HIGH LIFE: High altitude fatalities led to pulse oximetry

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Severinghaus JW. HIGH LIFE: High altitude fatalities led to pulse oximetry. J Appl Physiol 120: 236–243, 2016. First published August 6, 2015; doi:10.1152/japplphysiol.00476.2015.—In 1875, Paul Bert linked high altitude danger to the low partial pressure of oxygen when 2 of 3 French balloonists died euphorically at about 8,600 m altitude. World War I fatal crashes of high altitude fighter pilots led to a century of efforts to use oximetry to warn pilots. The carotid body, discovered in 1932 to be the hypoxia detector, led to most current physiologic understanding of the body’s respiratory responses to hypoxia and CO2. The author describes some of his UCSF group’s work: In 1963, we reported both the brain’s ventral medullary near-surface CO2 (and pH) chemosensors and the role of cerebrospinal fluid in acclimatization to altitude. In 1966, we reported the effect of altitude on cerebral blood flow and later the changes of carotid body sensitivity at altitude and the differences in natives of high altitude. In 1973, pulse oximetry was invented when Japanese biophysicist Takuo Aoyagi read and applied to pulses a largely forgotten 35-year-old discovery by English medical student J. R. Squire of a method of computing oxygen saturation from red and infrared light passing through both perfused and blanched tissue.

HISTORICAL BACKGROUND

Ancient High Altitude Reports of Effects on Humans

High altitude effects on humans were first described in 32 BC in western China when Too Kin, an official, wrote of “headache mountain” with vomiting while going from the area around Kashgar in China to Hunza and Gilgit in India. That is now called Karakoram pass at 4,700 m altitude. In ~1600 CE, a Spanish priest, José de Acosta, wrote about experiencing severe altitude sickness in the Andes at about 4,300 m altitude (2). Many others also noted problems, but the reason remained unexplained until the late 19th century.

Paul Bert and Partial Pressure of Oxygen

The brilliant physician and physiologist Paul Bert [Fig. 1, left] was the first to write that the important effect on humans at altitude is the reduced partial pressure of oxygen in the air and thus in the blood. In his 1,055-page masterpiece “La Pression Barometrique” (1) (1875), he reviewed 264 published histories of effects on humans ascending mountains, 42 publications of ballooning effects, and 33 more about decreased pressure effects. He had been the advisor for a team of three ballooning experts who used a hydrogen-filled balloon called Zenith to attempt in 1875 to outdo a British team’s highest altitude. Bert provided each man with a 300-liter goatskin bag of about 60% oxygen. However, above 6,000 m, they failed to use O2 because of a feeling of intense hypoxic euphoria before losing consciousness. Two died. The third, M. Gaston Tis-
Italian Queen Margeritha, at age 43, climbed to officially open it.

Mosso tried but failed to prove that altitude sickness was due to acapnia, now called hypocapnia (20).

Capanna Regina Margeritha is primarily an alpine hut for climbers nowadays, but it remains a research station for interested scientists. It can be reached by a 1,300-m climb from the cable car top or by helicopter but not by road. The hut was rebuilt in 1977-80. It now has several labs and a 70-bed hotel.

**Lung Oxygen Transport Debate**

In 1900, C. Bohr, a Danish pulmonary physiologist, calculated that the lung must use active transport to explain its ability to take up oxygen into blood especially at high altitude. J. S. Haldane (Oxford) visited Bohr and was convinced he was right. Being skeptical about that claim, Danish medical physiologist Marie Krogh over the next decade invented the still-used carbon monoxide method of accurately measuring diffusing capacity of the lung. She showed that lung-diffusing capacity had been underestimated by previous methods. In 1910, she and her husband August, a favorite physiology student of Bohr, with much apologizing, published seven “little devils,” papers disputing Bohr’s active oxygen transport claim. With extremely careful tests they proved that PO₂ is always lower in arterial blood than alveolar gas even while breathing low oxygen mixtures (19).

Despite the seven papers that disproved any active transport of oxygen, in 1911 Haldane tried once more to prove active O₂ transport. He organized and led a high altitude study in Colorado with three established physiologists to Pikes Peak where they could ride the train to the 4,300 m summit of Pikes Peak and stay in a comfortable hotel. Haldane, carefully using his own methods, reported finding a reversed gradient. He believed it until his death 25 years later (3). Although Haldane’s methods should have been right, in the century since then, many have tried but failed to find any errors in his methods and results. But he was wrong.

**Heymans Discovery of the Carotid Body**

Corneille Heymans [Fig. 2] accidentally discovered the carotid body’s role as the driver of hypoxic hyperventilation while studying its role in arterial blood pressure control. For this he received the 1938 Nobel Prize (4). Hundreds of later studies noted that the carotid body afferent nerve response rose semihyperbolically as PO₂ fell (6) and later that each sensor glomus cell responds interactively to both hypoxia and PaCO₂ and pH (9).

**Understanding Interaction of O₂ and CO₂ on Regulation of Ventilation**

The difference between the ventilatory stimulation by lab hypoxia and high altitude depends on the PaCO₂. This was clearly shown by Nielsen and Smith in 1952 (17). At alveolar PO₂ = 37 Torr, the response to rising Pco₂ is 5X steeper than in normoxia. But when altitude hypoxia drives Pco₂ down below 30 Torr, ventilation becomes almost independent of PO₂ [Fig. 3]. At high altitude, low Pco₂ from hypoxic hyperventilation partly blocks the carotid body’s hypoxic ventilatory drive and can lead to the euphoria and coma that killed the Zenith balloonists and World War fighter pilots. This “dogleg” bend of hypoxic HCVR should be called the “deadly dogleg.”

**The First Operation Everest**

In 1949, physicians Charles Houston and Richard Riley organized the first physiologic simulation of an Everest climb in a World War II Navy bends test chamber in Florida. Four volunteers were gradually decompressed over 34 days to the barometric pressure of Everest summit, 253 Torr. No blood was sampled in the chamber. Soon after the subjects came out of the chamber, their arterial pH was measured. It was high, about 7.48, and total blood CO₂ content was half of normal. SBE (standard base excess) was later estimated to be −8 and Pco₂ was estimated to be less than 20 Torr due to persisting...
hyperventilation. The cause of continued hyperventilation and alkalemia was not explained by current theory but was thought to be due to residual brain metabolic acidosis as sudden normoxia let PCO$_2$ rise slightly toward normal.

Houston initiated the biennial hypoxia meetings at Lake Louise in the early 1970s and organized Operation Everest II, again in a chamber, in 1985.

PHYSIOLOGICAL BACKGROUND

Discovery of Ventral Medullary Surface Chemosensitive Areas

In 1950, physiologist Isidoor Leusen in Liege, Belgium, had stimulated ventilation in dogs by acidifying their cisternal cerebral spinal fluid (11). Hans Winterstein confirmed his results. Hans Loeschcke in Götingen began searching for the site of chemosensitivity in 1958 and found the most sensitive site to be in the lateral recesses of the 4th ventricle (13).

At UCSF, internist Robert Mitchell [Fig. 4, inset] after reading the Leusen & Loeschcke reports, injected 20 ml of mildly acidified mock spinal fluid into the lumbar subarachnoid space in two of his severely hypercapnic COPD patients. This stimulated an increase in ventilation enough to normalize their PCO$_2$ to about 40 Torr within 1 hour.

He joined my lab in Julius Comroe’s CVRI (Cardio-Vascular Research Institute) in 1959. Comroe told him not to publish or continue his study in patients without institutional permission. Mitchell never published that human experiment.

He abandoned clinical medicine and decided to hunt in cats for the ventilatory chemoreceptors responding to cerebrospinal fluid (CSF) acid. We sponsored Hans Loeschecke to come and work with Mitchell on this hunt. Working through the dorsal exposure of the brain stem, they were unable to find a site. As a last ditch effort, the day before Loeschcke was to return to Germany, Mitchell slid a catheter in the subarachnoid space from the dorsal 4th ventricle to the inaccessible ventral brain surface. Injecting slightly acid mock CSF there generated a strong ventilatory response. Over the following months, Mitchell then developed a new bloody, destructive surgical approach to the ventral surface of the brain through the palate of cats [Fig. 4]. He used tiny bits of filter paper wet with acidified mock spinal fluid with which he localized the chemosensitive areas near the anterior inferior cerebellar arteries (16).

In 1969, using Mitchell’s surgical approach, Loeschcke reported a more caudal pH sensitive area below the 12th nerve roots, and M. Schlafke reported an intermediate region, not sensitive to topical acid, but where electrical stimulation resulted in hyperpnea (12). Bilateral cauterization of this area eliminated all brain CO$_2$ chemosensitivity as if it were the fovea for the pH and Pco$_2$ sensory neurons.

Identification of Chemosensor Cells in Ventral Medullary Surface

Anatomist Alan Basbaum at UCSF had developed a new method to stain brain neural cells for c-fos generated by 1 hour of vigorous neural stimulation. CVRI Japanese post doc Motoo Sato used it to identify chemosensitive cells only <0.1 mm below the ventral medullary surface in rats after breathing 15%
CO₂ for 1 hour (22). These cells were found even when the animals were pretreated with morphine to eliminate the ventilatory response to high PCO₂. Sato et al. (22) inferred that these cells are the chemosensitive sources of the neural ventilatory drive.

ACCLIMATIZATION STUDIES

Role of Ventral Medullary Surface Sensors in Altitude Acclimatization

Soon after discovering the ventral medullary surface chemosensor areas, Mitchell and I decided to investigate whether the spinal fluid acid-base balance might in some way explain puzzles about high altitude acclimatization.

In the 1950s, UC had built three high altitude labs in the White Mountains of eastern California, northeast of Bishop, near the bristlecone pines, the world’s oldest living things that thrive on alkaline white dolomite rock. The two highest altitude labs are the Barcroft Labs at 3,810 m and a summit hut at 4,345 m. Although these labs were built for altitude physiology studies, they were soon used by radioastronomers seeking the big bang radiation, by all sorts of biologists, geologists, tree-ring experts, and anthropologists. Access to the White Mt. summit lab requires a 3 mile 500 m climbing hike or a four-wheel drive after the snow melts.

We recruited two anesthesia research fellows, loaded up UCSF station wagons, shoveled our way up to the Barcroft lab after a late spring blizzard, and set up lab facilities. That lab had heat, a kitchen with cook and food, and power for lights and my home made thermostatted blood gas pH, PCO₂, and PO₂ electrodes (before any were commercially available). We took turns sampling each other’s lumbar CSF and arterial blood [Fig. 5].

Arterial and CSF PCO₂ fell about 10 Torr after a night at 3,810 m altitude. This should have raised CSF pH about 0.10 units. But we found that CSF pH had risen only 0.02. It remained slightly elevated for our 9-day stay (27). CSF bicarbonate ion fell overnight by 4 meq/l, whereas blood plasma bicarbonate and blood SBE fell slowly over a week of renal compensation for respiratory alkalosis. The cause of the prompt CSF pH fall is now thought to be due to brain tissue hypoxic lactic acid production, not by my prediction of active transport across the blood-brain barrier. Even at sea level, the brain continuously excretes lactic acid. This is increased in hypoxia and decreased when above normal flow is forced by breathing oxygen with slightly elevated CO₂.

Cerebral Blood Flow at High Altitude

We then wondered whether cerebral blood flow (CBF) was also controlled by the pH of the CSF surrounding cerebral arteries and arterioles. In the early 1960s, cerebral blood flow could only be measured by the Kety-Schmidt method. This involved 10 min of breathing 15% nitrous oxide with frequent sampling of both arterial and internal jugular venous blood. The flow can be computed from the uptake of N₂O by brain over that wash-in period. University of Washington anesthesiologist Thomas Hornbein joined our team at Barcroft, flown there by the Wt. Mt. UC helicopter stationed at the Owens valley base station in the summer of 1964 [Fig. 6]. He was both a team member and subject [Fig. 7].

In seven volunteers, CBF rose 24% within a few hours at 3,810 m altitude. After 4 days it had fallen to 13% above sea level controls. With acute normoxia, CBF fell part way, remaining 8% above normal, driven by the altitude-induced metabolic acidosis of CSF. Then raising PaCO₂ to 35 Torr...
increased flow 34% (well above normal). The 3-day acclimatization fall of CSF bicarbonate to about 20 mM/l had "reset" the relationship of CBF to PaCO2 and CSF pH (26). Many similar data have confirmed that study. In 1990, Krasney and Lassen (8) showed that CBF remains high in sheep in hypoxia if PCO2 is maintained at its normal level.

CSF and Arterial pH in Altitude Natives

In 1962, we determined CSF and arterial pH in 20 Peruvian high altitude natives in villages at 3,700, 4,500, and 4,800 m altitude. The values were not significantly different from sea level normal, except for the fall of oxygen saturation with increased altitude (24).

Ventilatory Responses to CO2 and Hypoxia in High Altitude Natives

In 1964, UCSF anesthesiologist Cedric Bainton, Peruvian physician Amador Carcelen, and I tested hypoxic and CO2 responses in natives of Cerro de Pasco, Peru at 4,300 m altitude. We used a delivery room in the local social security hospital, unused because term women were taken down below 10,000 ft for delivery to avoid the high incidence of patent ductus. That first night, Dr. Bainton got HAPE [Fig. 8]. The distinctly perihilar distribution of edema remains unexplained. Mean isocapnic hypoxic response in the five newly arrived lowlanders was 21 l/min at PETCO2 of 40 Torr but averaged only 5 l/min in natives (normalized to body surface). The mean isocapnic response in four polycythemic altitude natives (Hct > 70%) was not significantly lower than "normal" natives. Two other lowlanders after 1 and 9 mo at altitude had become polycythemic and had blunted responses similar to the highlanders (25).

S. Lahiri and J. Milledge reported a similar “blunting” of hypoxic sensitivity in Sherpas in the weekly “Hillary” letter in the Manchester Guardian in 1965 (21), just in time for me to include their newspaper letter in our references.

J. Weil at the University of Colorado found that this blunting developed slowly over about 20 years in 9 newcomers moving up to Leadville, Colorado at 3,300 m (31).

CBF, CMRO2, and Brain Lactate in Andean Natives

J. Milledge and S. Sørensen, while UCSF fellows, reported that CBF fell below normal when eight Peruvian altitude natives at 4,300 m breathed oxygen. O2 does not have that effect at sea level. This implies that hypoxic vasodilation is chronically keeping CBF normal in natives at altitude (14).

In 1972, Niels Lassen (Copenhagen) arranged for Sørensen and me to join him in La Paz, Bolivia, with local physicians to measure blood flow with a new radioactive krypton method, brain metabolic rate, and lactate production in some or all of 23 natives living at about 4,000 m altitude. The data were surprisingly similar to normals at sea level (29).

Measuring Hypoxic Ventilatory Responses (HVR)

Using published human data of isocapnic acute hypoxic ventilatory response (HVR), in 1972 J. Weil generated a hyperbolic equation of the usual ventilatory response to isocapnic hypoxia (32). Quantifying it was difficult. Fortunately, in 1974, A. Rebuck and E. Campbell reported that the isocapnic ventilatory response to hypoxia was a nearly linear slope of arterial oxygen desaturation of about 1 l/min rise of ventilation for each 1% fall in SaO2 (18). This discovery and the 1985 newly available pulse oximeters rapidly resulted in use of the term HVR = \( \Delta V_E/\Delta SpO_2 \), usually reported as a positive slope.

Acclimatization at Altitude

In 1994, Sato et al. confirmed HVR linearity over 100-70% SpO2 in six subjects after 2 days at the Barcroft Lab (23). HVR slope was 1.12. Over a 2-wk acclimatization at 3,810 m altitude, their isocapnic HVR doubled to over two, beginning a rise on the 3rd day after PCO2 had stabilized at 32 Torr (21). This doubling of hypoxic chemosensitivity happens within the...
carotid body chemoreceptors. It is an important factor during acclimatization.

**Hypoxic Ventilatory Decline**

In acute isocapnic hypoxia, the ventilatory response begins to fall after 5 min. By 20 min it has usually lost about half the peak response. Brain endorphin release is not the cause, because naloxone (Narcan), an endorphin blocker, has no effect (7). HVR should be tested after only 5 min of acute stable hypoxia (e.g., at 80% SpO2).

**TECHNICAL DEVELOPMENT OF PULSE OXIMETRY**

**Linking Zenith and Fighter Pilot Fatalities to Pulse Oximetry**

As noted earlier, high altitude fatalities, both from balloonists and fighter pilots, led to efforts for prevention. Lord Adrian (for the English government) asked an American scientist Glen Millikan, working on blood oxygen reaction rates with F. Roughton in Cambridge in the 1930s, to find a way to test hypoxia in pilots. Using several earlier German and English reports, he designed an
ear oximeter using red and green filtered wavelengths of light (15). World War II drove him back to the United States where he arranged its manufacture. However, it could not be used in aircraft because, before transistors, the tiny current optical signals required a stable galvanometer.

Discovery of the Unique Role of a Ratio of Ratios

In 1940 in England, a medical student, J. R. Squire, discovered that if the red and infrared light passing through tissue was measured before and again after blanching tissue with pneumatic pressure, the log of the ratio of the ratios of those four transmitted light values (red and infrared when perfused and when blanched) was a unique function of blood oxygen saturation (30).

Earl Wood, a physiologist at the Mayo clinics, aware of Squire's discovery, added a pressure capsule to the Millikan earpiece to blanche the ear for calibration (33) after setting it to 100% while breathing oxygen. Wood was able to obtain an accuracy of about 2%. Wood's modification of Millikan's ear oximeter was widely used from the 1930s through the 1970s in research and occasionally in patients.

The First Accurate Ear Oximeter

An eight-wavelength fiber optic ear oximeter was invented in San Francisco by surgeon-engineer Robert Shaw about 1963. It did not require calibration and was accurate to within 1% SO2 at least above 70% saturation. Hewlett Packard marketed it for about $13,000 in 1970. Its weight and cost limited its use to a few specialized pulmonary laboratories. Shaw donated one of his early ones for our high altitude work. I used it on physiologist Bruce Dill (age 87) at the Barcroft lab at the University of Washington until his retirement in 1993, and a pioneering mountaineer who first conquered the West Ridge route up Everest with Willi Unsoeld as part of the first American Mt. Everest Expedition in 1963. He wrote an unusually insightful, fascinating report of the expedition, published in large format size by the Sierra Club [Fig. 10A]. He is a keen editor with an unusual talent for interesting writing. He edited both the two-volume “Regulation of Breathing,” vol. 17 in 1981 and the major text “High Altitude,” vol. 161, 2001, both in the National Institutes of Health series “Lung Biology in Health and Disease.”

He now lives in Estes Park, CO. In 2014, at age 84, he and friends climbed Spearhead on the side of Long’s peak in the Colorado Rockies (12,575 ft, 3,833 m altitude).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


Today pulse oximetry measured saturation is a mandatory vital sign in clinical settings. But pulse oximetry is not only pervasive in clinical settings. Cheap finger probes can be bought freely and are regularly used by the lay public when traveling to altitude, and nowadays pulse oximetry is even built into wrist watches.
15. Millikan GA. The oximeter, an instrument for measuring continuously the 


