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RESPIRATORY AND CIRCULATORY CONTROL AT HIGH ALTITUDES

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SUMMARY

Hyperventilation is one of the most important features of acclimatization to high altitude. Resting ventilation at extreme altitudes increases up to fourfold and exercise ventilation for a given work level increases to the same extent. Hypoxic stimulation of the peripheral chemoreceptors is the chief mechanism for the hyperventilation but there is also evidence that central sensitization of the respiratory centres occurs. Permanent residents of high altitude have a blunted hypoxic ventilatory response compared to acclimatized lowlanders. Cardiac output increases in response to acute hypoxia but returns to normal in acclimatized lowlanders. Oxygen uptake at extreme altitudes is markedly limited by the diffusion properties of the blood gas barrier. As a consequence the maximal oxygen consumption of a climber near the summit of Mount Everest is near his basal oxygen requirements. Maximal oxygen consumption is so sensitive to barometric pressure that it may be that day-to-day variations will affect the chances of a climber reaching the summit without supplementary oxygen.

ACCLIMATIZATION TO HIGH ALTITUDE

Man and some other animals show a remarkable ability to adapt to living at high altitudes, a process known as acclimatization. Various factors participate in this acclimatization process including hyperventilation, increases in the red blood cell concentration of the blood and in the number of capillaries in peripheral tissues, and changes in the oxidative enzymes within the cells. Some people also believe that the rightward shift of the oxygen dissociation curve which sometimes occurs is also beneficial.

Of all these changes, probably the most important is the hyperventilation. As an example of the value of this we can consider a climber standing on the summit of Mt Everest (altitude 8848 m) who elects to maintain the same alveolar ventilation as he had at sea level. The result would be a fall in alveolar and arterial P_{O_2} to zero! Indeed, while the importance of hyperventilation is clear to see, many physiologists now question the roles of polycythemia and the rightward shift of the oxygen dissociation curve in the acclimatization process. For example, Winslow *et al.* (1979) showed that when some permanent residents of high altitude who had marked polycythemia were bled over a period of two or three weeks to reduce their haematocrit to normal sea level values, their exercise tolerance was substantially unaltered, or

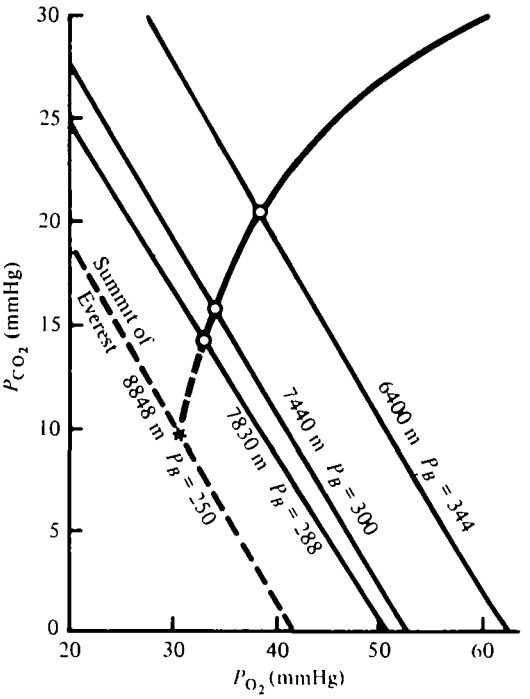

Fig. 1. Oxygen–carbon dioxide diagram showing alveolar gas composition at extreme altitudes (open circles). Extrapolation to the summit of Mt Everest (250 torr) gives a P_{O_2} and P_{CO_2} of approximately 30 and 10 torr, respectively. (From West & Wagner, 1980.)

even improved. Furthermore, during the American Medical Research Expedition to Everest which has just concluded, we found that reducing the haematocrit of some climbers at the end of the expedition by replacing whole blood with human albumin solution at an altitude of 5400 m did not appear to alter work capacity (as measured on a stationary bicycle) or psychological function.

Again the role of the rightward shift of the oxygen dissociation curve in acclimatization has recently been disputed. First, the extent of the shift in well-acclimatized subjects may be insignificantly small. But the most provocative relevant finding was reported by Hebbel *et al.* (1978) who showed that patients with haemoglobin Andrew–Minneapolis, who had a markedly left-shifted oxygen dissociation curve, apparently tolerated exercise better at medium altitudes than their siblings who had a normal oxygen dissociation curve. Theoretical studies of pulmonary gas exchange at high altitudes support this. Bencowitz *et al.* (1982) showed that a left-shifted oxygen dissociation curve results in a higher P_{O_2} in mixed venous blood during exercise at high altitude when oxygen transfer across the blood–gas barrier is partially limited by diffusion. Indeed, climbers may well exploit this leftward shifting at extreme altitudes. A common practice when climbing an 8000 m peak is to put in the high camps and then descend to a medium altitude for several days. Following this the climber moves as rapidly as possible to the summit. This procedure results in a partially compensated respiratory alkalosis at extreme altitudes which will cause a leftward shift in the oxygen dissociation curve and may well enhance oxygen transfer (West & Wagner, 1980).

Fig. 2. Christopher Pizzo, M.D., taking alveolar gas samples on the summit of Mt Everest during the course of the American Medical Research Expedition to Everest, 1981.

Thus, hyperventilation is one of the most important features of high altitude acclimatization. The extent of the hyperventilation that occurs is remarkable and is best considered under the headings of resting and exercise ventilation.

VENTILATION DURING REST

Measurements of ventilation at rest are notoriously unreliable because the experimental subject is distracted by the mouthpiece and other equipment. For this reason it is usual to report the alveolar or arterial P_{CO_2}; this is inversely proportional to the alveolar ventilation if carbon dioxide production is constant. Fig. 1 is an oxygen–carbon dioxide diagram showing alveolar gas composition at extreme altitudes (Gill *et al.* 1962). The data were obtained on the Himalayan Scientific and Mountaineering Expedition, 1960–1. The curve line at the top right of the diagram is essentially a continuation of the line drawn by Rahn & Otis (1949) for men acclimatized to high altitudes. Note that extrapolation of the line through the barometric pressure on the summit of Mt Everest predicts a P_{O_2} and P_{CO_2} of about 30 and 10 torr respectively. During the recent physiological research expedition to Everest, several alveolar gas samples were obtained on the summit by Dr Christopher Pizzo (see Fig. 2). These samples are still being analysed at the time of writing.

These data show the enormous degree of hyperventilation which occurs during rest at extreme altitudes. Since the normal sea level value for alveolar P_{CO_2} is 40 torr, the value of 10 torr predicted for the summit of Mt Everest represents a fourfold increase in resting alveolar ventilation.

VENTILATION DURING EXERCISE

Just as resting ventilation increases dramatically at high altitude, so does ventilation during exercise. In fact, at moderate levels of exercise, there is little or no change in arterial P_{CO_2} between rest and exercise. Since carbon dioxide production for a given work level is essentially independent of altitude, this means that ventilation measured at STPD is independent of altitude at a given work level. At work levels approaching maximal values at any altitude, alveolar and arterial P_{CO_2} fall compared with the resting level and exercise ventilation measured at STPD correspondingly rises. Naturally, if exercise ventilation is reported as BTPS which is the usual practice, the values for a given level of exercise increase markedly with altitude.

Very high levels of ventilation (BTPS) during maximal exercise are seen at altitudes of about 6000 m. Fig. 3 shows data obtained by Pugh *et al.* (1964) at sea level, 4650 m (440 torr), 5800 m (380 torr), 6400 m (340 torr), and 7440 m (300 torr). These data are shown by crosses on the diagram. The barometric pressure axis is non-linear for reasons which will be explained below. Note the very high values for maximal exercise ventilation at barometric pressures between 340 and 400 torr. Indeed, one measurement of maximal exercise at an altitude of 6400 m where the barometric pressure was 340 torr gave a value for ventilation of over 200 l/min BTPS (Pugh *et al.* 1964).

Fig. 3 also shows that at even higher altitudes (lower barometric pressures) maximal exercise ventilation falls off. Thus, at an altitude 7440 m (300 torr) the mean value was only 120 l/min. Predictions based on a model of gas exchange for a climber on

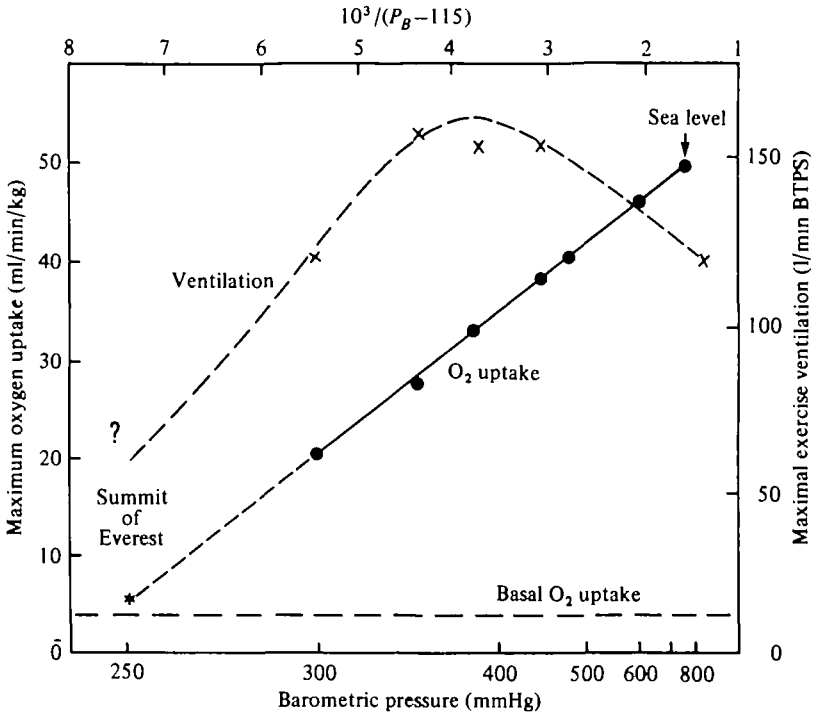

Figure 3. Maximal exercise ventilation and maximal oxygen consumption plotted against barometric pressure. The barometric pressure axis has been transformed according to the expression at the top of the graph so that the data for maximal oxygen consumption lie on a straight line. Note that maximal ventilation increases with falling barometric pressure up to a certain point and then decreases strikingly. The maximal oxygen consumption predicted for the summit is close to the basal oxygen requirements.

the summit of Mt Everest give values as low as about 50 l/min for maximal exercise ventilation there. Some measurements of ventilation during maximal climbing activity were made during the recent physiological expedition to Mt Everest at an altitude of about 8300 m (271 torr) but the results are not available at the time of writing.

The reason for the decline in maximal exercise ventilation at extreme altitudes is the reduction in maximal work level as indicated by the values for maximal oxygen uptake shown in Fig. 3. In this figure, data on maximal oxygen consumption at various altitudes reported by Pugh *et al.* (1964) are plotted on a non-linear barometric pressure axis which was chosen so that the data points lie on a straight line. The transformation is according to the hyperbolic function shown at the top of the diagram. Note that maximal oxygen uptake fell to approximately one third of its sea level value in a climber at an altitude of 7440 m (300 torr). A somewhat bold extrapolation of the data predicts a maximal oxygen uptake for a climber on the summit of Mt Everest of little more than his basal oxygen consumption. Since the work levels at these extreme altitudes are so low, the levels of maximal exercise ventilation are also reduced though, as stated previously , for a given work level, exercise ventilation (BTPS) continues to increase as the climber goes higher.

REGULATION OF VENTILATION AT HIGH ALTITUDE

If a resting subject at sea level is given a low oxygen mixture to breathe, ventilation generally increases through stimulation of the peripheral chemoreceptors. In acute hypoxia, the response is somewhat variable and is usually not seen until the alveolar P_{O_2} is reduced to between 50 and 60 torr corresponding to a simulated altitude of about 4000 m. With more severe degrees of alveolar hypoxia, increasing hyperventilation is seen though the levels of ventilation are considerably less than those observed in lowlanders acclimatized to high altitude. Not only is the resting ventilation increased in acute hypoxia but so is the ventilatory response to carbon dioxide as measured by the change in ventilation per unit rise in alveolar P_{CO_2} (Nielsen & Smith, 1952).

With chronic hypoxia such as caused by exposure to high altitude, ventilation initially increases as in acute hypoxia but there is a further increase which occurs over several days. The mechanism of this 'ventilatory acclimatization' is still obscure. One early explanation was that the initial hyperventilation increased the plasma pH, which tended to inhibit a further increase in ventilation until renal excretion of bicarbonate took place and returned the arterial pH to normal (Rahn & Otis, 1949). Another explanation was that similar acid-base changes occurred in the cerebral spinal fluid thus affecting the extra-cellular environment of the central chemoreceptors (Severinghaus *et al.* 1963). However, neither of these explanations is now accepted because the time course of changes in arterial blood pH and cisternal CSF pH are not consistent with the observed levels of ventilation (Forster *et al.* 1975). Physiologists working in this rather technical area now believe that some central sensitization of the respiratory centres occurs though the mechanism for this is far from understood. This explanation is consistent with the observation that if acclimatized lowlanders are given 100% oxygen to breathe at high altitude, while both resting and exercise ventilation for a given work level are reduced, they do not return to the sea level values (Pugh *et al.* 1964).

If we compare the hypoxic ventilatory response of acclimatized lowlanders with permanent residents of high altitude (including both the South American Andes and the Himalayas) we find that the native highlanders have a blunted hypoxic response. The response is still present as shown, for example, by the single or double oxygen breath test (Dejours *et al.* 1958) but it is less marked than in acclimatized lowlanders. The same phenomenon is seen in children born at sea level who have chronic arterial hypoxemia caused by cyanotic congenital heart disease. One consequence of the blunted hypoxic ventilatory response is that permanent high altitude residents have slightly higher alveolar P_{CO_2} values than acclimatized lowlanders at the same altitude.

CARDIAC AND CIRCULATORY FUNCTION

Acute hypoxia causes both an increase in cardiac output and heart rate. For example, when the arterial P_{O_2} is reduced to levels of approximately 35 to 45 torr, both cardiac output and heart rate are some 40 to 50% higher than normoxic control values (Kontos, *et al.* 1967; Vogel & Harris, 1967).

However after several weeks at high altitude, both the resting pulse rate and cardiac

output return to the sea level values, at least up to altitudes of about 6000 m. Above this altitude, resting pulse rate tends to increase. Very few measurements of cardiac output have been made above an altitude of 5000 m. However both Cerretelli (1976) and (Pugh (1964*a*) agree that cardiac output for a given work level at these high altitudes is similar to the sea level values. When oxygen is breathed by acclimatized lowlanders at high altitude, the heart rate for given work level decreases. However, the maximal heart rate increases because the maximal work level is so much higher. The fact that the cardiac output for a given work level at high altitude (during ambient air breathing) is essentially the same as at sea level suggests that the heart does not play a role in the acclimatization process. However, it should be pointed out that because of the associated polycythemia, the haemoglobin flow per unit time is actually increased at high altitude.

Changes in systemic arterial blood pressure are generally unremarkable in sea level dwellers acclimatized to high altitude. However, both they and high altitude natives show an increase in pulmonary artery pressure as a consequence of the hypoxic pulmonary vasoconstriction. The pulmonary hypertension is particularly marked on exercise, is accentuated by the increased viscosity of the polycythemic blood, and results in the characteristic changes of right heart hypertrophy in the electrocardiogram. High altitude pulmonary oedema which is occasionally seen is probably related in some way to the pulmonary hypertension though the mechanism remains obscure.

GAS EXCHANGE AT HIGH ALTITUDE

The changes in ventilation and cardiac output which occur at high altitude are part of the organism's response to oxygen deprivation. It is therefore pertinent to look at the overall picture of oxygen and carbon dioxide transport at high altitude. Our own recent preoccupation has been with extreme altitudes, stimulated in part by the remarkable physiological event which occurred just three years ago when Messner and Habeler reached the summit of Mt Everest for the first time without the help of supplementary oxygen. That this is very near the limit of human tolerance is supported by Fig. 4 which shows the greatest heights attained by climbers this century. Note that although men had ascended to within 300 m of the summit of Everest as early as 1924, the mountain was not climbed until 1953, and then only with supplementary oxygen. It was not until 1978 that climbers were successful breathing ambient air. Thus, the last 300 m took 54 years!

Recently we have analysed the gas exchange which is predicted to occur in a climber resting on the summit of Mt Everest. We were stimulated in part to do this by the climb of Messner and Habeler and by data such as those shown by the circles in Fig. 3 which suggest that the available maximal oxygen uptake at the summit is very close to the basal oxygen consumption. This theoretical analysis was partly made to identify the most important measurements that could be made during the recent physiological expedition to Mt Everest.

One of the most critical pieces of data needed for such an analysis is the barometric pressure on the summit. There has been some uncertainty about this but fortunately Dr Pizzo (Fig. 2) managed to make a measurement confirming that it is between 250

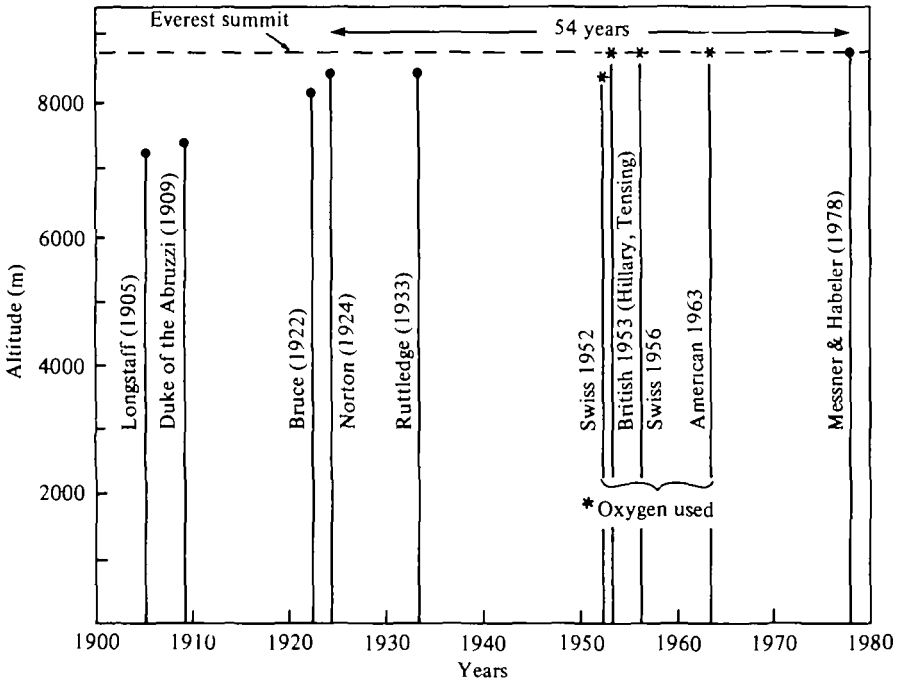

Fig. 4. Highest altitudes attained by climbers during this century. Note that as early as 1924 climbers ascended to within 300 m of the summit of Mount Everest. However the mountain was not climbed without supplementary oxygen until 54 years later. (From West & Wagner, 1980.)

and 253 torr. Incidentally, this is substantially higher than the pressure predicted from the ICAO Standard Atmosphere because the pressure at a given altitude is higher near the equator than the poles as a result of the presence of a large mass of cold air in the stratosphere above the equator. Many physiologists in the past have used the standard atmosphere which gives a pressure of only 235 torr at the altitude of Mt Everest. One conclusion of our analysis is that if the pressure were that low it would certainly be impossible to climb the mountain without supplementary oxygen.

Another critical variable is the alveolar P_{CO_2}. The extrapolation from data already obtained up to altitudes of 7830 m (288 torr) shown in Fig. 1 gives a value at rest of 30·5 torr and we have used this. We have also assumed that the alveolar P_{CO_2} remains constant as the exercise level is increased. This was found to be the case (Pugh *et al.* 1964) for oxygen consumptions of up to about 1 l/min at an altitude of 5800 m (380 torr). However, note that as the respiratory exchange ratio increases from about 0·8 to 1 during exercise, there is a gain in alveolar P_{O_2} of approximately 2 torr.

Other data needed for this analysis include the haemoglobin concentration, cardiac output, and diffusing capacity of the blood–gas barrier. For haemoglobin concentration we have assumed a figure of 20·5 g/dl, a mean value reported for acclimatized climbers during Himalayan expeditions (Pugh, 1964*b*) although measurements on the recent physiological expedition to Everest give a slightly lower value. Both cardiac output and diffusing capacity were assumed to be the same as at sea level for the same work level as was the case in measurements at 5800 m (Pugh, 1964*a*; West, 1962).

Based on these considerations, we have calculated the time-course of oxygenation along the pulmonary capillary by the method of forward integration using Runge–Kutta technique (Wagner, 1977). Reaction times for both oxygen and carbon dioxide were taken into account. Fig. 5A shows a typical result for a climber resting on the summit of Mt Everest, and Fig. 5B shows the normal time course of P_{O_2} in the pulmonary capillary at sea level for comparison. The oxygen uptake and carbon dioxide are constrained to be 250 and 200 ml/min respectively, giving a respiratory exchange ratio of 0·8. A striking finding of the calculations at extreme altitude is that even under these essentially basal conditions, there is marked diffusion limitation of oxygen transfer resulting in an alveolar end-capillary difference of approximately 6 torr. This is about 60% of the P_{O_2} difference between alvaolar gas and mixed venous blood. Thus even under these extreme resting conditions, the arterial P_{O_2} is only 25 torr while the alveolar P_{O_2} is 31 torr and the P_{O_2} in mixed venous blood is only 21 torr.

Additional calculations show that the situation rapidly worsens if the oxygen consumption is increased. This results in a further fall in the P_{O_2} of mixed venous blood. If we assume that there is a value of mixed venous P_{O_2} below which increases in oxygen consumption will not be tolerated, this places a limit on the oxygen consumption of the climber. Using reasonable values for diffusing capacity and the other variables, the analysis concludes that the maximal oxygen uptake can only be increased to about 700 ml/min before the P_{O_2} of mixed venous blood falls below 15 torr. This very low work capacity is consistent with the account of the extreme difficulties of reaching the summit of Mt Everest without supplementary oxygen (see for example Messner, 1979).

FACTORS LIMITING WORK AT EXTREME ALTITUDES

In view of the very restricted maximal oxygen consumption at extreme altitude, it is pertinent to ask what are the most important limiting factors. One way of answering this is to calculate the percentage increase in maximal oxygen consumption for the same percentage change of various parameters as shown in Fig. 6. To prepare this graph, calculations were made by changing only one variable at a time, all others being kept the same for the appropriate work level. Maximal oxygen consumption was assumed to occur when the P_{O_2} of mixed venous blood fell to 15 torr.

Fig. 6 shows that barometric pressure is by far the most critical variable. Thus, only a 6% fall in barometric pressure from 250 to 235 torr (the value predicted from the ICAO Standard Atmosphere) results in a decrease in predicted maximal oxygen uptake of 45% (from 470 to 260 ml/min). Indeed, it may be that even day-to-day variations in barometric pressure are significant. Radiosonde data indicate that a decrease of up to 4 torr can be expected in May or October (the preferred climbing months) as a result of daily changes in weather. A decrease of barometric pressure of 4 torr is predicted to result in a fall in calculated maximal oxygen consumption of about 10%, and this may well be sufficient to determine whether a climber is successful or not. Thus, a climber who plans to ascend to the summit of Mt Everest without supplementary oxygen might do well to consult his barometer first.

Fig. 6 also emphasizes the sensitivity of maximal oxygen consumption to the diffusing capacity of the blood–gas barrier. This is not surprising since Fig. 5A

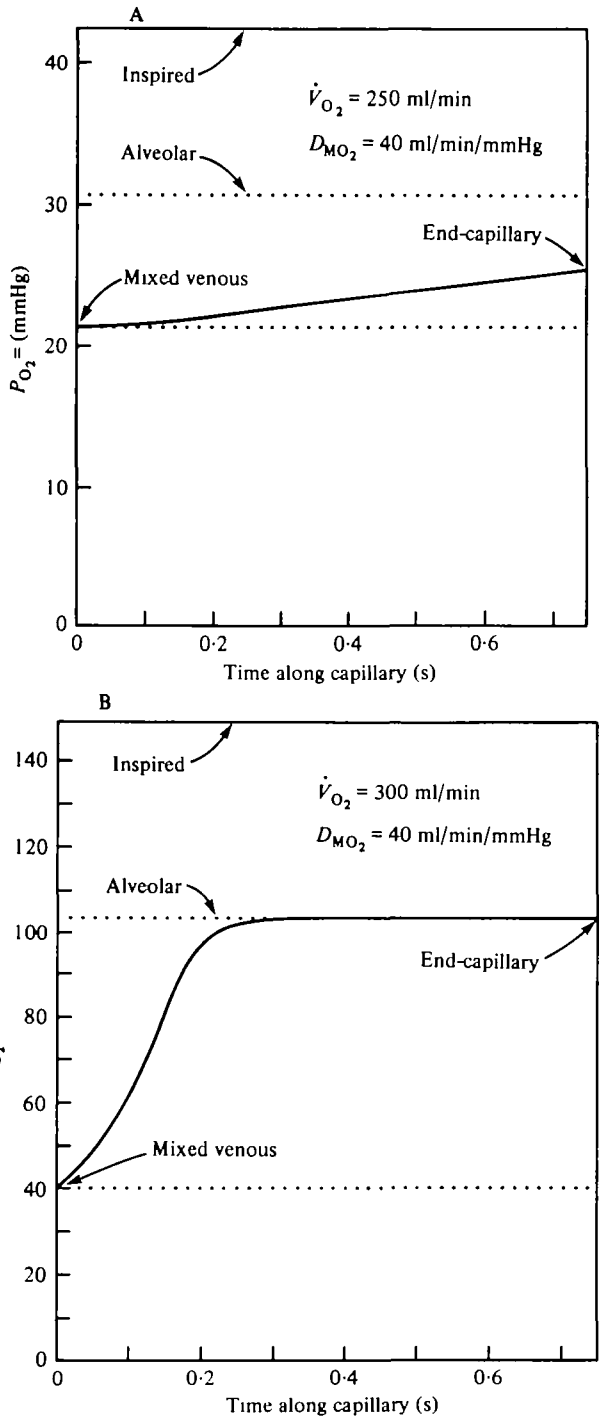

Fig. 5. (A) Shows the calculated time course of the P_{O_2} in the pulmonary capillary of a climber at rest on the summit of Mt Everest. Note the very slow rate of rise of P_{O_2} and the marked difference in P_{O_2} between alveolar gas and in capillary blood. (B) Shows the normal time course at sea level for comparison. (From West & Wagner, 1980).

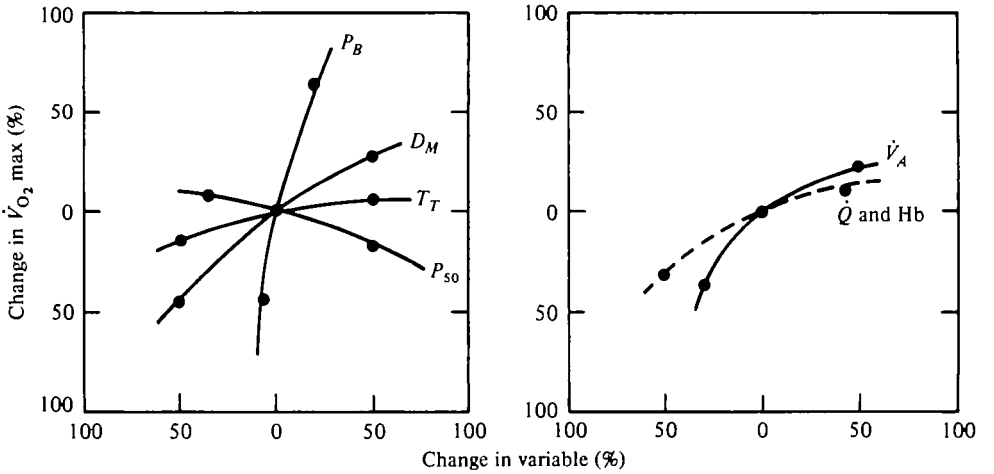

Fig. 6. Analysis of factors limiting maximal oxygen uptake at a barometric pressure of 250 torr. Note the extreme sensitivity to barometric pressure (P_B). The membrane diffusing capacity (D_M) is also a critical variable. Other parameters studied are capillary transit time (T_T), P_{50} of the oxygen dissociation curve, total alveolar ventilation (VA), haemoglobin concentration (Hb) and cardiac output (Q). (From West & Wagner, 1980).

emphasizes the extent to which oxygen transfer is diffusion-limited under these very hypoxic conditions. The reason for the marked diffusion limitation is the steepness of the slope of the blood–oxygen dissociation curve expressed as ml O_2/dl blood/torr. This steep slope can be ascribed to two factors: first, the capillary P_{O_2} is very low on the oxygen dissociation curve during the entire oxygenation process along the capillary, and second, the haemoglobin concentration is much increased.

How valuable would increases in ventilation and cardiac output be in improving maximal work capacity under these conditions? The right panel of Fig. 6 shows that both an increase in alveolar ventilation, and an increase in total pulmonary blood flow or haemoglobin would provide useful gains. This raises the question of why the climber does not increase his maximal exercise inflation which, as Fig. 3 shows, is restricted to low values at these extreme altitudes. One possibility is that the oxygen cost of additional ventilation would steal a significant portion of the total oxygen available. Another is that the action of the respiratory muscles themselves is limited by hypoxia.

The situation with cardiac output is equally puzzling. Pugh (1964*a*) showed that the relationship between cardiac output and work rate was the same at an altitude of 5800 m (380 torr) in acclimatized subjects as at sea level. It is known that acute exposure to altitude increases cardiac output at a given work level (Alexander *et al.* 1967) but apparently with acclimatization the relationship reverts to that seen at sea level. Why this should be when an increase in cardiac output would clearly improve oxygen delivery to the exercising muscles is obscure. However the answer to this paradox may have to wait until we understand the control of cardiac output at sea level which, as far as I can determine, is far from the case at the present moment.

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