The Journal of Experimental Biology 204, 3121–3127 (2001)
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JEB3296

Limits of human lung function at high altitude

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Accepted 2 July 2001

Summary

This paper will review the function of the lung at high altitude in humans. As the first interface between the environment and the body, the lung serves a vital role in the transfer of oxygen from the air to the blood. I will describe the limits of response and adaptation of the lung to this hypoxic stress, both at rest and during exercise when oxygen and carbon dioxide flux from the tissues is greater. First, ventilation will be described in terms of the hypoxic stimulus that causes an increase in breathing (ventilatory drives) and the metabolic cost from the respiratory muscles incurred by this increase. Individuals at high altitude also have a substantial sense of dyspnea which, in and of itself, may limit exercise tolerance. The final function of the lung is to exchange oxygen and carbon dioxide, which it does at the alveolar–capillary interface. Here, important limitations are encountered because the driving pressure for oxygen from the air to the blood is lower and the more rapid transit time of blood across the pulmonary capillary allows less time for equilibration of oxygen with the blood. Both these phenomena lead to a limitation of diffusion of oxygen across the alveolar–capillary membrane and, thus, more accentuated hypoxemia. In spite of these restrictions, humans still do remarkably well in times of great stress from the hypoxic environment.

Key words: high altitude, ventilation, exercise, gas exchange, ventilatory drive, dyspnoea.

Limits of lung function in humans at high altitude

The lungs are the first interface between oxygen in the environment and the metabolic machinery of the body. Both at rest and at high levels of work, successful gas exchange at the alveolar–capillary membrane is necessary to achieve an adequate supply of oxygen to the tissues and for the elimination of carbon dioxide. To achieve this goal, the mechanical function of the lungs, chest wall and respiratory muscles must move a large enough volume of air to supply oxygen to the body. Furthermore, gas exchange at the alveolar–capillary membrane must allow transfer of oxygen to the blood, which includes diffusion of oxygen from the air to the hemoglobin in the red blood cells. In addition, the drive to breathe from the central nervous system must be finely tuned to increase ventilation instantaneously as metabolic demand increases. Finally, the sense of breathlessness, or dyspnea, which may inhibit attempts to increase work, must achieve a compromise with the metabolic demand so that work is not impaired.

At high altitude, respiration extracts utilizes a high proportion of the overall energy expenditure. In spite of a slight decrease in the work of breathing resulting from the lower density of the ambient air at high altitude, much greater volumes of air are necessary to supply enough oxygen to the body from atmospheric air, in which the level of oxygen is reduced. Delivery of oxygen is further impaired by a diffusion limitation of oxygen from the air to the blood, which increases with altitude. At extreme altitudes, a disabling sense of dyspnea is compounded by cerebral hypoxia, which may further limit exercise. Climbers to these heights have reported taking as many as 10 breaths per step as the rate of ascent progressively and tortuously slows. Reinhold Messner wrote of his first ascent of Mount Everest (8828 m, barometric pressure 33.3 kPa) without supplemental oxygen that ‘I am nothing more than a single narrow, gasping lung, floating over the mists and summits’. Thus, we come back to the lung as the primary and essential organ for human function and survival at high altitude without which the first step up could not be taken.

The purpose of this manuscript is to review work that has been carried out on the control of ventilation, the mechanics of respiration and gas exchange that pertain to the limits of exercise performance at high altitude. Both field and laboratory work will be drawn upon to gain insight into the understanding of lung function under the stress of high altitude.

Ventilatory demand at high altitude

For any given energy expenditure, the ventilation ($\dot{V}_{E\mathrm{BTPS}}$; $\mathrm{l\,min^{-1}}$) increases proportionately with altitude. Since barometric pressure decreases, there is less oxygen per volume

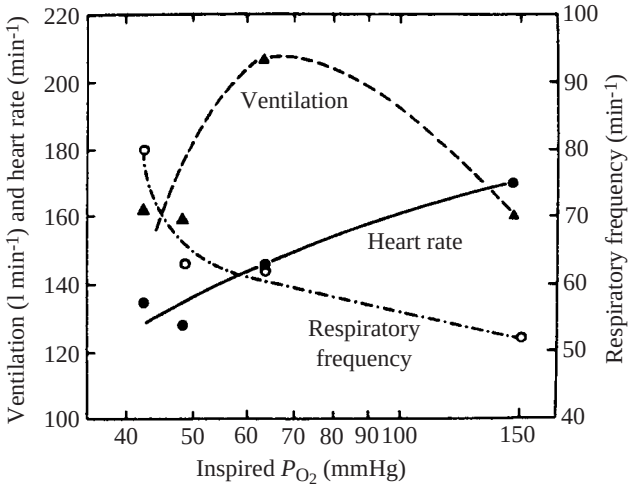

Fig. 1. Data from the 1981 American Medical Research Expedition to Everest showing that maximal exercise ventilation in liters per minute (BTPS) (dashed line) increased as the inspired partial pressure of oxygen decreased from sea-level values (150 mmHg) to approximately 60 mmHg (at an altitude of approximately 6300 m), but decreased as climbers approach the extreme altitude of the summit of Mount Everest, where the inspired partial pressure of oxygen was 42 mmHg. The increase in ventilation is secondary to the hypoxic stimulation of exercise hyperpnea and the level of exercise, which was approximately 200 W of work at 6300 m, while the hypoxic stimulus was greater at 8848 m, but the work capacity was greatly reduced (from West et al., 1983, with permission). 1 mmHg=0.133 kPa.

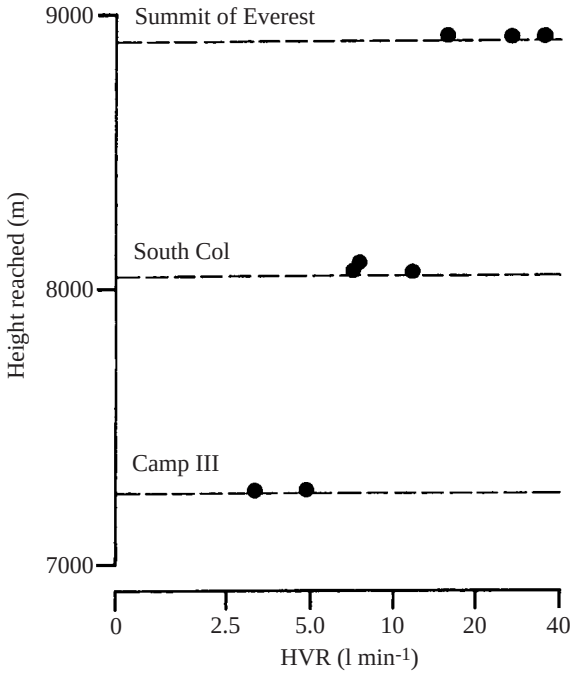

Fig. 2. Data from the 1981 American Medical Research Expedition to Everest showing that individuals with higher hypoxic ventilatory responses (HVR) performed better at higher altitudes that those with lower HVRs (redrawn from data of Schoene et al., 1984).

of gas than at sea level. Thus, supplying the same amount of oxygen for any given rate of work requires that the lungs must take in a greater total volume of air. A number of field and low-altitude (Sutton et al., 1988; West et al., 1983) studies (in both hypobaric and normobaric hypoxia) have demonstrated this phenomenon on repeated occasions.

Data from the 1981 American Medical Research Expedition to Everest (AMREE) obtained on Mount Everest (Fig. 1) and the 1985 Operation Everest II (OE II) hypobaric chamber experiments demonstrated a marked increase in ventilation up to altitudes of 6300 m (barometric pressure approximately 46 kPa) which, when expressed as ventilatory equivalent ($\dot{V}_{EBTPS}/\dot{V}_{O_2,STPD}$), where $\dot{V}_{O_2}$ is the rate of oxygen uptake, show that for any given level of work $\dot{V}_E$ is approximately four times greater at this altitude than at sea level. At 200 W of work during AMREE (at 6300 m), the mean ventilation for all subjects was 207 l min^{-1} (BTPS) compared with sea-level values at that workload of approximately 65 l min^{-1} (West et al., 1983). On OE II at comparable simulated altitudes, $\dot{V}_E$ was approximately 160 l min^{-1} and 89 l min^{-1} respectively (Sutton et al., 1988). The lower $\dot{V}_E$ may reflect less ventilatory acclimatization in OE II because of the shorter time at altitude. On AMREE, maximum $\dot{V}_E$ on the simulated summit in two subjects was substantially lower (approximately 160 l min^{-1}), which may reflect a lower metabolic demand from a decreased workload and/or a rather blunted ventilatory response in one of the subjects. The ventilatory responses at intermediate altitudes and workloads are correspondingly lower, but much higher than at sea level. Thus, the demand on lung mechanics and respiratory muscles is greater at high altitude and may impose a limit to exercise.

Ventilatory drives

The ventilatory response to exercise and hypoxia is complex and not completely understood. In spite of this limitation, hypoxemia, which stimulates the carotid body, effects an increase in ventilation. This response is proportional to the individual's inherent hypoxia ventilation response (HVR) (Schoene et al., 1984; Schoene et al., 1990), to the altitude and to the state of acclimatization incurred by a sojourn at high altitude. Although the actual increase in the sensitivity of the carotid body to hypoxemia during the course of acclimation is not fully understood, it appears that each individual's HVR, as measured at sea level, is roughly proportional to the ventilatory response to exercise at high altitude (Schoene et al., 1984; Schoene et al., 1990). In other words, subjects with a low HVR at rest measured at sea level have a relatively more blunted ventilatory response to exercise at high altitude than those with a high HVR, and *vice versa*. A large ventilatory response to exercise conveys a greater respiratory alkalosis and higher arterial oxygen saturation and may confer a better climbing performance at very high altitudes (Schoene et al., 1984) (Fig. 2). However, individuals with very large HVRs may incur a greater work of breathing at extreme altitude. Thus, there may be a trade-off between increased arterial blood

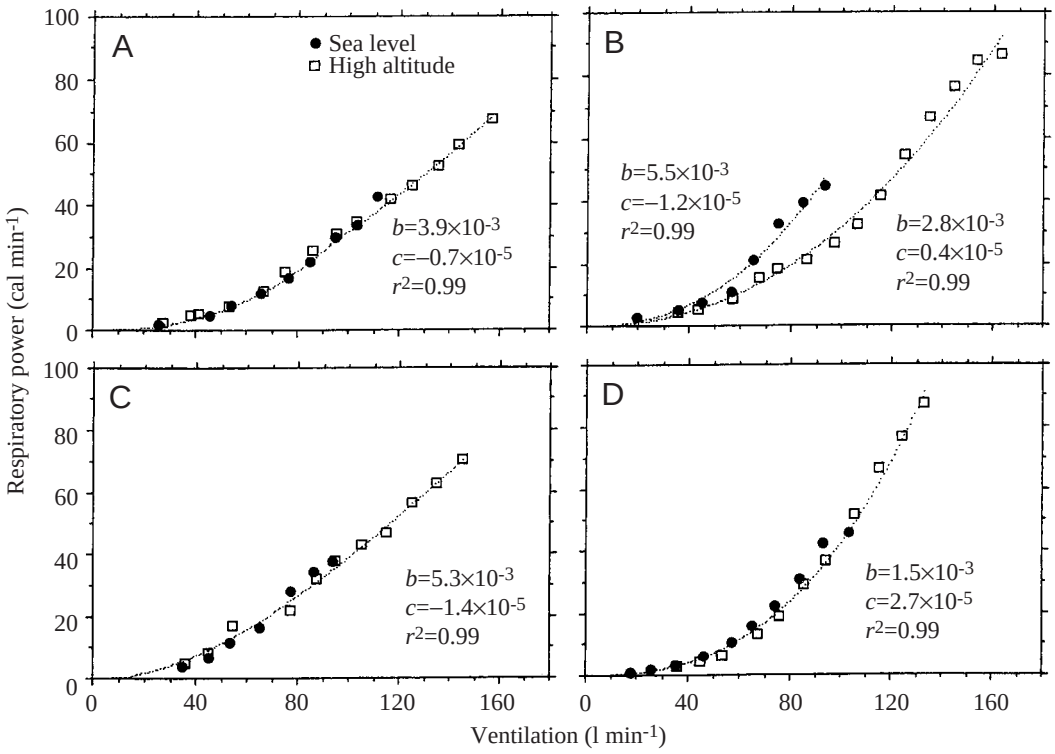

Fig. 3. Data from four subjects (A–D) exercising at sea level (filled circles) and 5050 m altitude (open squares) showing that the work of breathing, expressed as respiratory power (cal min^{-1}), was substantially greater at high altitude (from Cibella et al., 1999, with permission). 1 cal=4.19 J.

oxygenation and the increased work of breathing in these individuals.

The work of breathing and mechanical limitation

As we consider the limitations to exercise imposed by high levels of ventilation, either at sea level or at high altitude, we must first consider the effect of air density on the work of breathing. Theoretically, at high altitude, the decreased gas density could substantially decrease the resistive load of the convection of gas during the movement of air at high levels of exercise. This alleviation of the work of breathing must be balanced against the increase in ventilatory demands from the necessary hypoxic stimulation of ventilation during exercise. A recent study by Cibella et al. (Cibella et al., 1999) in a small number of subjects showed that, in spite of the lower gas density, the net result was that there was still a greater energy expenditure upon breathing at high altitude for any given work load than at low altitude. Thus, it still costs more to breathe at high altitude.

At high levels of exertion, there is a finite amount of energy that can be expended. The delivery of oxygen by the circulation must be apportioned carefully to optimize the balance between the energy utilized to produce work and the work output itself. More specifically, exercising at high altitude, which requires a high level of ventilation, extracts a fair amount of energy to achieve that degree of ventilation. The respiratory muscles require a substantial proportion of the overall maximum rate of oxygen consumption ($\dot{V}_{O_2max}$), not only at high altitude but also at sea level. At low altitude, Hanson et al. (Hanson et al., 1982) exercised 15 highly trained runners to maximum and decided that the net effects of the hyperventilatory response to high levels of exercise were an advantage in that the improved gas exchange and respiratory alkalosis outweighed the expense of some inefficiency and ventilatory work during exhaustive exercise.

The next avenue of investigation looked at the limits of air flow during high levels of exertion at sea level in highly trained athletes and the work necessary to generate the pressure differential for this degree of air flow. Johnson et al. (Johnson et al., 1992) studied athletes at exhaustive levels of exercise and found that the flow limitation in the airways incurred a substantial metabolic cost. Subsequent investigations focused on actual respiratory muscle fatigue during high levels of work. This same investigative group (Johnson et al., 1993) found that in highly trained athletes the diaphragm functioned quite well up to approximately 85 % of $\dot{V}_{O_2max}$, after which the transdiaphragmatic pressure, a reflection of the force generated from the diaphragm, decreased by approximately 25 %. This finding suggests diaphragmatic fatigue at levels of work greater than 85 % of $\dot{V}_{O_2max}$ and impairment for prolonged high level exercise. In these studies and others (e.g. Marciniuk et al., 1994), respiratory muscle fatigue, particularly from the diaphragm, was not apparent at levels of exercise of 70 % of $\dot{V}_{O_2max}$ or less. Trying to exercise for prolonged periods above this level may extract too great a price in the overall balance of energy, a delicate situation at high altitude.

Investigators then began to consider the fraction of the overall cardiac output required to supply the muscles of respiration. Did this ‘cardiac steal’, dedicated to the muscles of respiration, limit blood flow to the exercising muscles in such a way that work output was impaired. Babcock et al.

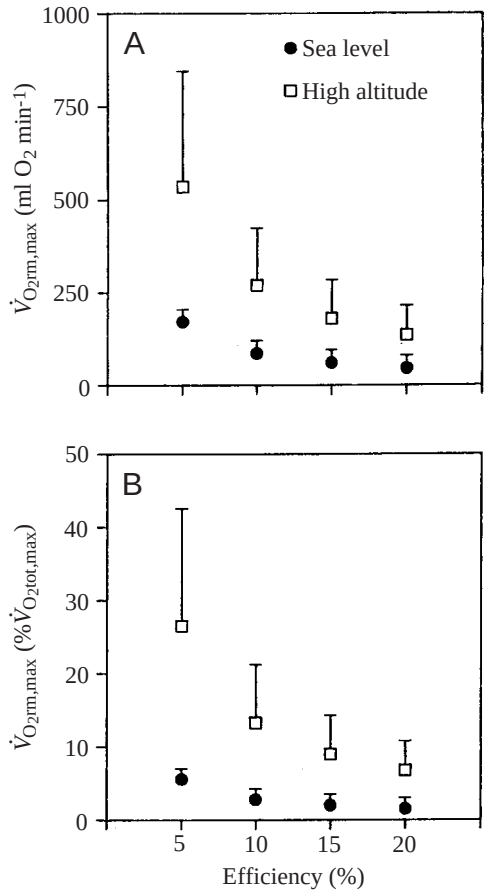

Fig. 4. (A) Data from subjects exercising at sea level (filled circles) and 5050 m altitude (open squares) demonstrating the maximal oxygen cost of breathing ($\dot{V}_{O_2rm,max}$) during maximal ventilation at physiological levels of mechanical efficiency (range 5–20 %). (B) Similar data except that $\dot{V}_{O_2rm,max}$ is expressed as a percentage of the total maximal rate of O_2 uptake ($\dot{V}_{O_2tot,max}$). These data show that the work of breathing is substantially higher at this altitude than at sea level (from Cibella et al., 1999, with permission). Values are means + S.E.M.

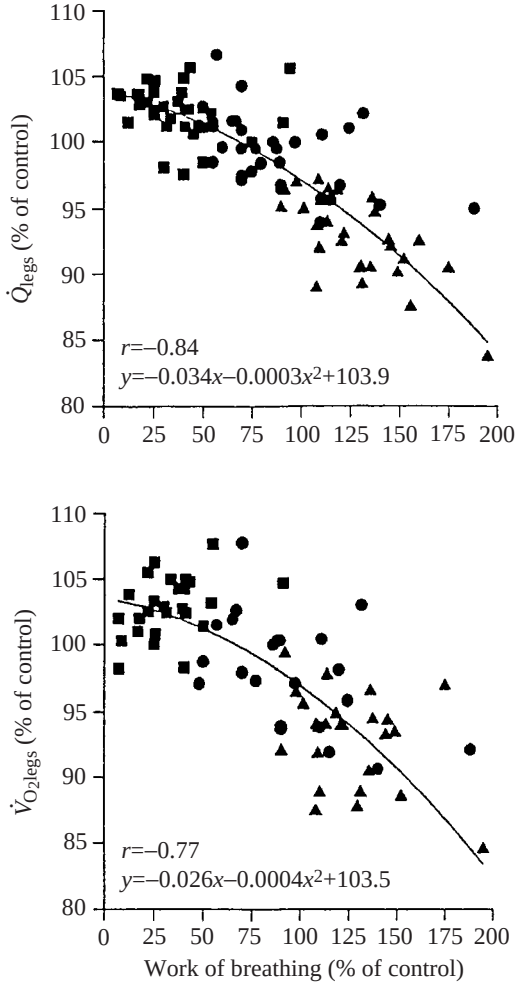

Fig. 5. Data from highly trained cyclists showing that, at maximum exercise, as the work of breathing increases, both the blood flow to the legs ($\dot{Q}_{legs}$) and the rate of oxygen consumption of the legs ($\dot{V}_{O_2legs}$) decrease. These studies were performed at resting ventilation and maximal ventilation both in a control state and with inspiratory loading (from Harms et al., 1997, with permission).

(Babcock et al., 1995) used supramaximal bilateral phrenic nerve stimulation at a number of frequencies in humans at 86–92 % of $\dot{V}_{O_2max}$ for approximately 13 min. They found a consistent and significant fall of approximately 26 % in the transdiaphragmatic pressures at all levels of work. They felt that there was competition for blood flow between the locomotor muscles and the diaphragm that eventually led to a steal of blood flow from the diaphragm and subsequent muscle fatigue. Cibella et al. (Cibella et al., 1999) tried to calculate the mechanical efficiency of breathing at low and high (5050 m) altitude and estimated that the oxygen cost of breathing at high altitude and sea level amounted to 26 and 5.5 % of $\dot{V}_{O_2max}$ respectively (Fig. 3, Fig. 4). They felt that the work of breathing at high altitude may limit external work unless mechanical efficiency was extremely high.

A number of older and more recent studies have tried to measure the effect of an increased amount of respiratory muscle work on the blood flow to the working muscles of locomotion. Peripheral vascular resistance in the exercising muscles is increased as one approaches maximal exercise. This phenomenon may, in fact, decrease the blood flow to these muscles while an increase in respiratory muscle blood flow is observed (Fig. 5) (Barclay, 1986; Harms et al., 1997; Wetter et al., 1999).

In summary, although because of the decreased density of the gas, the work of breathing at any given workload decreases progressively with increasing altitude, the net effect is an overall greater work of breathing, which may substantially impair energy supply to the locomotor muscles.

Gas exchange in the lung at high altitude

High altitude imposes a diffusion limitation of oxygen from the air to the blood (Fig. 6). This diffusion limitation is secondary to several factors: (i) a lower driving pressure for

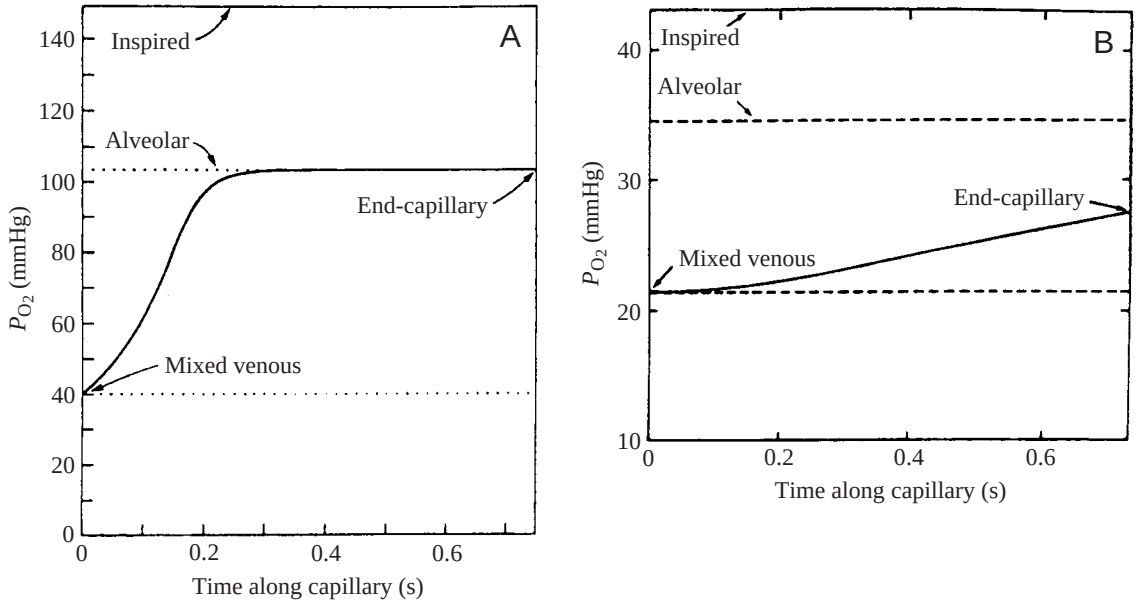

Fig. 6. Plots of the partial pressure of oxygen (mmHg) at sea level (A) and the summit of Mount Everest (B) *versus* the transit time of blood across the pulmonary capillary. These schematic representations demonstrate that, as one ascends, the driving pressure for oxygen from the air to the blood is lower, such that there is not time for equilibration for oxygen across the pulmonary capillary. This phenomen results in arterial oxygen desaturation, which is accentuated with higher levels of exercise (from West and Wagner, 1980, with permission). 1 mmHg=0.133 kPa.

oxygen from the air to the blood, (ii) a lower affinity of hemoglobin for oxygen on the steep portion of the oxygen/hemoglobin curve, and (iii) a decreased and inadequate time for equilibration of oxygen as the red blood cell traverses the pulmonary capillary. As mentioned above, the decreased alveolar partial pressure of oxygen at high altitude is in part minimized by ongoing ventilatory acclimation. This response to acclimation, however, is never adequate to overcome the ambient hypobaria. But, because of the large volume of gas that is required to supply an adequate quantity of oxygen, especially during the high metabolic demands of exercise, the lung is well designed to minimize the diffusion limitation in that the alveolar–capillary interface provides a large surface area for gas exchange that is instantly adaptable (West and Mathieu-Costello, 1992). Oxygen flux depends on the demand for oxygen, and the greater the ratio of diffusion capacity to perfusion the more successful is the loading of oxygen to the blood.

Arterial oxygen saturation thus decreases with exercise at high altitude, as has been documented in a number of human studies in both field and laboratory settings (Gale et al., 1985; Torre-Bueno et al., 1985; Wagner et al., 1986; Wagner et al., 1987; West et al., 1983) (Fig. 7). Using sophisticated evaluations of gas exchange (the multiple inert gas elimination technique, MIGET), investigators have been able to apportion the decline in arterial oxygen saturation by looking at ventilation/perfusion relationships as well as diffusion characteristics (Fig. 8). During acute hypobaric hypoxia to simulate an altitude of 4700 m, Gale et al. (Gale et al., 1985), Torre-Bueno et al. (Torre-Bueno et al., 1985) and Wagner et al. (Wagner et al., 1986) showed both a ventilation/perfusion

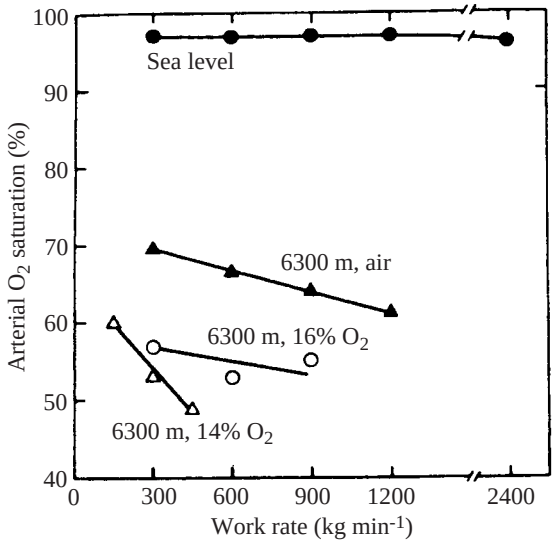

Fig. 7. Arterial oxygen saturation, as measured by ear oximetry, plotted against work rate at sea level and 6300 m altitude in humans exercising to maximal effort. The lower two lines were obtained with subjects breathing 16 and 14 % oxygen at 6300 m (from West et al., 1983, with permission).

inequality and a diffusion limitation in the lung, both of which accounted for worsening hypoxemia with increasing work loads at higher altitudes. In Operation Everest II, the assimilated ascent to 8828 m (P_{O_2}, approximately 33.3 kPa) demonstrated that the ventilation/perfusion heterogeneity persisted to a modest degree while the diffusion limitation of oxygen became greater with increasing altitude (Wagner et al., 1987) (Fig. 8). The increase

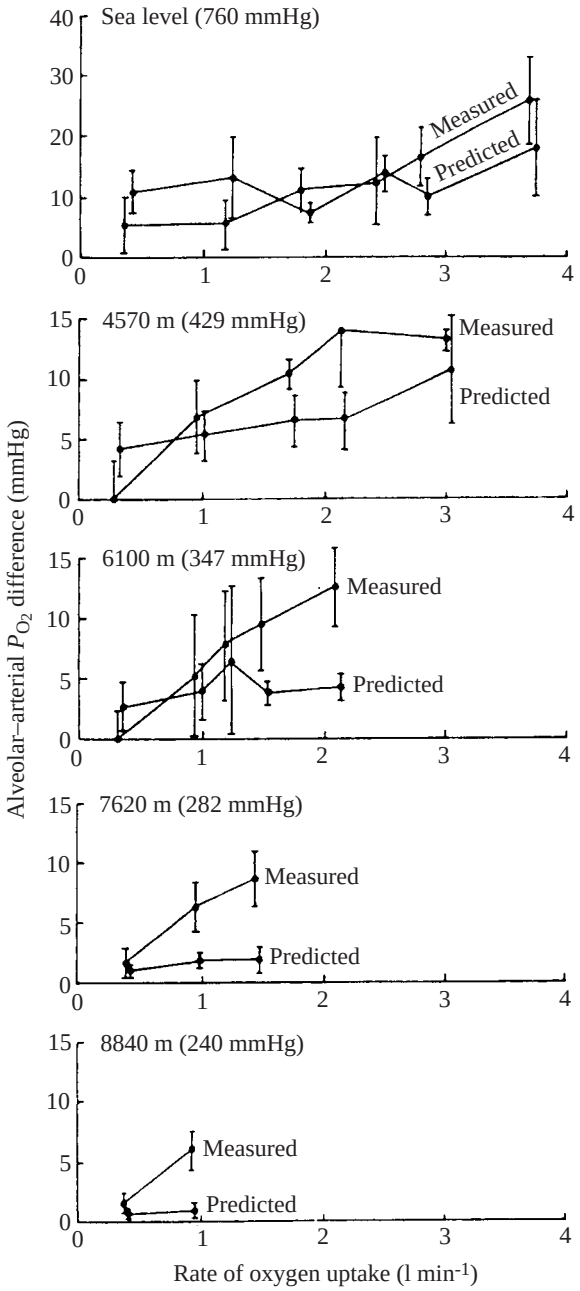

Fig. 8. Relationship between alveolar–arterial P_{O_2} difference and the rate of oxygen uptake in Operation Everest II, a high-altitude chamber study designed to simulate an ascent by humans over 40 days to the summit of Mount Everest (8828 m). These data were obtained from a multiple inert gas elimination technique that measures ventilation/perfusion relationships and show that the predicted alveolar–arterial P_{O_2} difference (mmHg) could be accounted for only in part by ventilation/perfusion inequality. The remaining difference was attributed to a diffusion limitation of oxygen from the air to the blood (from Wagner et al., 1987, with permission). 1 mmHg=0.133 kPa. Values are means + S.E.M.

in diffusion limitation was thought to be secondary to the marked decrease in driving pressure for oxygen from the air to the blood at these extreme simulated altitudes. The ventilation/perfusion heterogeneity was attributed to interstitial edema from high intervascular pressures, which correlated with the increase in pulmonary artery pressures. Much controversy exists regarding the effect on gas exchange of increased intervascular pressures during exercise at high altitude. During acute hypoxia, extravasation of fluid from the intra- to the extravascular space has been documented both at high altitude and at sea level in human and equine experiments (Hopkins et al., 1997; Pascoe et al., 1981; Seaman et al., 1995; Whitwell and Greet, 1984).

In summary, lung function at high altitude is accompanied by both impairment of gas exchange and diffusion limitation of oxygen from the air to the blood. The net effect is worsening hypoxemia, which is proportional both to the increase in energy expenditure and to high altitude.

Dyspnea

All accounts of climbing to extreme altitude convey that the climbers are overcome by extreme dyspnea. This sense of dyspnea, *per se*, inhibits further exercise or at least makes it laboriously painful and slow with increasing altitudes. At the same time, with attempts to exercise to a greater degree, climbers describe an almost euphoric haze of mental acuity, which further limits exercise and may be secondary to depression of central nervous system output resulting from brain hypoxia. Further work is necessary to measure the effects of high altitude upon exercise and cerebral blood flow, which may affect performance.

Concluding remarks

In conclusion, the lung is an elegant gatekeeper between environmental hypoxia and physical performance at high altitude. Because of the necessity of moving large quantities of air during exercise at altitude, the success of this task requires intact and functional lung mechanics, which are driven by central respiratory drive. An impairment of flow and a mechanical limitation may both be encountered, especially at extreme altitude. This process is facilitated by ongoing ventilatory acclimation, which is secondary to progressively increasing carotid body sensitivity to hypoxia. In spite of impressive lung mechanics and air flow, total body function is further impaired by arterial oxygen desaturation with increasing exercise and altitude, which is secondary both to the ventilation/perfusion heterogeneity and to the diffusion limitation of oxygen from the air to the blood. Further limitation is encountered from an extreme sense of dyspnea as well as depression of central nervous system output resulting from brain hypoxia.

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