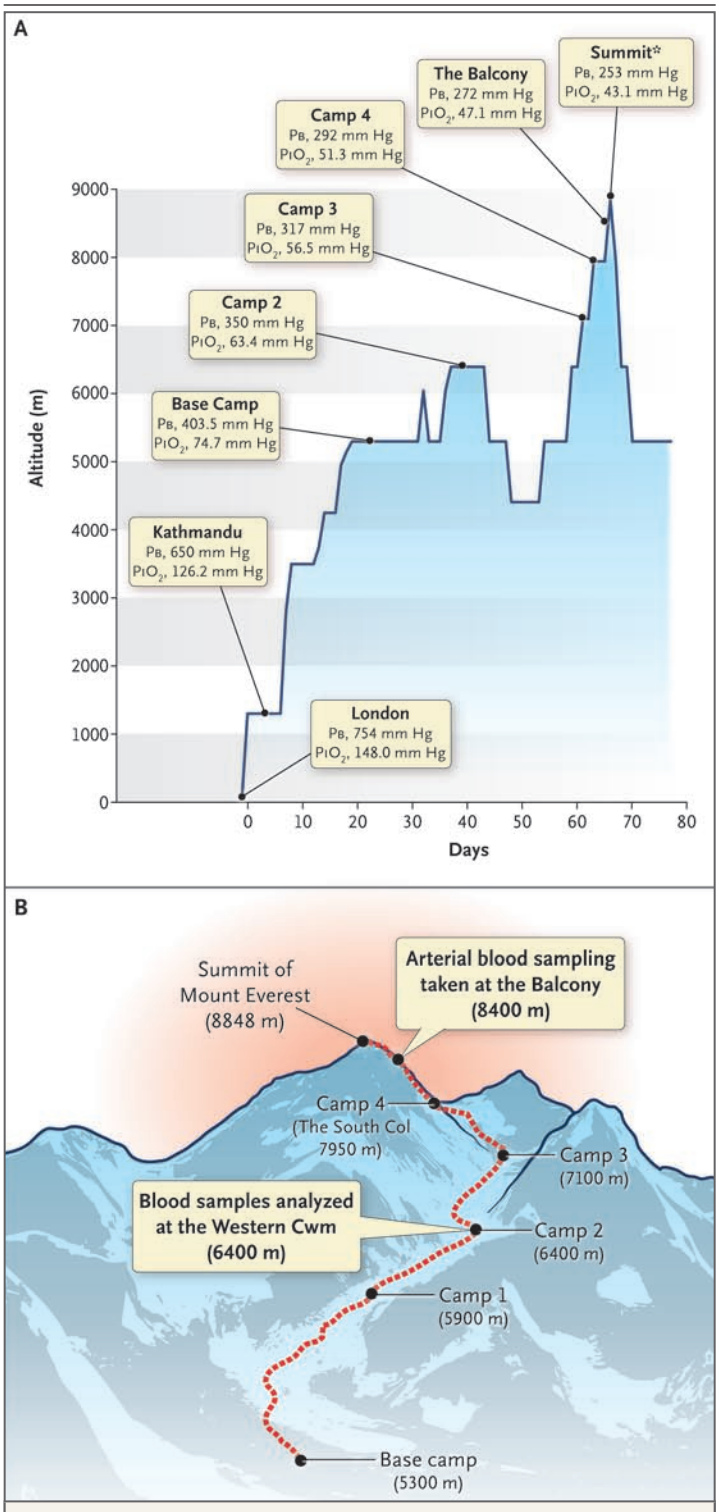


**Figure 1. Barometric Pressure ($P_B$) and Partial Pressure of Inspired Oxygen ($P_IO_2$) in Blood Samples Obtained from Subjects Breathing Ambient Air at Various Altitudes between London and the Summit of Mount Everest.**

In Panel A, the measurements at the summit are reported from West et al.[7] The other measurements were performed by the investigators.

climbing and 0.5 liter per minute while the subject was sleeping. Supplemental oxygen was infrequently used while the subjects were resting at Camp 3 and Camp 4 (7950 m). At Camp 3, arterial samples were obtained after the subjects had been breathing ambient air for at least 4 hours. At the Balcony, samples were obtained after the subjects had been breathing ambient air for 20 minutes in order to achieve an adequate washout of supplemental oxygen.

### ANALYSIS OF BLOOD SAMPLES

Arterial blood samples were analyzed with the use of the RapidLab 348 (Siemens Medical Solutions Diagnostics) blood gas analyzer, which does not contain a co-oximeter. The $PaO_2$, the $PaCO_2$, and the pH were measured. Values for the bicarbonate concentration, blood base excess, and oxygen saturation ($SaO_2$) were calculated with the use of formulas currently approved by the Clinical Laboratory Standards Institute[10] (Table 1). The blood lactate concentration was measured with a separate device (Lactate Scout, EKF Diagnostic). Barometric pressure was measured at the site of analysis with the use of the same model of barometer as that used at the sampling site.

The blood gas analyzer was altered from its original specification so that it would function at high altitude. The analyzer's internal barometer was bypassed with a fixed resistor so that the analyzer always read as if the barometric pressure was a constant 450 mm Hg (60.0 kPa), regardless of altitude. This modification was necessary in order to circumvent an inbuilt mechanism that prevented the analysis of samples at a barometric pressure lower than 400 mm Hg (53.3 kPa). To replicate the barometric-pressure correction that the machine would normally apply in its unmodified form, true gas partial-pressure values were obtained by inserting the machine-derived values into Equation 1, shown in Table 1. This calculation is identical to that performed internally by the arterial blood gas analyzer during normal function at lower altitudes.

The subjects' temperatures at the time of sampling were assumed to be the same as the temperature of the blood gas analyzer — namely, 37.0°C (98.6°F). The analyzer was validated in a hypobaric chamber at the equivalent of 4000 m (13,123 ft) and then revalidated in the field, at 5300 m and 6400 m, the altitudes at which measurements of arterial blood gas were performed

**Table 1. Equations Used for the Calculation of Arterial Blood Gas Values and Arterial Oxygen Content.***

**1. Actual partial pressure of oxygen in arterial blood samples ($PaO_2$)**

$$PaO_2 = \frac{\text{measured } P_B \text{ at site of ABG machine} - SVP}{\text{resistor set } P_B \text{ (i.e., 450 mm Hg)} - SVP} \times \text{value of } PO_2 \text{ given by ABG machine}$$

**2. Arterial oxygen saturation ($SaO_2$)†**

$$SaO_2(\%) = \frac{N^4 - (15 \times N^3) + (2045 \times N^2) + (2000 \times N)}{N^4 - (15 \times N^3) + (2400 \times N^2) - (31{,}100 \times N) + (2.4 \times 10^6)} \times 100$$

$$N = PO_2 \times 10^{[0.48 \times (pH - 7.4) - 0.0013 \times BE]}$$

**3. Bicarbonate concentration ($HCO_3^-$)†**

$$HCO_3^- \text{ (mmol/liter)} = 0.0307 \times PaCO_2 \times 10^{(pH - 6.105)}$$

**4. Blood base excess (BE)†**

$$BE = (1 - 0.014 \times Hb) \times (HCO_3^- - 24.8) + (7.7 + 1.43 \times Hb) \times (pH - 7.4)$$

**5. Partial pressure of inspired oxygen ($PIO_2$)**

$$PIO_2 = (P_B - SVP) \times FIO_2$$

**6. Partial pressure of alveolar oxygen ($PAO_2$) — The "alveolar gas equation"**

$$PAO_2 = PIO_2 - \frac{PACO_2}{RER} + \left[PACO_2 \times FIO_2 \times \frac{1 - RER}{RER}\right]$$

$PACO_2$ was assumed to be equal to $PaCO_2$

**7. Arterial oxygen content ($CaO_2$)**

$$CaO_2 = SaO_2 \times Hb \times 1.39 + (PaO_2 \times 0.03)$$

* ABG denotes arterial blood gas, BE base excess, $FIO_2$ fraction of inspired oxygen, Hb hemoglobin concentration, $PACO_2$ partial pressure of alveolar carbon dioxide, $PaCO_2$ partial pressure of arterial carbon dioxide, $P_B$ barometric pressure, $PO_2$ partial pressure of oxygen, RER respiratory exchange ratio, and SVP saturated vapor pressure at body temperature (47 mm Hg).

† This equation is currently approved by the Clinical Laboratory Standards Institute (http://www.clsi.org).[10]

in this study. Validation involved the analysis of aqueous trilevel quality-control solutions (RapidQC Plus, Bayer HealthCare) with known values of pH, $PaO_2$, and $PaCO_2$. Two-point calibration of the RapidLab 348 gas sensors and electrodes was performed automatically according to the manufacturer's specifications with the use of standard gases and electrolyte solutions, respectively. Each arterial blood sample was analyzed three times, and the mean of these values is reported. Because the pulse oximeters available to us were not calibrated below 70% $SaO_2$, we chose to calculate $SaO_2$ using Equation 2, shown in Table 1. All reported values for $SaO_2$ are calculated values, except for the values for four subjects at an altitude of 5300 m; for these subjects, values obtained by peripheral-pulse oximetry (Onyx 9500, Nonin) are reported owing to an isolated failure of the pH electrode on the blood gas machine, an electrode that was subsequently replaced. All measured and calculated values for $SaO_2$ at an altitude of 5300 m fell within the calibrated range of the pulse oximeter.

The hemoglobin concentration was measured in venous blood collected from subjects in London before the expedition, at the Everest base camp (at 2-week intervals during the expedition), and at Camp 2, with the use of a handheld photo-

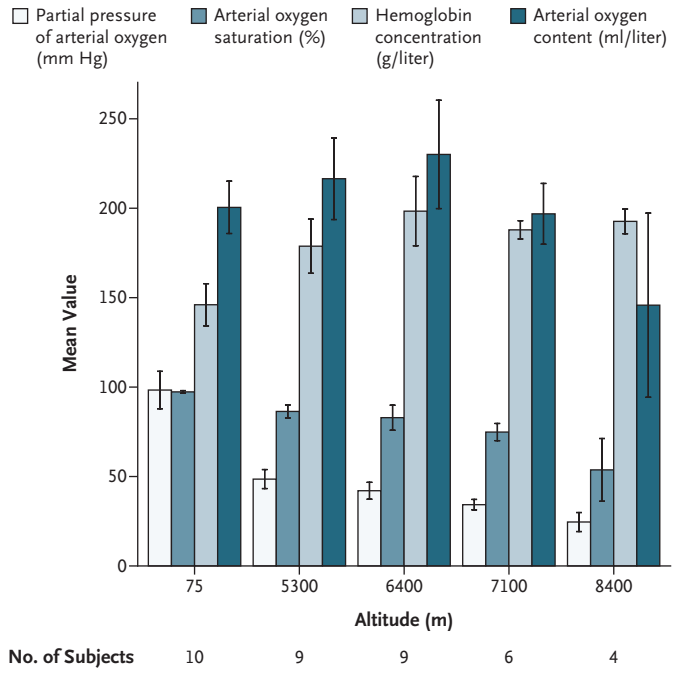


**Figure 2. Changes in the Arterial Mean Partial Pressure of Oxygen, Oxygen Saturation, Hemoglobin Concentration, and Oxygen Content in Climbers on Mount Everest.**

I bars denote standard deviations.

metric device (HemoCue Whole Blood Hemoglobin System, HemoCue). Venous samples were obtained at the same time as arterial samples in London, at the Everest base camp, and at Camp 2. For the hemoglobin concentration at Camp 3 and the Balcony, we used the mean of the hemoglobin values obtained at the Everest base camp 9 days before and 8 days after the arterial sample at the Balcony was obtained (Fig. 1); these values were used in the calculation of $CaO_2$, bicarbonate concentration, and blood base excess.

The partial pressure of alveolar oxygen ($PAO_2$) at the time of sampling was estimated by applying the alveolar gas equation to the calculated $PIO_2$ (Equations 5 and 6 in Table 1). The resting respiratory exchange ratios necessary for these calculations were obtained for three of the subjects at the South Col of Everest on the day before summiting, with the use of breath-by-breath analysis equipment (MetaMax 3B, Cortex Biophysik).

## RESULTS

### COLLECTION OF SAMPLES

The climbers reached the summit of Mount Everest on the morning of May 23, 2007, after having spent 60 days at an elevation higher than 2500 m (8202 ft). The location, altitude, barometric pressure, and $PIO_2$ for each sampling site are shown in Figure 1. All femoral arterial blood samples were obtained without complications on the first attempt. Ten samples were obtained in London, nine at the Everest base camp, nine at Camp 2, six at Camp 3, and four at 8400 m. The reasons for not obtaining samples were as follows: at the Everest base camp, one subject was unwell; at Camp 2, one subject was unwell; at Camp 3, four subjects were not present when the Sherpa was available to transport the sample; and at the Balcony, two subjects did not reach this altitude, and four subjects were not present when the Sherpa was available to transport the sample. One sample at Camp 2 repeatedly clotted in the arterial blood gas machine, so no data are available for that sample. In all cases, the interval between sampling and analysis was less than 2 hours.

### ARTERIAL BLOOD GASES

Measured $PaO_2$ and hemoglobin values, along with calculated $SaO_2$ and $CaO_2$ values, are shown in Figure 2. The $CaO_2$ value at sea level was maintained up to an altitude of 7100 m and fell below baseline only at 8400 m; at this altitude, the mean $CaO_2$ for the four subjects was calculated to be 145.8 ml per liter. Mean $PaCO_2$ values fell with increasing altitude, from 36.6 mm Hg (4.88 kPa) at sea level to 20.4 mm Hg (2.72 kPa) at 5300 m, 18.2 mm Hg (2.43 kPa) at 6400 m, and 16.7 mm Hg (2.23 kPa) at 7100 m; corresponding pH values were 7.40, 7.46, 7.51, and 7.53.

The results of the arterial blood gas analysis and the hemoglobin and lactate concentrations in four subjects at 8400 m are shown in Table 2. The mean $PaO_2$ and $PaCO_2$ values were 24.6 mm Hg (3.28 kPa) and 13.3 mm Hg (1.77 kPa), respectively. The mean $PAO_2$ value at 8400 m was calculated to be 47.0 mm Hg (6.27 kPa) at the time of arterial sampling. Calculated values for $PAO_2$, resting respiratory exchange ratios, and the alveolar–arterial oxygen difference in four subjects at 8400 m are shown in Table 2. The mean $PAO_2$ and

**Table 2. Arterial Blood Gas Measurements and Calculated Values for Pulmonary Gas Exchange from Four Subjects at an Altitude of 8400 m, during Descent from the Summit of Mount Everest.***

| Variable | Subject No. | | | | Group Mean |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| pH | 7.55 | 7.45 | 7.52 | 7.60 | 7.53 |
| $PaO_2$ (mm Hg)† | 29.5 | 19.1 | 21.0 | 28.7 | 24.6 |
| $PaCO_2$ (mm Hg)† | 12.3 | 15.7 | 15.0 | 10.3 | 13.3 |
| Bicarbonate (mmol/liter)‡ | 10.5 | 10.67 | 11.97 | 9.87 | 10.8 |
| Base excess of blood‡ | −6.3 | −9.16 | −6.39 | −5.71 | −6.9 |
| Lactate concentration (mmol/liter) | 2.0 | 2.0 | 2.9 | 1.8 | 2.2 |
| $SaO_2$ (%)‡ | 68.1 | 34.4 | 43.7 | 69.7 | 54.0 |
| Hemoglobin (g/dl)§ | 20.2 | 18.7 | 18.8 | 19.4 | 19.3 |
| Respiratory exchange ratio¶ | 0.81 | 0.74‖ | 0.72 | 0.70 | 0.74 |
| $PAO_2$ — mm Hg†** | 32.4 | 26.9 | 27.4 | 33.2 | 30.0 |
| Alveolar–arterial oxygen difference — mm Hg† | 2.89 | 7.81 | 6.44 | 4.51 | 5.41 |

* $PaCO_2$ denotes partial pressure of arterial carbon dioxide, $PAO_2$ partial pressure of alveolar oxygen, $PaO_2$ partial pressure of arterial oxygen, and $SaO_2$ calculated arterial oxygen saturation.
† To convert the values for $PaO_2$, $PaCO_2$, $PAO_2$, 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.[10]
§ The values for hemoglobin 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 7950 m 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.
** $PAO_2$ was calculated with the use of the full alveolar gas equation.

the mean alveolar–arterial oxygen difference were 30.0 mm Hg (4.00 kPa) and 5.4 mm Hg (0.72 kPa), respectively. None of the subjects were considered, on clinical grounds, to have high-altitude pulmonary edema during the study period.

## DISCUSSION

These measurements of arterial blood gases and hemoglobin levels in climbers on Mount Everest provide a picture of the pattern and limits of changes in human blood gases in response to hypobaric hypoxia on the earth's highest mountain. Because of adverse weather conditions, we were unable to obtain arterial samples at the summit of Mount Everest as originally planned. Consequently, the samples at the highest altitude were obtained during the descent from the summit. A small shelter was erected at the first safe location, an area known as the Balcony, which is located at an altitude of 8400 m, and the blood sampling took place in this shelter. The values for $PaO_2$ and $SaO_2$ reported here are, to our knowledge, among the lowest ever documented in humans. The results of a study of alveolar breath samples obtained from divers suggest that breath-hold divers may have $PaO_2$ levels that are lower than 30 mm Hg (4.0 kPa), but no direct measurements have been reported.[11] Similar values have been reported in a study of samples obtained at a high altitude, but in that study, measurements were obtained from subjects who had high-altitude pulmonary edema.[12,13]

Decreases in $PaO_2$ are broadly proportional to the fall in barometric pressure with increasing altitude, whereas $SaO_2$ is relatively well maintained (in relation to barometric-pressure changes) owing to the characteristics of the oxygen–hemoglobin dissociation curve and the effects of respiratory acclimatization (decreased $PaCO_2$). Increases in the hemoglobin concentration compensate for the fall in $SaO_2$ such that $CaO_2$ is maintained until

a person reaches an altitude of at least 7100 m. Thus, changes in $CaO_2$ do not provide an explanation for the significant limitations in individual performance previously reported at these altitudes (a reduction in maximum oxygen consumption of 30 to 35% at 5300 m[1,7]). $CaO_2$ at 8400 m is significantly lower than that at sea level, and the marked interindividual variability at this altitude is related predominantly to differences in $SaO_2$, probably reflecting a combination of variation in ventilatory acclimatization, hypoxic ventilatory response, hypoxic ventilatory depression, and the alveolar–arterial oxygen difference, as discussed below.

At the highest altitude at which samples were obtained, the subjects had an impressive adaptive response (i.e., acclimatization) to prolonged and extreme environmental hypoxia. Persons who are not acclimatized lose consciousness within 2 to 3 minutes when they are exposed suddenly to levels of ambient hypoxia equivalent to those at altitudes higher than 8534 m (27,999 ft).[1,4] In contrast, our subjects had apparently clear cognition, as evidenced by effective radio communication and, in the case of two of the subjects, the performance of complication-free sampling of arterial blood gases. The absence of obvious neurocognitive abnormalities suggests that cerebral hypoxia was not manifested as a substantial dysfunction at the time of blood sampling. This is of interest in view of the evidence that there is a risk of long-term cognitive deficit and structural neurologic damage from exposure to these extreme altitudes.[15-17] Despite chronic hypoxemia, none of the subjects in this study had clinically significant hyperlactatemia (mean lactate concentration, 2.2 mmol per liter at the highest altitude), consistent with findings in resting subjects exposed to hypobaric hypoxia.[5] This suggests that anaerobic metabolism does not contribute substantially to energy production at an extreme altitude while a person is at rest. An alternative, or additional, explanation is the possibility of increased lactate use as a fuel source at extreme altitudes.[18]

We cannot exclude the possibility that the use of supplemental oxygen at and above Camp 3 was a confounding influence on the acclimatization process and thus on $PaO_2$ and $PaCO_2$. Supplemental oxygen benefits climbers subjectively and improves $SaO_2$ in the resting state and during exercise.[19] During this study, the safety benefits related to supplemental oxygen were considered to be of overriding importance while the subjects were climbing on Mount Everest.[20] We believe that the 20-minute rest period that the subjects had without supplemental oxygen before arterial sampling should have been more than adequate to ensure a washout of supplemental oxygen from the circulation. However, the effects on ventilation of suddenly removing supplemental oxygen at such an altitude are unknown. Climbers who reach the summit of Mount Everest without using supplemental oxygen may have more effective ventilatory acclimatization than those who use supplemental oxygen, and they may therefore have a higher $PaO_2$ while breathing ambient air than do those who choose to use supplemental oxygen. Removing supplemental oxygen in a hypoxic environment is known to trigger two sequential yet variable phenomena. The hypoxic ventilatory response leads to hyperventilation within minutes after exposure to hypoxia and is followed by hypoxic ventilatory depression approximately 10 to 30 minutes after exposure.[21] The effect of these opposing responses to hypoxia on the $PaO_2$ and $PaCO_2$ values in this study is difficult to quantify. Interindividual variability in the hypoxic ventilatory response and hypoxic ventilatory depression may account for the variability in arterial blood gas values in our subjects as compared with the results of a study involving subjects in a hypobaric chamber, in which supplemental oxygen was not used immediately before sampling.[5]

The methods of storage and transportation of the blood samples in this study were used by our group on two previous expeditions to extreme altitudes and were shown to be effective. The time lapse between sampling and analysis was 2 hours or less in all cases. The effect of storing blood in this manner has been described previously[22]; the partial pressure of oxygen in the blood samples rose approximately 0.75 mm Hg (0.1 kPa) after 2 hours of storage. Our own experiments at sea level have shown a similar mean rise in the partial pressure of oxygen (1.1 mm Hg [0.15 kPa]) in samples of venous blood after 2 hours. Therefore, any effect of the duration of storage and transportation on the reported values would tend to lead to a small overestimation of measured $PaO_2$.

Our findings are consistent with the results of the previous three studies of $PaO_2$ in extreme

hypobaric conditions.[5-7] The mean measured $PaO_2$ in our study was 24.6 mm Hg (3.28 kPa) at 8400 m, as compared with 30.3 mm Hg (4.04 kPa)[5] or 30.6 mm Hg (4.08 KPa)[6] at a simulated altitude of 8848 m, and 28.0 mm Hg (3.73 kPa) as estimated by West et al. from an alveolar gas sample obtained at 8848 m.[7] The mean $PaO_2$ in our subjects was lower than these values, despite the fact that our subjects were at a slightly higher barometric pressure (lower altitude). The $PaCO_2$ reported in the study by West et al.[7] was only 7.5 mm Hg (1.0 kPa), slightly more than half the mean $PaCO_2$ reported in this study (13.3 mm Hg [1.78 kPa]). This finding may be explained by the fact that the subject from whom the alveolar gas sample was collected in the study of West et al.[7] was known to have an extremely brisk hypoxic ventilatory response.[23] Possible explanations for the differences between the data in this study and the results of previous hypobaric-chamber studies may be related to differences in ascent profiles, activity levels, and the use of supplemental oxygen. In the hypobaric-chamber studies, the subjects were exposed to hypobaric conditions for a period of 37 to 40 days,[5,6] as compared with 60 days in this study (Fig. 1), and although they underwent periodic exercise tests, activity levels were much lower than those in our subjects, who were climbing to the summit of Everest. Whereas subjects in our study used supplemental oxygen as described, subjects in Operation Everest II were similarly exposed to an elevated fraction of inspired oxygen either because the chamber pressure was increased at night to help them sleep or during the conduct of pulmonary artery catheterization studies.[5,24]

At an altitude of 8400 m, the mean calculated $PAO_2$ was 30.0 mm Hg (4.00 kPa), and the mean calculated alveolar–arterial oxygen difference was 5.4 mm Hg (0.72 kPa) (Table 2). It is known that the alveolar–arterial oxygen difference decreases as the $PIO_2$ falls.[25] Both theoretical considerations and empirical data suggest that the alveolar–arterial oxygen difference should be less than 2 mm Hg (0.27 kPa) under these conditions[26]; Sutton et al. report a mean alveolar–arterial oxygen difference of 1.5 mm Hg (0.20 kPa) in resting healthy persons at the simulated altitude of 8848 m.[5]

Hypoxia associated with an increased alveolar–arterial oxygen difference may be attributable to shunting, a ventilation–perfusion mismatch, or a limitation in pulmonary diffusion. We speculate that the relatively high alveolar–arterial oxygen difference in the subjects in this study may be the result of subclinical high-altitude pulmonary edema contributing to both a ventilation–perfusion mismatch and impairment of pulmonary diffusion. An alternative explanation might be disequilibrium in pulmonary alveolar–end-capillary diffusion, which has been shown to occur in conditions of hypobaric hypoxia.[27,28] Previous investigators have observed an increased alveolar–arterial oxygen gradient after strenuous exercise in subjects exposed to hypobaric hypoxia,[25,29,30] and this may be a key difference between the results of this study and those of previous investigations involving subjects in a hypobaric chamber.

In our study, arterial blood sampling was performed with subjects in the supine position, and this factor may have confounded measurements through mechanisms such as increased basal atelectasis or central fluid shifts that can be detrimental to pulmonary gas exchange. $PaO_2$ has been reported to be inversely related to the alveolar–arterial oxygen difference[30]; this finding may explain the low $PaO_2$ in Subject 2 (19.1 mm Hg [2.55 kPa]), the subject in the group who had the highest alveolar–arterial oxygen difference. The respiratory exchange ratios in subjects who had just reached the summit of Mount Everest may be higher than those that were measured at a resting steady state the previous day on the South Col at 7950 m. However, such an elevation in respiratory exchange ratios would only serve to increase the alveolar–arterial oxygen difference and increase the significance of these findings. For example, if the respiratory exchange ratio was assumed to be 1.0 in all four subjects at the time of blood sampling, the mean alveolar–arterial oxygen difference would be 9.1 mm Hg (1.21 kPa), instead of 5.4 mm Hg (0.72 kPa).

Tissue hypoxia is a universal phenomenon among persons who are critically ill[31] and is often the result of arterial hypoxemia. In conjunction with the initiating factor and the presence of any coexisting condition, hypoxia triggers numerous adaptive and maladaptive systemic responses that remain poorly understood. Defining the limits of hypoxia tolerance is of direct relevance to physicians who care for critically ill patients because many interventions that are aimed at restoring or maintaining cellular oxygenation have proven ineffective or even detrimental. For ex-

ample, a high $P_IO_2$ can have pulmonary toxic effects.[32] Moreover among patients with established critical illness, increasing the hemoglobin concentration to increase oxygen carriage may not provide a clinical benefit,[33] and a goal-directed elevation of systemic oxygen can be detrimental.[34] Useful insights may be gained by examining the biophysiologic responses of healthy persons who are exposed to low levels of environmental oxygen.

In summary, we report field measurements of the partial pressure of oxygen and carbon dioxide, pH, and hemoglobin and lactate concentrations in the arterial blood of humans at extreme altitudes. We speculate that the calculated alveolar–arterial oxygen difference in these subjects suggests a degree of functional limitation in pulmonary diffusion or subclinical pulmonary edema, conditions that may explain why the values for $PaO_2$ are lower than expected.

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## APPENDIX

The members of the Caudwell Xtreme Everest Research Group are as follows: *Investigators* — V. Ahuja, G. Aref-Adib, R. Burnham, A. Chisholm, K. Clarke, D. Coates, M. Coates, D. Cook, M. Cox, S. Dhillon, C. Dougall, P. Doyle, P. Duncan, M. Edsell, L. Edwards, L. Evans, P. Gardiner, M. Grocott, P. Gunning, N. Hart, J. Harrington, J. Harvey, C. Holloway, D. Howard, D. Hurlbut, C. Imray, C. Ince, M. Jonas, J. van der Kaaij, M. Khosravi, N. Kolfschoten, D. Levett, H. Luery, A. Luks, D. Martin, R. McMorrow, P. Meale, K. Mitchell, H. Montgomery, G. Morgan, J. Morgan, A. Murray, M. Mythen, S. Newman, M. O'Dwyer, J. Pate, T. Plant, M. Pun, P. Richards, A. Richardson, G. Rodway, J. Simpson, C. Stroud, M. Stroud, J. Stygal, B. Symons, P. Szawarski, A. Van Tulleken, C. Van Tulleken, A. Vercueil, L. Wandrag, M. Wilson, J. Windsor; *Scientific Advisory Group* — B. Basnyat, C. Clarke, T. Hornbein, J. Milledge, J. West.

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**THE AUTHORS REPLY:** Malgarini and Pimpinella inquire about the difference in baseline characteristics between the Latino and non-Latino white patients and the effect that these differences might have on the ability to conclude that the two groups have different responses to peginterferon alfa-2a and ribavirin. In designing our study, we took into consideration factors that could affect the response in the Latino versus non-Latino white patients with chronic HCV infection. These factors included black race and the presence or absence of cirrhosis, alcohol and drug abuse, human immunodeficiency virus infection, and other forms of liver disease, including hepatitis A and B. We limited the proportion of patients with cirrhosis in both ethnic groups. One of our goals was to identify factors that are predictive of a response in each group, in addition to investigating the overall difference between the two groups. As we noted in our article, we performed a multivariable logistic-regression analysis to evaluate the effects of baseline prognostic factors, such as the body-mass index, on the probability of a sustained virologic response. As we show in Figure 2C of our article, the difference in sustained virologic response between Latino whites and non-Latino whites remained significant, and ethnic background was the strongest predictor of a response after adjustment for other significant factors. Therefore, we can confidently conclude that Latino whites have a lower rate of response to standard therapy for HCV than do non-Latino whites.

Schildgen shares his research findings regarding the altered host response to adefovir in HBV infection. We cannot make any relevant association between the findings in hepatitis B and those in hepatitis C, because they are very different diseases caused by biologically distinct viruses. In our article, we alluded to the fact that the difference in response rates between Latino whites and non-Latino whites could be due to dissimilar host factors, including genetic and immune characteristics; however, our objective — to explore whether there is a difference in the rate of response — has been achieved. Further research is needed to define the molecular mechanisms of this difference.

Maribel Rodriguez-Torres, M.D.
Fundacion de Investigacion de Diego
San Juan, Puerto Rico 00909
rodztorres@coqui.net

Fayez Hamzeh, M.D., Ph.D.
Roche
Nutley, NJ 07110

## Blood Oxygen on Mount Everest

**TO THE EDITOR:** Grocott et al. (Jan. 8 issue)[1] measured arterial blood gases in healthy climbers breathing ambient air on Mount Everest. The authors acknowledge the potential confounding influence of the subjects' use of supplemental oxygen before the sampling of blood gases, but further medication history is not provided. Apart from oxygen, a variety of medications, including acetazolamide, inhaled salmeterol, dexamethasone, sildenafil, and tadalafil, have been used by healthy climbers as prophylaxis against altitude-related illnesses.[2] Use of these medications may affect the physiological response and subsequent blood gas values in hypoxic, hypobaric conditions, particularly with respect to the pulmonary vasculature and the oxygen–hemoglobin dissociation curve.

In addition, the subjects' hemoglobin concentrations at 8400 m, and hence their arterial oxygen content, were estimated from the hemoglobin values measured at 5300 m. It is plausible that this calculation underestimates the hemoconcentration in the subjects at 8400 m that is likely to have occurred as a result of further dehydration and hypothalamic–renal effects,[3] resulting in an underestimate of the subjects' true arterial oxygen content at the Balcony on Mount Everest.

Mark R. Daley, B.Med.
Royal Prince Alfred Hospital
Sydney, NSW 2050, Australia
mark.daley@email.cs.nsw.gov.au

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**TO THE EDITOR:** Grocott et al. calculated alveolar–arterial oxygen differences. But do the study's calculations accurately reflect in vivo values? Oxygen solubility in whole blood is influenced by temperature,[1] but the actual body temperatures of the mountaineers were not taken into account in the authors' calculations. A significant decrease in core temperature can be observed in climbers, owing to adaptive hyperventilation, which occurs when supplemental oxygen is suddenly diminished, withdrawn, or not used at all (Dujmovits R, AMICAL alpin: personal communication). Hypothermia leads to falsely elevated measurements of the partial pressure of oxygen ($PO_2$) and can thereby falsely decrease the calculated alveolar–arterial oxygen difference.[2] Exercise-induced hyperthermia would have an opposite effect.

Jan N. Hilberath, M.D.
Daniel J. FitzGerald, C.C.P.
Brigham and Women's Hospital
Boston, MA 02115
jhilberath@partners.org

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**TO THE EDITOR:** The calculation of arterial-blood oxygen content ($CaO_2$) by Grocott et al. uses a value of 1.39 ml of oxygen per gram of hemoglobin as the constant for oxygen-combining capacity. This constant is based on the molecular weight of hemoglobin.[1] Gregory reported a constant of approximately 1.31 ml of oxygen per gram of hemoglobin with the cyanmethemoglobin method for calculating hemoglobin concentration.[2] The difference between the constants can be attributed to iron hemochromogens. Since the Everest study used the azidemethemoglobin method for hemoglobin measurement, it is subject to the limitation described by Gregory.[2] Recalculation with the lower constant gives a new, lower estimate for $CaO_2$ at 8400 m, approximately 137 ml of oxygen per liter of blood, which is equivalent to the $CaO_2$ in persons at sea level who are anemic (hemoglobin level of approximately 10.5 g per deciliter).

Robert C. Tasker, M.B., B.S., M.D.
Cambridge University School of Clinical Medicine
Cambridge CB2 2QQ, United Kingdom
rct31@cam.ac.uk

1. Braunitzer G. Molekulare struktur der hämoglobine. Nova Acta Acad Caesar Leopold Card 1963;26:113-25.
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**TO THE EDITOR:** It is unusual to see bicarbonate concentrations of less than 14 to 16 mmol per liter in response to chronic hypocapnia, as were found in the study by Grocott et al. Below this level, on the basis of studies in dogs at an arterial partial pressure of carbon dioxide ($PaCO_2$) of 22 to 25 mm Hg[1] with extrapolation to clinical practice, some handbooks on acid–base disorders suggest that metabolic acidosis is present in addition to chronic hypocapnia. Few studies have been performed in humans because of the difficulty of studying humans under extreme hypoxic conditions; the studies that have been performed have not shown bicarbonate concentrations below 17 to 20 mmol per liter in response to chronic hypocapnia ($PaCO_2$ of 28 to 30 mm Hg at an altitude of 3450 to 4880 m).[2,3] Although the study by Grocott et al. involves more extreme altitudes, the bicarbonate concentrations of 10 to 11 mmol per liter at 8400 m strongly suggest a mixed acid–base disorder consisting of a chronic respiratory alkalosis and metabolic acidosis, which is also evidenced by the negative base excess. Since lactate levels were only minimally increased, the presence of a normal anion-gap acidosis is suggested. Did climbers use acetazolamide, a carbonic anhydrase inhibitor used for protection against mountain sickness?

Aiko P.J. de Vries, M.D.
Leiden University Medical Center
2300 RC Leiden, the Netherlands
a.p.j.de_vries@lumc.nl
Kenrick Berend, M.D., Ph.D.
St. Elisabeth Hospital
Willemstad, Curacao, Netherlands Antilles

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**TO THE EDITOR:** Grocott et al. speculate about the lower limit of arterial hypoxemia in humans and

the relevance of their findings to critically ill patients. However, I think that the relevance to the critically ill patients in the intensive care unit (ICU) is limited. Oxygen consumption and oxygen transport in the mountaineers were probably elevated (maybe these data can be provided). These values depend not only on arterial-oxygen content but also on blood flow, which is much more fluctuating. With respect to the latter, trained mountaineers differ considerably from patients in the ICU, who usually have multiple coexisting conditions.

Alfred Hager, M.D.
Deutsches Herzzentrum München
D-80636 Munich, Germany
a-hager@web.de

**THE AUTHORS REPLY:** Daley questions whether hemoconcentration due to dehydration might have resulted in an underestimation of the hemoglobin values used in the calculation of oxygen content at 8400 m. We cannot exclude this possibility, since hemoglobin was not directly measured at the time of sampling and the climbers had been active for 12 hours with limited rehydration (approximately 500 ml of fluids). However, immediately before the ascents to the summit, all subjects had free access to adequate fluids and were judged, on the basis of good volumes of clear urine, to be well hydrated. Daley also asks whether our subjects took any medications other than supplemental oxygen. Subjects took no medications, except for simple analgesics (acetaminophen and nonsteroidal antiinflammatory drugs), from the start of the expedition to the end of measurement.

Hilberath and FitzGerald ask whether hypothermia (or hyperthermia) may have altered the in vivo solubility of oxygen in whole blood and thereby falsely elevated (or lowered) the reported values. Although body temperature was not measured in the subjects at the time of sampling, all subjects were subjectively comfortable (neither cold nor hot), and this was confirmed by the clinical impression of attending investigators. Samples were taken with subjects at rest in a shelter (no wind chill), and they had recently shed layers of insulation in order to maintain comfortable normothermia.

Tasker suggests that the oxygen-combining capacity of hemoglobin should be 1.31 ml of oxygen per gram,[1] rather than the theoretical capacity of 1.39.[2] We chose 1.39 because the degree by which the oxygen-combining capacity of hemoglobin at high altitudes differs from the theoretical maximum is unknown. Furthermore, we highlighted the relative changes in oxygen content in comparison with sea-level values, and these relative values would not have been affected by the choice of constant.

De Vries and Berend are surprised by the metabolic acidosis observed in the measurements at 8400 m. This is a well-documented response to the respiratory alkalosis that occurs with acclimatization to high altitude, and similar values have been reported previously in both hypobaric-chamber[3] and field[4] studies. No subject took acetazolamide.

Hager expresses skepticism about the relevance of findings in mountaineers at high altitude to critically ill patients. Although we recognize that there are important differences between the two groups, we contend (and we have argued elsewhere[5]) that prolonged exposure to hypoxia (at high altitudes or in a hypobaric chamber or tent) in healthy, normal subjects provides a means of exploring the integrative physiology of adaptation to hypoxia in a controlled manner that is not currently achievable by other means.

Michael P.W. Grocott, M.B., B.S.
Daniel S. Martin, M.B., Ch.B.
Denny Z.H. Levett, B.M., B.Ch.
University College London Institute of Human Health and Performance
London N19 5LW, United Kingdom
mike.grocott@ucl.ac.uk

1. Braunitzer G. Molekulare struktur der hämoglobine. Nova Acta Acad Caesar Leopold Card 1963;26:113-25.
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