Clinical Physiology (1990) **10**, 265–272

Limiting factors for exercise at extreme altitudes

J. B. West

Department of Medicine, University of California, San Diego, La Jolla, USA

Summary. Man can only survive and do work in the severe oxygen deprivation of great altitudes by an enormous increase in ventilation which has the advantage of defending the alveolar P_{O_2} against the reduced inspired P_{O_2}. Nevertheless the arterial P_{O_2} on the summit of Mt Everest at rest is less than 30 Torr, and it decreases with exercise because of diffusion limitation within the lung. One of the consequences of the hyperventilation is that the marked respiratory alkalosis increases the oxygen affinity of the haemoglobin and assists in loading of oxygen by the pulmonary capillary. Although ventilation is greatly increased, it is a paradox that cardiac output for a given work level is the same in acclimatized subjects at high altitude as at sea level. Stroke volume is reduced but not because of impaired myocardial contractility because this is preserved up to extreme altitudes. Indeed the normal myocardium is one of the few tissues whose function is unimpaired by the very severe hypoxia. There is evidence that oxygen delivery to exercising muscle is diffusion limited along the pathway between the peripheral capillary and the mitochondria. At the altitude of Mt Everest, maximal oxygen uptake is reduced to 20–25% of its sea level value, and it is exquisitely sensitive to barometric pressure. Seasonal variations of barometric pressure affect the ability of man to reach the summit without supplementary oxygen. In spite of the greatly reduced aerobic capacity, anaerobiosis is greatly curtailed, and it is predicted that above 7500 m, there is no rise in blood lactate on exercise. The paradoxically low lactate is possibly related to plasma bicarbonate depletion.

Key words: anaerobiosis, barometric pressure, cardiac output, diffusion limitation, hyperventilation, hypocapnia, hypoxaemia, hypoxia, lactate, myocardial contractility, oxygen affinity, respiratory alkalosis.

The responses of human beings to extreme environments often clarify normal physiological processes, and how these are perturbed by disease. Maximal exercise during the severe hypoxia of extreme altitude is a good example. This brief review summarizes some recent work.

When man ascends to the summit of Mt Everest, the inspired P_{O_2} falls to about 42 Torr. A moment's thought (or use of the alveolar gas equation) shows that if he maintains an alveolar P_{CO_2} of 40 Torr, his alveolar and therefore arterial P_{O_2} will fall to

Correspondence: Dr J. B. West, Department of Medicine M-023A, University of California, San Diego, La Jolla, CA 92093-0623, USA.

zero! Therefore man can only survive and do work in the severe oxygen deprivation of great altitudes by an enormous increase in ventilation. Alveolar gas samples obtained on and near the summit of Mt Everest indicate that the P_{CO_2} falls approximately linearly with barometric pressure reaching the astonishingly low value of about 7·5 Torr on the summit (West *et al.*, 1983a). Incidentally this was considerably lower than we had predicted prior to our 1981 American Medical Research Expedition to Everest (West & Wagner, 1980). The alveolar P_{CO_2} values were not quite so low during the pressure chamber simulation, Operation Everest II (Sutton *et al.*, 1988), but this can largely be explained by the shorter acclimatization time (West, 1988).

The chief advantage of this extreme hyperventilation is that it helps to defend the alveolar P_{O_2} against the very low value in the inspired gas. When the alveolar P_{O_2} and P_{CO_2} were plotted on an O_2–CO_2 diagram for acclimatized man from sea level to the summit of Mt Everest, an interesting result emerged. Both values fell with increasing altitude, but above an altitude of about 7000 m, the alveolar P_{O_2} was maintained at a steady value of about 35 Torr. This was accomplished by the increasing hyperventilation which reduced the P_{CO_2} to such low levels.

Although the alveolar P_{O_2} is maintained reasonably well at about 35 Torr, there is evidence that the arterial value is less than 30 Torr at rest, and that it falls even lower on exercise (West *et al.*, 1983a; Sutton *et al.*, 1988). The reason for this is diffusion limitation of oxygen transfer across the pulmonary blood–gas barrier. The P_{O_2} in pulmonary capillary blood rises very slowly as oxygen is taken up for two reasons. First, the oxygen loading occurs so low on the oxygen dissociation curve where it is very steep, and second, there is considerable polycythaemia (haemoglobin concentration approximately 19 g dl^{-1}). Both these factors increase the change in oxygen concentration per Torr P_{O_2} of the blood, and therefore slow the rate of rise of P_{O_2} in the pulmonary capillary (Piiper & Scheid, 1980). Indeed oxygen is beginning to take on some of the characteristics of carbon monoxide under these extraordinary conditions.

An interesting consequence of the extreme hyperventilation is the marked respiratory alkalosis. The base excess of two Everest summiters measured the morning after their summit climb averaged $-7{\cdot}2$ mEq l^{-1}, and using the measured alveolar P_{CO_2} of 7·5, this gave an arterial pH of over 7·7 on the summit (Winslow *et al.*, 1984). One of the consequences of this severe respiratory alkalosis is an increased oxygen affinity of the haemoglobin. It can be shown that this increased affinity assists the loading of oxygen by the pulmonary capillary more than it interferes with the unloading in peripheral capillaries (Bencowitz *et al.*, 1982). Thus the alkalosis enhances the overall oxygen transfer from the air to the tissues, and is one of the important features of acclimatization.

An intriguing question is why the kidney does not eliminate more bicarbonate in order to reduce the degree of respiratory alkalosis. A possible clue is the volume depletion which was demonstrated in subjects living at an altitude of 6300 m (Blume *et al.*, 1984). The significantly increased serum osmolality at this altitude occurred in spite of a reasonably normal life-style and adequate fluids to drink. Interestingly, the

increased osmolality was not associated with an increased ADH concentration. These findings suggest that fluid balance is impaired at high altitudes and there are many other observations to support this. It is known that when the kidney is given the option of correcting volume depletion or correcting respiratory alkalosis, it gives higher priority to the former. In order to eliminate bicarbonate, a cation has to be lost, and this aggravates the fluid depletion. Thus the dehydration may explain, in part, the persistence of the severe respiratory alkalosis.

Because of the severe oxygen deprivation, aerobic power is greatly reduced as shown in Fig. 1. It can be seen that at an inspired P_{O_2} of 42 Torr, the maximal oxygen uptake was reduced to 20–25% of its sea level. These measurements were obtained by exercising well-acclimatized subjects at an altitude of 6300 m while giving them 14% oxygen to breathe, thus providing the same inspired P_{O_2} as the Everest summit (West *et al.*, 1983b). Note that the results obtained at extreme simulated altitude during Operation Everest II were almost identical (Sutton *et al.*, 1988), although the maximal oxygen uptakes at sea level were considerably lower.

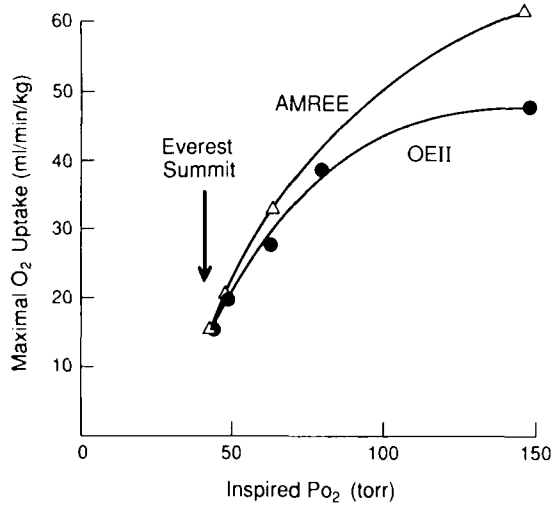

Fig. 1. Fall in $\dot{V}_{O_2}$max as altitude increased as measured during the 1981 American Medical Research Expedition to Everest (AMREE) and the low pressure chamber simulated ascent, Operation Everest II (OEII). At the inspired P_{O_2} corresponding to the Everest summit, $\dot{V}_{O_2}$max was just over 1 litre min^{-1}. Modified from West *et al.* (1983b) and Sutton *et al.* (1988).

A remarkable feature of maximal oxygen uptake at these extreme altitudes is the extreme sensitivity to barometric pressure. This can be seen from Fig. 1 where the fall in $\dot{V}_{O_2}$max per Torr inspired P_{O_2} was about 63 ml min^{-1} $Torr^{-1}$ on the summit. This means that seasonal variations of barometric pressure cause appreciable alterations in maximal oxygen uptake and therefore affect the ability of climbers to reach the Everest summit without supplementary oxygen. Figure 2 shows the variation in barometric pressure on the summit of Mt Everest throughout the months of the year as obtained from weather balloon data (West *et al.*, 1983c). It can be seen that the barometric

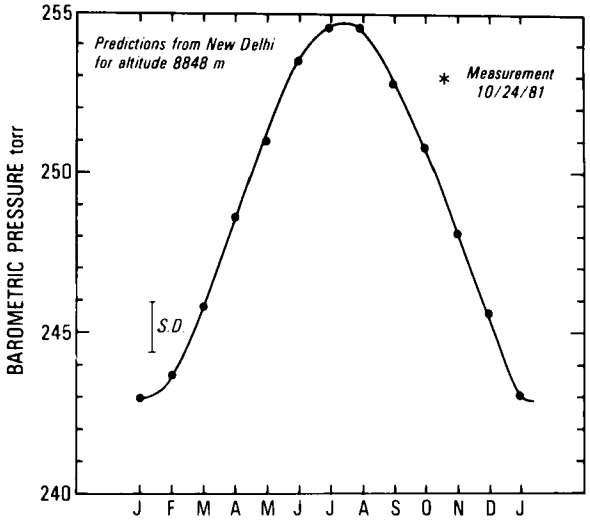

Fig. 2. Mean monthly barometric pressures for 8848 m altitude (summit of Mt Everest) as obtained from weather balloons released from New Delhi. Note the striking change between mid-summer and mid-winter. From West *et al.* (1983c).

pressure falls by approximately 12 Torr from mid-summer to mid-winter. This corresponds to a fall in $\dot{V}O_2max$ of approximately 160 ml min^{-1}, or 15% of the summit $\dot{V}O_2max$ shown in Fig. 1. It is interesting that when Reinhold Messner made his extraordinary solo ascent of Everest without supplementary oxygen in 1980, the barometric pressure was high at about 256 Torr, whereas when Sherpa Ang Rita made the first winter ascent without supplementary oxygen on 22 December 1987, the barometric pressure was considerably lower at about 247 Torr. The data shown in Fig. 1 suggest that Ang Rita's $\dot{V}O_2max$ at the summit was reduced by about 11% as a result of the decreased barometric pressure.

We have seen that ventilation is enormously increased at these great altitudes and that this confers a tremendous advantage for oxygen delivery to the tissues by raising the alveolar and therefore arterial P_{O_2}. It is a paradox that the other great convection system for transporting oxygen, that is the cardiac output, is not changed in acclimatized subjects at high altitudes compared with sea level. In other words, the relationship between cardiac output and oxygen uptake (or power) is the same in acclimatized subjects at high altitudes as it is at sea level (Pugh, 1964; Reeves *et al.*, 1987). The reasons for this are obscure. It is well known that cardiac output for a given work level increases during acute hypoxia (Vogel & Harris, 1967). Why the relationship returns to the sea level value in acclimatized subjects is unknown. It should be pointed out that because polycythaemia develops during acclimatization, haemoglobin flow in relation to power is increased. However why the body does not take advantage of the possibility of increasing the delivery of oxygen to the peripheral tissues by raising

cardiac output is a mystery. Indeed it emphasizes how little we know about the control of cardiac output.

Although the cardiac output/oxygen uptake relationship is the same as that at sea level, heart rate is increased and stroke volume correspondingly reduced (Pugh, 1964). The reason is not clear although there may be some effect from circulating catecholamines which increases heart rate. It has been suggested that stroke volume is reduced under these conditions of severe hypoxaemia because of impaired myocardial contractility. However measurements of myocardial contractility by cardiac catheterization and two-dimensional echocardiography carried out during Operation Everest II up to simulated altitudes of 8000 m indicate that contractility is well maintained (Reeves *et al.*, 1987; Suarez *et al.*, 1987). Indeed there was a suggestion that contractility was even better under these conditions of extreme hypoxia than in normoxia. This is a fascinating finding indicating as it does that the normal myocardium is extremely tolerant to severe hypoxia. It emphasizes the fundamental difference between hypoxaemia and ischaemia. Of course it should not be assumed that someone with coronary artery disease is not at increased risk at high altitudes, although this has been suggested (Rennie, 1989).

It is not easy to think of an organ system whose function is not impaired at very high altitudes. Certainly there is evidence of impaired function of the central nervous system, gastrointestinal system, kidney and skeletal muscle (Ward *et al.*, 1989). The fact that the myocardium tolerates extreme hypoxaemia so well is extraordinary.

What limits $\dot{V}O_2max$ under these conditions of severe hypoxia? Clearly there is no single limiting factor. For example, it was pointed out earlier that unless ventilation is increased, the alveolar and arterial P_{O_2} would fall to zero on the Everest summit. One way of approaching the question of limitation is to calculate the increase in $\dot{V}O_2max$ which would occur for a small (say 5%) change in one variable leaving all the other variables constant (West, 1983). When this was done for a climber on the summit of Mt Everest, it was found that $\dot{V}O_2max$ was extremely sensitive to barometric pressure, but that ventilation and pulmonary diffusing capacity also played important roles.

There is evidence that an important limiting factor at the tissue level is the rate of diffusion of oxygen from the peripheral capillaries to the mitochondria. This is based on the finding of a linear relationship through the origin of $\dot{V}O_2max$ and mean capillary P_{O_2} of muscle, or some approximation to this. Wagner (1988) retrospectively analysed the data obtained during near-maximal exercise in Operation Everest II and found a strong relationship between $\dot{V}O_2max$ and the P_{O_2} of mixed venous blood. Furthermore in a subsequent study carried out during normobaric hypoxia, a similar relationship was found between $\dot{V}O_2max$ and the P_{O_2} of femoral venous blood (Roca *et al.*, 1989). In a series of experiments using an isolated dog gastrocnemius preparation, additional evidence has been obtained for diffusion limitation of oxygen transfer between peripheral capillary and the mitochondria under conditions of maximal oxygen uptake. In particular, it is possible to show that $\dot{V}O_2max$ was better related to muscle capillary P_{O_2} than to oxygen delivery (muscle blood flow × arterial oxygen concentration) when the arterial P_{O_2} and blood flow were altered (Hogan *et al.*, 1989).

We have seen (Fig. 1) that aerobic capacity is enormously reduced at extreme altitudes. It might therefore be expected that anaerobic activity would increase as it does in acute hypoxia. However the opposite is apparently the case. Edwards (1936) first showed the acclimatized subjects working maximally at high altitude have very small rises in blood lactate concentration. This paradoxical observation has been amply confirmed and Fig. 3 shows data from Cerretelli *et al.* (1982) with additional points from the 1981 American Medical Research Expedition to Everest (West *et al.*, 1983b). It is clear that the higher the altitude, the lower the maximum blood lactate after exhausting exercise. Additional measurements made during Operation Everest II from biopsies obtained after fatiguing exercise show that skeletal muscle lactate concentrations are also low consistent with the low blood values (Green *et al.*, 1989).

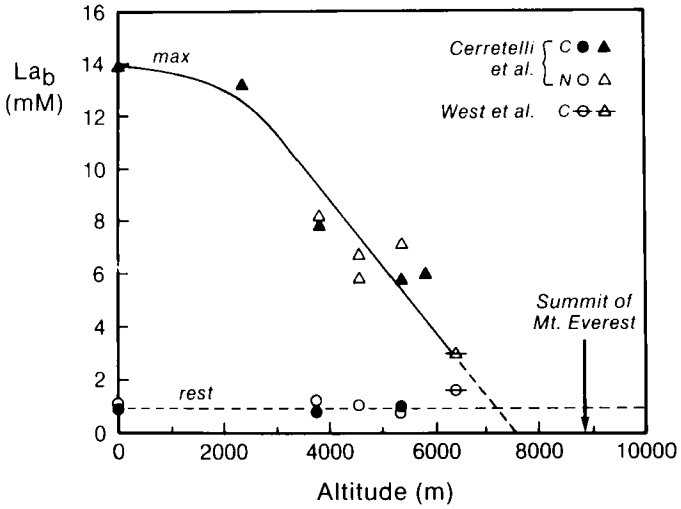

Fig. 3. Solid line shows maximal blood lactate as a function of altitude. Most of the data are redrawn from Cerretelli *et al.* (1982). The filled circles and triangles show data for acclimatized Caucasians (C); the open circles and triangles are for high altitude natives (N). The data for 6300 m are from West *et al.* (1983b) for acclimatized lowlanders. Modified from Cerretelli *et al.* (1982).

A remarkable feature of Fig. 3 is that if the line through the maximum blood lactate values is extrapolated, it predicts that a climber above an altitude of about 7500 m will have no increase in blood lactate at all, no matter how hard he works! Surely it is a paradox that when a normal subject performs exhausting exercise under the most severe hypoxic conditions that can be tolerated, lactate acidosis does not occur.

The reasons for the low blood lactates in acclimatized subjects at high altitudes are not well understood. One possibility is that the plasma bicarbonate depletion which is an important feature of acclimatization, reduces buffering to such an extent that hydrogen ion liberated by lactate formation in muscle causes a large abrupt fall in intracellular muscle pH. This in turn inhibits glycolysis possibly through inhibition of the enzyme phosphofructokinase. There is evidence that the activity of this enzyme is

reduced by a low pH (Danforth, 1965). It is known that lactate efflux from isolated frog sartorius is slowed when the bicarbonate concentration of the superperfusate is greatly reduced (Mainwood *et al.*, 1972). However there is no direct evidence as yet that these extraordinarily low blood lactate levels are indeed related to plasma bicarbonate depletion.

References

Bencowitz H.Z., Wagner P.D. & West J.B. (1982) Effect of change in P50 on exercise tolerance at high altitude: a theoretical study. *J Appl Physiol: Respirat Environ Exercise Physiol*, **53**, 1487–1495.

Blume F.D., Boyer S.H., Braverman L.E. & Cohen A. (1984) Impaired osmoregulation at high altitude. *J Am Med Assoc*, **252**, 1580–1585.

Cerretelli P., Veicsteinas A. & Marconi C. (1982) Anaerobic metabolism at high altitude: the lactacid mechanism. In: *High Altitude Physiology and Medicine* (eds. Brendel W. & Zink R.A.). Springer-Verlag, New York.

Danforth W.H. (1965) Activation of glycolytic pathway in muscle. In: *Control of Energy Metabolism* (eds. Chance B., Estabrook R.W. & Williamson J.R.). Academic Press, New York.

Edwards H.T. (1936) Lactic acid in rest and work at high altitude. *Am J Physiol*, **116**, 367–375.

Green H.J., Sutton J., Young P., Cymerman A. & Houston C.S. (1989) Enzyme levels measured on muscle biopsies during Operation Everest II. *J Appl Physiol*, **66**, 142–150.

Hogan M.C., Roca J., West J.B. & Wagner P.D. (1989) Dissociation of maximal O_2 uptake from O_2 delivery in canine gastrocnemius *in situ*. *J Appl Physiol*, **66**, 1219–1226.

Mainwood G.W., Worsley P., Brown P. & Patterson R.A. (1972) The metabolic changes in frog sartorius muscle during recovery from fatigue at different arterial bicarbonate concentrations. *Can J Physiol Pharmacol*, **50**, 143–155.

Piiper J. & Scheid P. (1980) Blood–gas equilibration in lungs. In: *Pulmonary Gas Exchange*. vol. 1. *Ventilation, Blood Flow, and Diffusion* (ed. West J.B.), pp. 131–171. Academic Press, New York.

Pugh L.G.C.E. (1964) Cardiac output in muscular exercise at 5800 m (19,000 ft.). *J Appl Physiol*, **19**, 431–440.

Reeves J.T., Groves B.M., Sutton J.R., Wagner P.D., Cymerman A., Malconian M.K., Rock P.B., Young P.M. & Houston C.S. (1987) Operation Everest II: preservation of cardiac function at extreme altitude. *J Appl Physiol*, **63**, 531–539.

Rennie D. (1989) Will mountain trekkers have heart attacks? *J Am Med Assoc*, **261**, 1045–1046.

Roca J., Hogan M.C., Story D., Bebout D.E., Haab P., Gonzalez R., Ueno O. & Wagner P.D. (1989) Evidence for tissue diffusion limitations of $\dot{V}O_2$max in normal man. *J Appl Physiol*, **67**, 291–299.

Suarez J., Alexander J.K. & Houston C.S. (1987) Enhanced left ventricular systolic performance at high altitude during Operation Everest II. *Am J Cardiol*, **60**, 137–142.

Sutton J.R., Reeves J.T., Wagner P.D., Groves B.M., Cymerman A., Malconian M.K., Rock P.B., Young P.M., Walter S.D. & Houston C.S. (1988) Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol*, **64**, 1309–1321.

Vogel J.A. & Harris C.W. (1967) Cardiopulmonary responses of resting man during early exposure to high altitude. *J Appl Physiol*, **22**, 1124–1128.

Wagner P.D. (1988) An integrated view of the determinants of maximum oxygen uptake. *Adv Exp Med Biol*, **227**, 245–256.

Ward M.P., Milledge J.S. & West J.B. (1989) *High Altitude Medicine and Physiology*. Chapman & Hall, London.

West J.B. & Wagner P.D. (1980) Predicted gas exchange on the summit of Mt. Everest. *Resp Physiol*, **42**, 1–16.

West J.B. (1983) Climbing Mt. Everest without supplementary oxygen: an analysis of maximal exercise during extreme hypoxia. *Resp Physiol*, **52**, 265–279.

West J.B., Hackett P.H., Maret K.H., Milledge J.S., Peters R.M. Jr, Pizzo C.J. & Winslow R.M. (1983a) Pulmonary gas exchange on the summit of Mt. Everest. *J Appl Physiol: Respirat Environ Exercise Physiol*, **55**, 678–687.

WEST J.B., BOYER S.J., GRABER D.J., HACKETT P.H., MARET K.H., MILLEDGE J.S., PETERS R.M. JR, PIZZO C.J., SAMAJA M., SARNQUIST F.H., SCHOENE R.B. & WINSLOW R.M. (1983b) Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol: Respirat Environ Exercise Physiol*, **55**, 688–698.

WEST J.B., LAHIRI S., MARET K.H., PETERS R.M. JR & PIZZO C.J. (1983c) Barometric pressures at extreme altitudes on Mt. Everest: physiological significance. *J Appl Physiol: Respirat Environ Exercise Physiol*, **54**, 1188–1194.

WEST J.B. (1988) Rate of ventilatory acclimatization to extreme altitude. *Resp Physiol*, **74**, 323–333.

WINSLOW R.M., SAMAJA M. & WEST J.B. (1984) Red cell function at extreme altitude on Mount Everest. *J Appl Physiol: Respirat Environ Exercise Physiol*, **56**, 109–116.