


TOPICAL REVIEW

A revision of maximal oxygen consumption and exercise capacity at altitude 70 years after the first climb of Mount Everest

Guido Ferretti¹ and Giacomo Strapazzon^{2,3} 

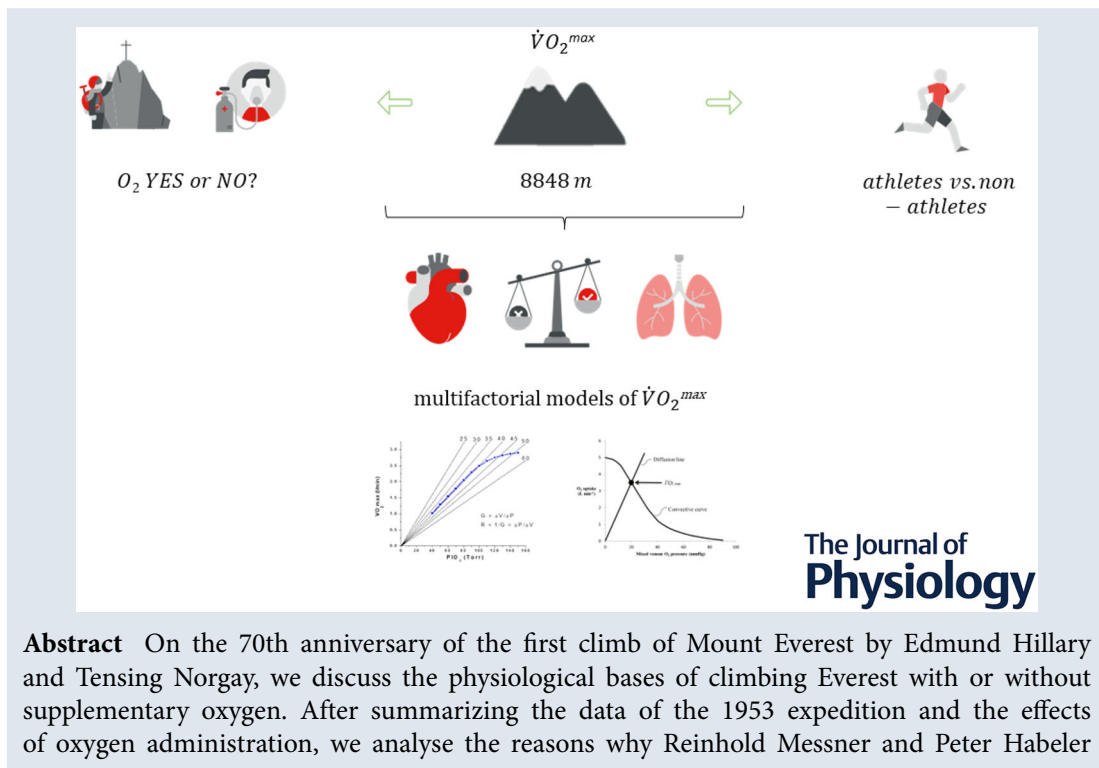
¹Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

²Institute of Mountain Emergency Medicine, Eurac Research, Bolzano, Italy

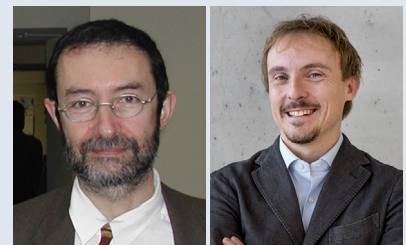
³SIMeM Italian Society of Mountain Medicine, Padova, Italy

Handling Editors: Laura Bennet & Philip Ainslie

The peer review history is available in the Supporting Information section of this article (<https://doi.org/10.1113/JP285606#support-information-section>).



Guido Ferretti was Professor of Physiology at the University of Geneva, Switzerland, and is now Professor of Physiology at the University of Brescia, Italy. He is active in exercise physiology and in the study of human adaptation to special environments. He is a co-author of the first multifactorial model of maximal oxygen consumption limitation and has investigated the reasons for the non-linear decrease of maximal oxygen consumption at altitude. **Giacomo Strapazzon** is the Head of the Institute of Mountain Emergency Medicine of Eurac Research, Bolzano, Italy and President of the Italian Society of Mountain Medicine. He is active in applied physiology and in the study of human adaptation to special environments, thus expanding the current knowledge on the human body's responses to hypoxia. He has worked in the development and capacity building of the terraXcube, a facility comprising hypobaric chambers capable of simulating special conditions in a safe, controlled environment.



succeeded without supplementary oxygen in 1978. The consequences of this climb for physiology are briefly discussed. An overall analysis of maximal oxygen consumption ($\dot{V}_{O_{2,max}}$) at altitude follows. In this section, we discuss the reasons for the non-linear fall of $\dot{V}_{O_{2,max}}$ at altitude, we support the statement that it is a mirror image of the oxygen equilibrium curve, and we propose an analogue of Hill's model of the oxygen equilibrium curve to analyse the $\dot{V}_{O_{2,max}}$ fall. In the following section, we discuss the role of the ventilatory and pulmonary resistances to oxygen flow in limiting $\dot{V}_{O_{2,max}}$, which becomes progressively greater while moving toward higher altitudes. On top of Everest, these resistances provide most of the $\dot{V}_{O_{2,max}}$ limitation, and the oxygen equilibrium curve and the respiratory system provide linear responses. This phenomenon is more accentuated in athletes with elevated $\dot{V}_{O_{2,max}}$, due to exercise-induced arterial hypoxaemia. The large differences in $\dot{V}_{O_{2,max}}$ that we observe at sea level disappear at altitude. There is no need for a very high $\dot{V}_{O_{2,max}}$ at sea level to climb the highest peaks on Earth.

(Received 7 September 2023; accepted after revision 3 January 2024; first published online 2 February 2024)

Corresponding author G. Strapazzon: Institute of Mountain Emergency Medicine, Eurac Research, Via Ipazia 2, 39100 Bolzano, Italy. Email: giacomo.strapazzon@eurac.edu.

Abstract figure legend Maximal oxygen consumption ($\dot{V}_{O_{2,max}}$) shows a non-linear fall with altitude that is a mirror image of the oxygen equilibrium curve. Di Prampero and Ferretti were the first to associate the non-linear behaviour of the respiratory system to the oxygen equilibrium curve. On the other hand, Wagner constructed his convective curve accounting for the effects of the oxygen equilibrium curve. The decrease is more accentuated in athletic subjects with elevated $\dot{V}_{O_{2,max}}$ compared to those who are non-athletic, so that the large differences in $\dot{V}_{O_{2,max}}$ that are observed at sea level disappear at altitude. Such consequences are due to the effect of ventilatory and pulmonary resistances to oxygen flow in limiting $\dot{V}_{O_{2,max}}$, which becomes progressively greater while moving toward higher altitudes compared to that of the cardiovascular resistance. On top of Everest, the pulmonary resistances provide most of the $\dot{V}_{O_{2,max}}$ limitation and the respiratory system provides linear responses.

Introduction

In 2023, we celebrated the 70th anniversary of the first climb to the summit of Mount Everest by Edmund Hillary from New Zealand (1919–2008) and Tensing Norgay (1914–1986), a Sherpa from the Khumbu Valley, Nepal, who conquered the mountain from the southern side on 29 May 1953. They were part of the British expedition to Everest organized by Sir John Hunt (1910–1998) (Hunt, 1953). Reaching the summit of Mount Everest and of the highest peaks of the Himalayas was perhaps the last pioneering exploration on Earth.

In 1953, it was an assumption to most physiologists that the summit of Mount Everest was unreachable without supplementary oxygen. The participation of Griffith Pugh (1909–1994) in the expedition as physician and physiologist led to the generation of pioneering data on respiration and exercise physiology at extreme altitude (Pugh, 1957, 1958; Stenbridge et al., 2022). Pugh was so convinced of the need for oxygen to conquer the summit that he took oxygen cylinders on the expedition despite the weight of the apparatus. His conviction remained deeply rooted in the physiological community for a further 25 years, until Reinhold Messner from the Dolomites, Italy and Peter Habeler from Austria on 8 May 1978 reached the summit without supplementary oxygen.

In this article, we discuss the physiological basis of climbing Everest with or without supplementary oxygen, summarizing the data of the 1953 expedition and analysing the reasons that led Messner to try and succeed without supplementary oxygen in 1978. We then analyse and discuss maximal oxygen consumption ($\dot{V}_{O_{2,max}}$) at altitude, highlighting the role of a non-linear oxygen equilibrium curve (OEC). In this context, $\dot{V}_{O_{2,max}}$ is defined as the maximal flow of oxygen from ambient air to mitochondria across the entire respiratory system. We finally discuss the role of the ventilatory and pulmonary resistances to oxygen flow (R_V and R_L , respectively) in limiting $\dot{V}_{O_{2,max}}$ at altitude.

Climbing Everest with supplementary oxygen

In 1953, the need of using supplementary oxygen in the final trial was outside discussion. Only the flow of oxygen to be used was under Pugh's scrutiny before departure. Physiologists expected a barometric pressure (P_B) on the summit lower than 250 mmHg (Pugh, 1952). The values determined during the 1953 expedition at various altitudes (Pugh, 1957) were in line with the predictions of Zuntz et al. (1906) and with the values obtained by Greene in 1933 (Greene, 1934). Physiologists predicted a $\dot{V}_{O_{2,max}}$ on the summit of about 0.3 litres min^{-1} ,

equivalent to the resting metabolic rate, by extrapolation to 8800 m of the reported relationships between $\dot{V}_{O_2\max}$ and altitude (Christensen, 1937; Margaria, 1929). Further data obtained by Paolo Cerretelli during Monzino's expedition to Kanjut-Sar and by Pugh himself during the 1960–1961 expeditions to the Himalayas confirmed and reinforced those predictions (Cerretelli & Margaria, 1961; Pugh et al., 1964).

The $\dot{V}_{O_2\max}$ of some climbers of the 1953 expedition, including Hillary, was measured during treadmill running at Oxford before departure. The mean value of $50.7 \pm 1.8 \text{ ml min}^{-1} \text{ kg}^{-1}$ was not as high as could be imagined. Hillary underwent two tests, yielding 48.9 and $50.9 \text{ ml min}^{-1} \text{ kg}^{-1}$. At 4000 m, during uphill walking, Hillary's $\dot{V}_{O_2\max}$ was $43.6 \text{ ml min}^{-1} \text{ kg}^{-1}$ and Norgay's was $41.4 \text{ ml min}^{-1} \text{ kg}^{-1}$ (Pugh, 1958). For Hillary, this value corresponded to 85.7% of his higher value at Oxford. It falls toward the upper limit of the classical $\dot{V}_{O_2\max}$ versus altitude curve (Cerretelli, 1980; Ferretti, 2014; Ferretti & Miserocchi, 2023). Such a value was sustained by a very strong ventilatory response to hypoxia (Pugh, 1957). The $\dot{V}_{O_2\max}$ during step exercise at altitudes between 6250 and 6500 m was 27.9 and $17.9 \text{ ml min}^{-1} \text{ kg}^{-1}$, respectively, for Norgay and Hillary (Pugh, 1958). The latter value corresponded to 37.1% of the higher $\dot{V}_{O_2\max}$ measured on him at Oxford and falls in the lower range of the classical $\dot{V}_{O_2\max}$ versus altitude curve. Extrapolation of this trend to the summit reinforced Pugh's conviction of the need for supplementary oxygen.

The breathing apparatus (Fig. 1) that the climbers carried to the summit in 1953 was an open-circuit system consisting of three oxygen cylinders mounted on a light tubular frame (Pugh, 1954). Overall, the apparatus weighed around 18 kg and was able to provide up to 2400 litres of O_2 . The rate of oxygen delivery could be varied between 2 and $5 \text{ litres min}^{-1}$, and this represented a technological improvement compared to previous systems. The apparatus used by the 1952 Swiss expedition provided a fixed rate of oxygen delivery at $2 \text{ litres min}^{-1}$. According to Pugh, this oxygen flow was too low and might have been one of the main causes of the failure of their spring attempt. Pugh participated in Eric Shipton's 1952 expedition to Cho Oyu, which was propaedeutic to an Everest attempt the following year (Shipton, 1952). During that expedition, Pugh tested the oxygen breathing apparatus and confirmed that a $4 \text{ litres min}^{-1}$ rate was necessary to obtain sufficient physiological benefit to attempt the climb to Mount Everest (Pugh, 1952, 1954; Stembridge et al., 2022; Ward, 2003).

Pugh was right in assuming an advantage by using the breathing apparatus under his conditions. The body mass of Hillary and Norgay in 1953 was 75 and 65 kg, respectively (Pugh, 1958). The breathing apparatus represented an extra-load corresponding to 24% and 28% of their body mass, respectively. The climbers had to walk

on a slope constantly steeper than 25% in the final climb to the summit. This implied that the rise of the body centre of mass was the sole contributor to the metabolic energy cost above resting during the final ascent (Margaria, 1938; Minetti et al., 2002). The additional load of the breathing apparatus led to a proportional increase in energy cost. The pulmonary ventilation, measured on other climbers while walking at their natural speed without breathing apparatus at 6100 m, was on average $1.28 \text{ litres min}^{-1} \text{ kg}^{-1}$, which roughly means an overall expired ventilation of $96 \text{ litres min}^{-1}$ for Hillary and $83 \text{ litres min}^{-1}$ for Norgay.

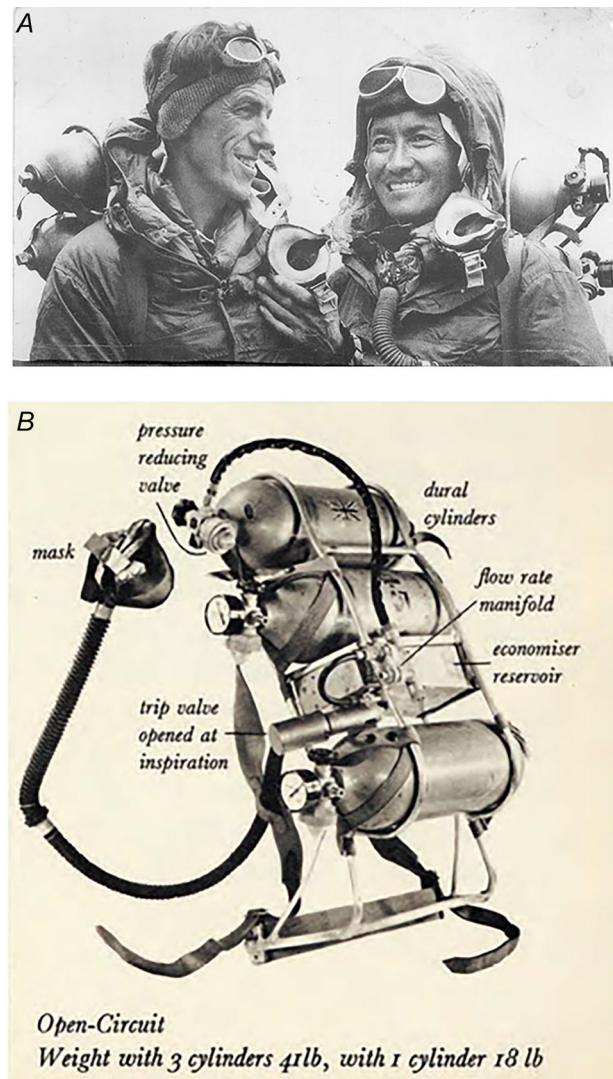


Figure 1. The oxygen apparatus used on the 1953 expedition A, a picture of Sir Edmund Hillary and Tensing Norgay, carrying the oxygen breathing apparatus that they would have used to attain the summit of Mount Everest on 29 May 1953. From Wikimedia Commons, courtesy of Tensing Norgay. B, the open-circuit oxygen breathing apparatus. From *Journal of Physiology* Cotes (1954).

Let us assume that these values apply also in the final 100 m of the climb. This is a somewhat arbitrary yet reasonable assumption, as long as two factors (the added load and the higher altitude) lead to an increased ventilation, whereas another two factors (the added oxygen and the slower walking speed) lead to a decrease of it. By making this assumption, and by assuming a P_B of 253 mmHg with an air oxygen pressure of 43 mmHg (West, Lahiri et al., 1983), we can try to estimate the inspired oxygen partial pressure ($P_{I_{O_2}}$) of Hillary and Norgay near the summit. Norgay inspired 79 litres of air and 4 litres of oxygen from the apparatus, in 1 min. Thus, he inhaled a volume of oxygen (\dot{V}_{O_2} , in litres BTPS) corresponding to:

$$\dot{V}_{O_2} = 79 \frac{43}{253} + 4 = 17.43 \quad (1)$$

This means that, in each 83 litres of the overall inhaled gas mixture, 17.43 litres consisted of oxygen, whence a mean inspired oxygen fraction ($F_{I_{O_2}}$) in wet air of $17.43/83 = 0.21$, and a mean inspired oxygen pressure of $253 \times 0.21 = 53.1$ mmHg on the summit, instead of 43 mmHg. The same computation carried out on Hillary's data yielded $\dot{V}_{O_2} = 19.64$ litres, $F_{I_{O_2}} = 0.205$ and $P_{I_{O_2}} = 51.9$ mmHg. When breathing air, such $P_{I_{O_2}}$ values are observed when P_B is about 300 mmHg, which is the prevailing value at around 7200 m, according to the ICAO standard atmosphere, or 7700 m according to the measurements made on Everest in 1953 and 1981 (Pugh, 1957; West, Lahiri et al., 1983). At an altitude of 7700 m, a light exercise like walking uphill at optimal speed is certainly feasible without the aid of supplementary oxygen. In fact, this is the most pessimistic calculation we could do, because it does not account for the frequent pauses that the climbers made on their way, during which ventilation was reduced and $P_{I_{O_2}}$ was increased. In sum, Pugh made Hillary and Norgay climb to the summit of Mount Everest in safe respiratory conditions. He balanced the negative effects of the extra load during uphill walking with the positive effects of supplementary oxygen, enhanced by the slow speed of the ascent and by the frequent pauses.

Climbing Everest without supplementary oxygen

Alexander Kellas (1868–1921, Fig. 2), a Scottish chemist, predicted the possibility of reaching the summit of Mount Everest without supplementary oxygen before World War I. He was Lecturer in Chemistry at Middlesex Hospital, London, from 1897 to 1919, but he is mostly renowned for his remarkable contributions to our understanding of the geography of the Karakorum and the Himalayas area (West, 1987). Before World War I, he participated in six exploratory expeditions to Karakorum and the Himalayas.

He travelled in Nepal and Sikkim and approached Everest from the east. In 1916, he made a communication to the Royal Geographical Society entitled 'A consideration of the possibility of ascending the loftier Himalaya', published in the *Geographical Journal* (Kellas, 1917). His analysis was further developed in an unpublished report, which John West found in the Alpine Club archives in London and published in 2001 (Kellas, 2001).

In his reports, Kellas, who was a friend of John Scott Haldane, one of the most eminent respiratory physiologists of Kellas's times, showed a remarkable acquaintance with physiology. He stated that hyperventilation due to hypoxia decreases alveolar CO_2 partial pressure (P_{ACO_2}) and increases alveolar oxygen partial pressure (P_{AO_2}). Then he stated that a low P_{ACO_2} causes a left shift of the OEC at extreme altitude, though corrected by a decrease of the alkaline reserve of blood. He estimated, using an analogous of the alveolar air equation (FitzGerald, 1913), and assuming a P_B of 267 mmHg on the summit, a P_{AO_2} of 23.6 mmHg and an arterial O_2 partial pressure (P_{aO_2}) of 18.6 mmHg. He also estimated an arterial oxygen saturation (S_{aO_2}) of 0.43. He discussed also the effects of altitude polycythaemia on oxygen transport. He inferred a \dot{V}_{O_2max} on the summit of about 1 litre min^{-1} , amazingly close to that measured on Chris Pizzo during the American Medical Research Expedition to Everest (AMREE; West, Boyer et al., 1983, see below). He concluded that 'Mt Everest can be ascended by a man of excellent physical and mental constitution in



Figure 2. Portrait of Alexander Mitchell Kellas

This picture accompanied his obituary in *The Alpine Journal*, the journal of the Alpine Club (image in the public domain).

first-rate training, without adventitious aids, if the physical difficulties of the mountain are not too great.' However, he suggested the use of oxygen on mountains that are technically difficult to climb.

Kellas and his work were overlooked and the physiological community remained unaware of him for a long time. Nevertheless, George Mallory (1886–1924), one of the greatest climbers of Kellas's times, who was obsessed by the dream of climbing Mount Everest, and who was with Kellas in the preparatory 1921 expedition, trusted him. Kellas died on that expedition. Mallory tried to reach the summit in 1924 following Kellas's principles. He died on the mountain and his body was not recovered. No proof exists for whether he reached the summit or not. The world of Physiology became convinced that reaching the summit of Mount Everest without supplementary oxygen was impossible. Nobody tried Mallory's way again before Messner and Habeler's successful attempt. In 1953, Sir John Hunt placed the final camp at the South Col, higher than suggested by Kellas. He organized logistics in order to have the oxygen breathing apparatus there. All repetitions of the Everest climb before 1978 made use of oxygen.

Then Messner and Habeler revolutionized Himalayan climbing and altitude physiology at once. We do not know whether they were aware of Kellas's conclusion, yet they might have been. Anecdotes tell that Messner's trusted doctor, Oswald Oelz from Bern, Switzerland, was convinced that it was possible to reach the summit of Mount Everest without supplementary oxygen. Messner demonstrated, on 8 May 1978, some 60 years after, that Kellas was right.

Physiological characteristics of extreme climbers

The climb of Messner and Habeler had essentially three consequences in the microcosm of altitude physiology. The first and more direct consequence was the study of the functional characteristics of extreme climbers, which Oelz promoted and Messner and Habeler participated in (Oelz et al., 1986). Their achievement so surprised the investigators that they expected extreme climbers to have extraordinary physiological characteristics during exercise, like elite endurance athletes. This was not the case. Figure 3 reports the climbers' $\dot{V}_{O_{2max}}$ as a function of age and compares it with that reported for athletic and non-athletic subjects. Although higher than in non-athletic subjects of equivalent age, $\dot{V}_{O_{2max}}$ was lower by far in climbers than in top-level endurance athletes. The climbers' $\dot{V}_{O_{2max}}$ corresponded approximately to that of non-athletic well-trained subjects. The same was the case for muscle fibre structure. Morphometric analysis showed small muscle fibres with low mitochondrial density. An unchanged capillary volume led to an increase in muscle capillary density, highlighting facilitation of peripheral oxygen diffusion. The maximal anaerobic power was

equal to that of sedentary controls. All subjects hyper-ventilated in hypoxia, but climbers did not show a stronger ventilatory response to hypoxia than sedentary controls.

The most striking feature of the Discussion in Oelz et al. (1986) is the astonishment of the authors. The conclusion was: 'The main features of a successful elite altitude climber are, besides an optimal functional balance and an unusual skill, strong motivation and exceptional drive. Reinhold Messner, the first mountaineer to overcome the barrier of 8500 m without supplemental oxygen, really typified these climbers. He was characterized by rather normal physiological features but by the obsessive need to be the first and the best, by 'fair means' as he states it, i.e. without the aid of oxygen in any phase of the ascent.' It was a bizarre conclusion for a scientific paper, but a sincere witness to the authors' inability to explain such unexpected climbing and scientific results.

The paper by Oelz et al. (1986) came out just too early. The monofactorial vision of $\dot{V}_{O_{2max}}$ limitation still predominated. The first version of a multifactorial model, based on the oxygen conductance equation, had appeared just a few months before (di Prampero, 1985). Pietro Enrico di Prampero realised the non-linear response of the respiratory system at maximal exercise and stated clearly that the lungs do not limit $\dot{V}_{O_{2max}}$ in normoxic exercise. Nonetheless, the physiological consequences of non-linearity were yet to be focused on. The concept of exercise-induced arterial hypoxaemia had just come on the scene again (Dempsey et al., 1984), after a long oblivion (Harrop, 1919), but its consequences were still largely not understood.

Ten years after, Ferretti & di Prampero (1995) expanded Prampero's multifactorial model to encompass hypoxia. They recalculated the fractional limitation of $\dot{V}_{O_{2max}}$

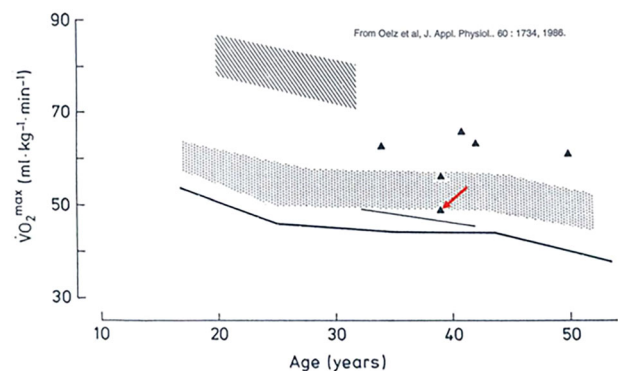


Figure 3. Maximal oxygen consumption ($\dot{V}_{O_{2max}}$) as a function of age

Triangles: data on elite climbers; dotted area: leisure marathon runners; thick line: sedentary controls; thin line, professional alpine guides; hatched area, elite marathon runners. The red arrow indicates Messner's $\dot{V}_{O_{2max}}$. Modified from *American Physiological Society* Oelz et al. (1986).

at various altitudes. They acknowledged the system's linearity at extreme altitude and suggested substantial pulmonary limitation to oxygen flow at maximal exercise (see below). Shortly afterward, Ferretti et al. (1997) demonstrated that athletes with high $\dot{V}_{O_{2max}}$ at sea level undergo a larger $\dot{V}_{O_{2max}}$ fall in hypoxia than non-athletic subjects, who have a low $\dot{V}_{O_{2max}}$ at sea level. Therefore, at extreme altitude, differences in $\dot{V}_{O_{2max}}$, which may be quite large at sea level, tend to disappear: there is no need of elevated $\dot{V}_{O_{2max}}$ values at sea level to successfully climb the tallest peaks on Earth! The relatively low $\dot{V}_{O_{2max}}$ values of Hillary and Messner at sea level were not bizarre.

An interesting feature of Messner's study (Oelz et al., 1986) concerns the data on muscle biopsies, showing elevated capillary density, higher than that of trained Caucasians (Hoppeler et al., 1985), and a relatively low muscle mitochondrial density, definitely lower than that of trained Caucasians. These data seem to suggest that the peripheral resistance to oxygen flow in the investigated extreme climbers may be slightly increased, if at all. Yet little inference can be drawn concerning $\dot{V}_{O_{2max}}$ limitation. A further study comparing muscle biopsies of extreme climbers obtained before departure to and upon return from an expedition to Lhotse is more informative (Hoppeler et al., 1990). The study showed the effects of altitude and climbing on muscle morphological characteristics; there was an 11.4% increase in muscle capillary density and an 18.6% decrease in muscle mitochondrial density after the expedition, suggesting that the peripheral resistance to oxygen flow might have been higher upon return than before departure.

AMREE and operation Everest II

The second, more indirect, consequence of 8 May 1978 was the AMREE expedition, organised by John West. West and colleagues aimed to demonstrate what made it possible to reach the summit of Mount Everest in a field study. Chris Pizzo, physician and climber, reached the summit and performed alveolar air sampling there (Fig. 4). He obtained a P_{ACO_2} of 7.5 mmHg, demonstrating the extremely high degree of hyperventilation on the summit, well beyond Pugh's expectations. P_{AO_2} was 34 mmHg. The authors attempted an estimate of arterial blood composition, assuming $P_{ACO_2} = P_{aCO_2}$: the resulting P_{aO_2} was 28 mmHg (West, Hackett et al., 1983). These estimates are coherent with the measured arterial blood gas data reported 25 years later during the Caudwell Xtreme Everest expedition (Grocott et al., 2007) at an altitude of 8400 m (Grocott et al., 2009). P_B on that day (24 October 1981) was 253 mmHg, much higher than predicted from the ICAO tables, whence the already mentioned P_{IO_2} of 43 mmHg (West, Lahiri et al., 1983). Upon return to the highest camp, Pizzo underwent,

with others, a $\dot{V}_{O_{2max}}$ test while breathing a gas mixture containing a P_{IO_2} of 43 mmHg. The famous mean $\dot{V}_{O_{2max}}$ value of 1.07 litres min^{-1} was obtained on that occasion (West, Boyer et al., 1983). Despite the increase of 2,3-diphosphoglycerate, the strong respiratory alkalosis shifted the OEC to the left (Winslow et al., 1984). This improved alveolar ventilation, prevented an excessive fall of P_{AO_2} and kept $\dot{V}_{O_{2max}}$ up. Yet the estimated P_{AO_2} remained so low that it lays on the steepest part of the OEC. At the top of Mount Everest, this implied a diffusion limitation of alveolar–capillary oxygen transfer, an important pulmonary limitation of $\dot{V}_{O_{2max}}$, and a linear behaviour of the respiratory system during maximal exercise (Ferretti, 2014).

The third scientific consequence of 8 May 1978 was a huge, comprehensive international study in a hypobaric chamber, called Operation Everest II (Houston et al., 1987). The overall aim of the project was to simulate the altitude patterns of a climb to Everest in a hypobaric chamber and to perform as many measurements as possible at various simulated altitudes concerning the response of the respiratory system to hypoxia exposure at rest and exercise during altitude acclimatisation. The respiratory system is defined here as the entire pathway for respiratory gases from ambient air to mitochondria. Thus, it includes lungs, heart, blood vessels and muscles. Clinical, functional, chemical and structural determinations were carried out. An overall summary of the results was published afterwards (Wagner, 2010). There is some interest in the present context in the demonstration that the subjects were not fully acclimatized when they reached an altitude equivalent to that of Everest (West, 1988). Notwithstanding this weakness, Operation Everest II remains an unequalled example of powerful cooperation among researchers of different cultural extraction, but it did not give the answer to all the open questions as well.



Figure 4. Chris Pizzo taking alveolar gas samples from himself on top of Mount Everest
From West & Lahiri (1984).

On maximal oxygen consumption limitation

Pugh's decision to use oxygen tanks to reach the summit relied on the postulated $\dot{V}_{O_2\max}$ on top of Mount Everest being too low to allow performance of exercise. Messner climbed without supplementary oxygen because Oelz and he were convinced that Pugh's postulate was erroneous. In any case, it was a matter of $\dot{V}_{O_2\max}$. In the next paragraphs, we introduce the concept of $\dot{V}_{O_2\max}$ limitation, we discuss how $\dot{V}_{O_2\max}$ diminishes in hypoxia and we analyse $\dot{V}_{O_2\max}$ limitation in hypoxia.

Initially and for a long time, physiologists searched for a single factor limiting $\dot{V}_{O_2\max}$. This factor was cardiovascular oxygen transport for most people, although some claimed that limitation was peripheral (muscular), especially during exercise with small muscle groups (Ferretti, 2014). The two parties fought fiercely for decades without a synthesis. A new vision emerged at the beginning of the 1980s, when Taylor & Weibel (1981) took up the oxygen cascade theory as a tool for describing oxygen transfer from ambient air to the mitochondria at maximal exercise on a whole-body level. Their idea started the process that led to a revolutionary approach to the subject of $\dot{V}_{O_2\max}$ limitation, whereby the focus was moved from the search for a single limiting factor to the simultaneous analysis of multiple factors that together limit $\dot{V}_{O_2\max}$, along the oxygen cascade. The way to a multifactorial model of $\dot{V}_{O_2\max}$ limitation was open. A detailed analysis of these models can be found in the original publications (di Prampero, 1985; di Prampero & Ferretti, 1990; Wagner, 1993, 1996a). di Prampero and Wagner proposed two apparently competing interpretations of the oxygen cascade theory. Differences in analysis depended on whether the cardiovascular oxygen transport step was considered merely convective (Wagner) or not (di Prampero). In the former theory, oxygen flows from lungs to muscle capillaries thanks to the convective movement of blood: the mean capillary oxygen partial pressure is the driving force allowing oxygen to flow inside the muscle fibres. Thus, Wagner (1993) constructed his system by combining the mass conservation equation for blood (Fick's principle) and the diffusion-perfusion interaction equations (Piiper & Scheid, 1981; Piiper et al., 1984). Development of this system led to three equations allowing a solution for P_{AO_2} , P_{aO_2} and the mixed venous oxygen partial pressure ($P_{\bar{V}O_2}$). Equality of these equations is compatible with only one $\dot{V}_{O_2\max}$ value (Wagner, 1993). In the pulmonary capillaries, the combination of a convective component with a diffusive component sets the maximal flow of oxygen in arterial blood. In the peripheral capillaries, the combination of a convective component with a diffusive component sets $\dot{V}_{O_2\max}$. The convective component of Wagner's model, based on Fick's equation, implies a non-linear negative relationship between $\dot{V}_{O_2\max}$ and $P_{\bar{V}O_2}$ (convective curve), the algebraic

expression of which depends on the solution that we give to the OEC. Concerning the diffusive component, it is described by a linear equation, showing that $\dot{V}_{O_2\max}$ is directly proportional to $P_{\bar{V}O_2}$ through a constant that includes tissue oxygen conductance. The value of this constant was determined experimentally (Roca et al., 1989). A graphical representation of the convective curve and of the diffusion line is shown in Fig. 5. In the latter theory, the difference between P_{aO_2} and $P_{\bar{V}O_2}$ is the driving force sustaining oxygen flow from lungs to muscle fibres through the circulating blood, thus making blood circulation tantamount to any in-series resistance step in a hydraulic system. On this premise, the cardiovascular step of the oxygen conductance equation in di Prampero's model is described by:

$$\dot{V}_{O_2\max} = G_Q (P_{aO_2} - P_{\bar{V}O_2}) = \frac{(P_{aO_2} - P_{\bar{V}O_2})}{R_Q} \quad (2)$$

where G_Q is the cardiovascular conductance and R_Q the corresponding resistance.

On maximal oxygen consumption in hypoxia

Climbing Everest without supplementary oxygen is largely a consequence of how $\dot{V}_{O_2\max}$ decreases at altitude. The fundamental question is whether $\dot{V}_{O_2\max}$ at extreme altitude is high enough to allow performance of light

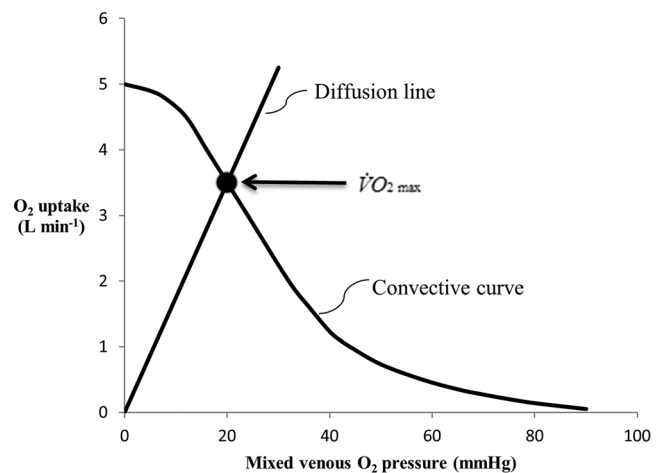


Figure 5. Graphical representation of Wagner's model of maximal oxygen consumption limitation (Wagner, 1996a)

Oxygen uptake (\dot{V}_{O_2}) is plotted as a function of mixed venous oxygen pressure ($P_{\bar{V}O_2}$). The curve with negative slope is Wagner's convective curve. The straight line with positive slope is Wagner's diffusion line, whose slope is Wagner's constant K_w . The convective curve intercepts the y-axis at a value equal to arterial oxygen flow, which is the case when $K_w = \infty$. It intercepts the x-axis when it is equal to arterial oxygen pressure, which is the case when $K_w = 0$. The value is found on the crossing of the convective curve with the diffusion line (black circle). From *Springer-Nature* Ferretti (2014).

exercise like walking uphill at slow speed. If the answer is no, supplementary oxygen is needed and the amount of added oxygen must be enough to override the negative effects of the extra load represented by a breathing apparatus. Kellas answered yes, Pugh answered no. Nobody dared to measure $\dot{V}_{O_2\max}$ at Everest altitude before 8 May 1978, not even in normobaric acute hypoxia. Predictions were made only by extrapolating empirical curves relating $\dot{V}_{O_2\max}$ to altitude (Åstrand, 1954; Christensen, 1937; Margaria, 1929; Pugh, 1958).

Cerretelli & Margaria (1961) reported that the $\dot{V}_{O_2\max}$ of acclimatized climbers at 5000 m corresponded to 44% of that measured for them at sea level before departure. What they called the energetic efficiency of respiration, defined as the $P_{IO_2} - P_{AO_2}$ difference, was 55% of that at sea level. Thus, the reported fall of $\dot{V}_{O_2\max}$ was greater than that of the $P_{IO_2} - P_{AO_2}$ difference. To their mind, this was a demonstration that $\dot{V}_{O_2\max}$ at altitude decreases more than the capacity of the respiratory system to deliver oxygen to the active muscle mass. They considered it a further strong argument against the possibility of climbing Everest without supplementary oxygen. To our mind, this was an invitation to investigate fibre structure, oxygen diffusion capacity and fibre metabolic capacity in subjects acclimatized to altitude, which, however, remained unheard of until Cerretelli's (1976) explicit postulate of a peripheral limitation of $\dot{V}_{O_2\max}$ and, thereafter, Messner and Habeler's climb. The baton was then taken up by Hans Hoppeler from Bern. The results of the ensuing studies, which drastically changed our vision of muscle structure at altitude, are subsumed in a dedicated chapter of the *Handbook of Physiology* (Cerretelli & Hoppeler, 1996).

$\dot{V}_{O_2\max}$ decreases in hypoxia because of the decrease of P_B , and thus of P_{IO_2} . However, there is no proportionality: in non-athletic subjects, the $\dot{V}_{O_2\max}$ fall is small at altitudes below 3000 m, and far smaller than one would predict from the curves of barometric pressure decrease at altitude (Pugh, 1957; West, Lahiri et al., 1983), and becomes progressively larger as we proceed toward higher altitudes. Shephard (1969) and di Prampero (1985) were the first to highlight the non-linear behaviour of the respiratory system. di Prampero & Ferretti (1990) proposed an interpretation of this non-linear behaviour, focusing on the sigmoidal shape of the OEC. In fact, the conductance term of Equation 2 is equal to:

$$G_Q = \dot{Q}\beta_b \quad (3)$$

where \dot{Q} is cardiac output, and β_b is the oxygen transfer coefficient for blood (Ferretti, 2014). β_b is given by:

$$\beta_b = \frac{C_{aO_2} - C_{vO_2}}{P_{aO_2} - P_{vO_2}} \quad (4)$$

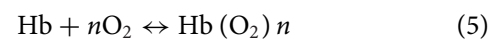
where the numerator is the oxygen concentration difference and the denominator the oxygen partial

pressure difference between arterial and mixed venous blood. Thus, β_b is the average slope of the OEC and its value depends on the encompassed portion of the OEC. If we operate on the flat part of the OEC, a decrease in P_{aO_2} at altitude does not lead to a decrease in C_{aO_2} . This carries along an increase in β_b , and thus in G_Q , with consequent reduction of R_Q . The total resistance to oxygen flow (R_T) falls, keeping $\dot{V}_{O_2\max}$ up.

The curve describing the $\dot{V}_{O_2\max}$ fall in hypoxia is reported in Fig. 6. Figure 6A shows its classic representation (Cerretelli, 1980). Figure 6B is a variation wherein P_{IO_2} instead of altitude appears on the x -axis, and $\dot{V}_{O_2\max}$ is expressed in absolute terms, rather than relative to its value at sea level (Ferretti, 2014). This variation allows construction of total conductance ($G_T = R_T^{-1}$) isopleths, highlighting that, as P_{IO_2} falls, the $\dot{V}_{O_2\max}$ curve moves toward isopleths of progressively higher G_T values (lower R_T values). At low P_{IO_2} , after having reached the steep segment of the OEC, not only P_{aO_2} but also C_{aO_2} starts decreasing. As these low P_{IO_2} values are reached, the $\dot{V}_{O_2\max}$ curve stabilizes on a linear segment, coinciding with a specific G_T isopleth.

Ferretti et al. (1997) demonstrated a linear relationship between $\dot{V}_{O_2\max}$ and S_{aO_2} . Their regression equation for non-athletic subjects – extreme climbers are non-athletic subjects – was $\dot{V}_{O_2\max} = 1.059S_{aO_2} - 0.091$. $\dot{V}_{O_2\max}$ was normalized with respect to the value obtained in hyperoxia ($F_{IO_2} = 0.3$, $P_{IO_2} = 220$ mmHg), in which $S_{aO_2} = 0.982 \pm 0.001$. The regression line was highly significant ($P < 0.0001$) and did not differ from the identity line. Thus, the function describing the $\dot{V}_{O_2\max}$ decrease at altitude is a mirror image of the OEC (Ferretti & Miserocchi, 2023; Ferretti et al., 1997).

The OEC has received numerous empirical polynomial solutions (Ferretti et al., 2022). None of them has sound physiological grounds and specific merits over the others, except Hill's model (Hill, 1910). Hill proposed that the shape of the OEC was a consequence of the equilibrium of the chemical reaction between haemoglobin and oxygen, described by:



where n is the stoichiometric ratio of the reaction. The equilibrium constant k of the reaction is then given by:

$$k = \frac{(HbO_2)^n}{(Hb^-)(O_2)^n} \quad (6)$$

Through a series of algebraic steps, Hill arrived at the equation:

$$\frac{S}{(1-S)} = \Sigma = \frac{(P_{O_2})^n}{P_k} \quad (7)$$

where S is oxygen saturation and P_k is a pressure constant. If we express Equation (7) in logarithmic terms, we have:

$$\log \Sigma = n \log P_{O_2} - \log P_k \quad (8)$$

It is noteworthy that when $S = 0.5$, $\Sigma = 1$ and $\log \Sigma = 0$. This implies that the constant corresponding to the x -axis intercept of the linear relationship between $\log \Sigma$ and $\log P_{O_2}$, which has a slope equal to n , is the logarithm of the prevailing P_{O_2} when $S = 0.5$ (the so called P_{50} of the OEC). Hill (1910) obtained $n = 2.8$ by linear regression. The correctness of this value was rejected after Perutz (1970) demonstrated $n = 4$. Notwithstanding this, the deep meaning of Hill's constant was not undermined: $n > 1$ indicates cooperativity, $n = 1$ absence of cooperativity. Hill found $n = 2.8$ because the experimental OEC deviates from the power model of Hill when $S < 0.2$. Severinghaus (1979) showed that Hill's model is a valid descriptor of the OEC in the S range between 0.98 and 0.20, encompassing the entire physiological range of P_{O_2} up to extreme altitude.

If indeed the $\dot{V}_{O_{2max}}$ decrease at altitude is a mirror image of the OEC, we can apply Hill's approach to

analyse the relationship between $\dot{V}_{O_{2max}}$ and P_{O_2} . Thus, Equation (8) can be rewritten as:

$$\frac{\dot{V}_{O_{2max}}}{(1 - \dot{V}_{O_{2max}})} = \Sigma = \frac{(P_{aO_2})^n}{P_k} \quad (9)$$

Expressing Equation 9 in logarithmic form, we obtain:

$$\log \frac{\dot{V}_{O_{2max}}}{(1 - \dot{V}_{O_{2max}})} = \log \Sigma = n \log P_{aO_2} - \log P_k \quad (10)$$

where $\dot{V}_{O_{2max}}$ is normalized for the value applying at $S_{aO_2} = 1.0$. Equation 10, for which we may predict $n = 2.8$ and a P_{50} between 26 and 30 mmHg, applies whatever the $\dot{V}_{O_{2max}}$ at sea level. To compute the parameters of Equation 10, we used the data of Ferretti et al. (1997) in acute hypoxia, providing $\dot{V}_{O_{2max}}$ and P_{aO_2} at various P_{IO_2} . Their relationship between $\dot{V}_{O_{2max}}$ and S_{aO_2} allows an estimate of the $\dot{V}_{O_{2max}}$ for $S_{aO_2} = 1.0$. The resulting relationship is shown in Fig. 7 (green circles, dashed line). The regression equation is:

$$\log \frac{\dot{V}_{O_{2max}}}{(1 - \dot{V}_{O_{2max}})} = \log \Sigma = 2.98 \log P_{aO_2} - 4.41 \quad (10)$$

Thus we have $n = 2.98$, which is very close to the value calculated by Hill, and $P_{50} = 10^{2.98} = 30.19$ mmHg. This

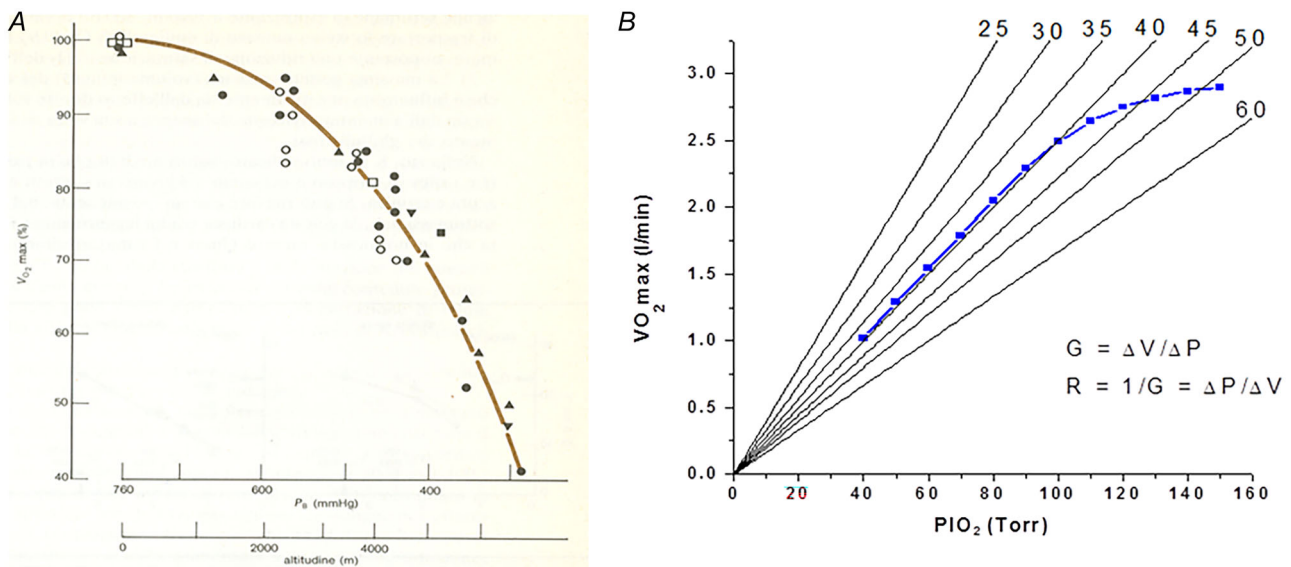


Figure 6. Changes of maximal oxygen consumption at altitude
 A, the classic curve describing how maximal oxygen consumption ($\dot{V}_{O_{2max}}$) falls at altitude (Cerretelli, 1980). $\dot{V}_{O_{2max}}$ is expressed relative to the value observed at sea level, set equal to 100%. Two x -axes are shown, one for barometric pressure (P_B), the other for altitude. Open and filled symbols refer to acute and chronic hypoxia, respectively. B, same curve as in A, calculated for a typical $\dot{V}_{O_{2max}}$ of a non-athletic subject at sea level (2.9 litres min^{-1} , Cerretelli and di Prampero, 1987). P_B is replaced by the inspired oxygen pressure (P_{IO_2}), and $\dot{V}_{O_{2max}}$ is shown in absolute values, not as a percentage of its value at sea level. The straight lines converging on the origin of the axes have a slope ($\Delta V/\Delta P$) equal to the overall oxygen conductance of the entire respiratory system. As we proceed toward higher altitude, the $\dot{V}_{O_{2max}}$ values move toward lines representing higher conductance values. This prevents $\dot{V}_{O_{2max}}$ from falling in proportion to P_{IO_2} . Numbers above isopleths indicate the corresponding resistance (R_T). From Springer-Nature Ferretti (2014).

value is the theoretical P_{aO_2} at which \dot{V}_{O_2max} is one-half of the value occurring at $S_{aO_2} = 1.0$ and is astonishingly similar to the P_{50} of the OEC in standard conditions (~ 27 mmHg). This is an amazing correspondence indeed, if we consider how many factors contribute to the \dot{V}_{O_2max} value, especially in hypoxia, where also the lungs become limiting.

We added to Fig. 7 also the values obtained on Hillary in 1953 (black circles; Pugh, 1958), and those obtained on Chris Pizzo up to the top of Everest during the AMREE in 1981 (red circles; West, Boyer et al., 1983). For the former, we have two \dot{V}_{O_2max} values and the P_B at which they were obtained, but we lack the corresponding P_{aO_2} . This was estimated using the empirical linear relationship between P_{aO_2} and P_{IO_2} derived from the data of Ferretti et al. (1997), which might have led to an underestimate of the P_{aO_2} incurred, because the stronger ventilatory response to hypoxia characterising acclimatized subject was not accounted for, since their data were obtained in acute normobaric hypoxia. This explains why the value at Oxford falls close to the line, whereas the value at 4000 m altitude on Everest was displaced upward with respect to

the line. Conversely, the data of Pizzo, for whom we know both \dot{V}_{O_2max} and P_{aO_2} , appear close to the regression lines at all altitudes. It is noteworthy that, in Fig. 7, the two points for Hillary and Pizzo at sea level almost coincide, although their absolute \dot{V}_{O_2max} at sea level differed markedly (3.57 and 4.63 litres min^{-1} , respectively).

Factors limiting maximal oxygen consumption in hypoxia

According to di Prampero & Ferretti (1990), the effects of moving along a non-linear OEC on β_b represent the main, if not the only, source of the non-linear response of the respiratory system in normoxia. Their reasoning can be summarized as follows. Assume that an acute manoeuvre (e.g. replacing nitrogen with helium in the inspired gas) induces a reduction of R_V only. This increases alveolar ventilation and elevates P_{AO_2} and P_{aO_2} . In spite of this, C_{aO_2} remains unchanged, because in normoxia we operate on the flat part of the OEC. Therefore, β_b and, because of Equation 3, G_Q are reduced, with a consequent increase in R_Q . No changes in R_V only are possible in normoxia

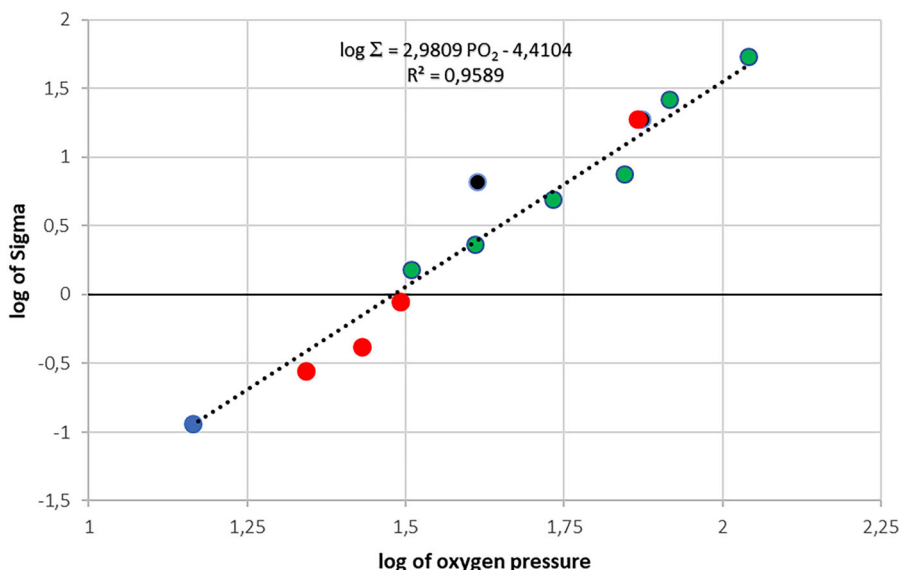


Figure 7. Linearization of the relationship describing the fall of maximal oxygen consumption (\dot{V}_{O_2max}) at altitude, on the assumption that this relationship is a mirror image of the oxygen equilibrium curve and thus can be analysed by means of an analogue of Hill's model (Hill, 1910)

The variable on the y-axis, $\log \Sigma$, is equal to $\log(\dot{V}_{O_2max}/1 - \dot{V}_{O_2max})$. The variable on the x-axis is the arterial oxygen pressure (P_{aO_2}). The line is a regression line calculated on the data reported by Ferretti et al. (1997) for non-athletic subjects in acute hypoxia (green circles on the plot). The \dot{V}_{O_2max} corresponding to an arterial oxygen saturation (S_{aO_2}) of 1 was computed from their relationship between \dot{V}_{O_2max} and S_{aO_2} . The regression equation was: $\log \Sigma = 2.9809P_{aO_2} - 4.4104$, $R = 0.979$. The blue circle at the bottom left end of the line indicates the condition when \dot{V}_{O_2max} becomes equal to the resting \dot{V}_{O_2} . Its coordinates are $\log \Sigma = -0.94$ and $\log P_{aO_2} = 1.164$, whence a minimum P_{aO_2} of 14.6 mmHg. The x-axis intercept is at $\log P_{aO_2} = 1.480$, whence a P_{aO_2} at $\log \Sigma = 0$, and thus $\Sigma = 1$, of 30.2 mmHg. The two black circles refer to Edmund Hillary on Everest in 1953, the \dot{V}_{O_2max} of whom at sea level and at 4000 m altitude were reported by Pugh (1958). Hillary's P_{aO_2} was estimated from the reported inspired oxygen pressure (P_{IO_2}), using the relationship between P_{aO_2} and P_{IO_2} computed after the data of Ferretti et al. (1997). The red circles refer to the data obtained on Chris Pizzo during the AMREE, for whom the measured \dot{V}_{O_2max} and the estimated P_{aO_2} was used (West, Boyer et al., 1983).

and the changes in both R_V and R_Q compensate each other. The acute induction of a change in R_V has no effects on $\dot{V}_{O_2\max}$, whence the conclusion that R_V does not limit $\dot{V}_{O_2\max}$ in normoxia. This line of reasoning applies also to R_L , even though we should remind that di Prampero & Ferretti (1990) defined R_L (G_L) as:

$$R_L = \frac{1}{G_L} = \frac{(P_{AO_2} - P_{aO_2})}{\dot{V}_{O_2\max}} \quad (11)$$

At altitude, as P_{IO_2} decreases, P_{aO_2} progressively moves towards the steeper part of the OEC. Therefore, (1) β_b becomes higher than in normoxia, and the more so the lower are P_{IO_2} and P_{aO_2} , (2) R_Q decreases in inverse proportion to G_Q , (3) the compensation of R_V changes by opposite inevitable variations in R_Q progressively weakens, to disappear when blood operates on the steep part of the OEC only; (4) the role R_V and R_L , nil at sea level, becomes progressively greater. At extreme altitude, the response of the respiratory system becomes linear and R_V and R_L play a major role in limiting $\dot{V}_{O_2\max}$, in addition to R_Q and R_p .

In the context of di Prampero's model, if this is the case, we can predict the fractional limitation of $\dot{V}_{O_2\max}$ by assuming that the respiratory system behaves as a linear hydraulic system of resistances in-series. On this premise, Ferretti & di Prampero (1995) analysed the evolution of the fractional limitation of $\dot{V}_{O_2\max}$ provided by each step along the respiratory system in acute normobaric hypoxia. Figure 8 summarizes the readjustments of F_Q , F_p , F_V and F_L as a function of P_{IO_2} . Whereas in normoxia most of $\dot{V}_{O_2\max}$ is provided by R_Q ($R_Q = 0.7$), when P_{IO_2} attains 90 mmHg, the fractional limitation of $\dot{V}_{O_2\max}$ is almost equally partitioned among F_Q , F_L and F_V (between 0.28 and 0.30 each), with F_p around 0.13.

The analysis by Ferretti & di Prampero (1995) generated some predictions that received experimental support. The stronger the fall of $\dot{V}_{O_2\max}$ in hypoxia, the higher the subject's $\dot{V}_{O_2\max}$ in normoxia (Ferretti et al., 1997; Gavin et al., 1998; Koistinen et al., 1995; Wehrin & Hallén, 2006), because of exercise-induced arterial hypoxaemia. Conversely, the smaller the fall of $\dot{V}_{O_2\max}$, the stronger the ventilatory response to hypoxia (Benoit et al., 1995; Gavin et al., 1998; Giesbrecht et al., 1991; Marconi et al., 2004; Ogawa et al., 2007). A reduction in airway resistance induced by replacing nitrogen with helium has no effects on $\dot{V}_{O_2\max}$ in normoxia ($F_V = 0$), but increases $\dot{V}_{O_2\max}$ in hypoxia ($F_V > 0$) (Esposito & Ferretti, 1997; Ogawa et al., 2010). Respiratory muscle training increases $\dot{V}_{O_2\max}$ in hypoxia, but not in normoxia (Downey et al., 2007; Esposito et al., 2010). It is interesting to note in this context that inspired gas density decreases at altitude due to Boyle's law. At extreme altitude, when blood oxygen transport takes place on the steep part of the OEC, this may also contribute to lower R_V , keeping $\dot{V}_{O_2\max}$ up. This

factor was usually neglected in all early reasoning about $\dot{V}_{O_2\max}$ in hypoxia.

The simulation by Ferretti & di Prampero (1995) cannot be translated as such into an analysis of $\dot{V}_{O_2\max}$ limitation in chronic hypobaric hypoxia. On top of Mount Everest, with respect to acute normobaric hypoxia at the same P_{IO_2} , (1) the increase in blood haemoglobin concentration slightly increases β_b , thereby reducing R_Q to some extent; (2) the extremely strong hyperventilation due to peripheral chemoreceptor stimulation strongly reduces R_V ; (3) the reduction of mitochondrial density is opposed by the increase in capillary density, so that R_p depends on the equilibrium between these variables and the ensuing degree of reciprocal compensation. Moreover, it is likely that Ferretti & di Prampero (1995) overestimated F_L , since they assumed no changes in R_L , whereas R_L probably decreases as we move toward the steep part of the OEC, because the component of R_L related to the effects of ventilation-perfusion heterogeneity on the alveolar-arterial O_2 gradient is minimized by the fact of operating on the steep part of the OEC. The fractional

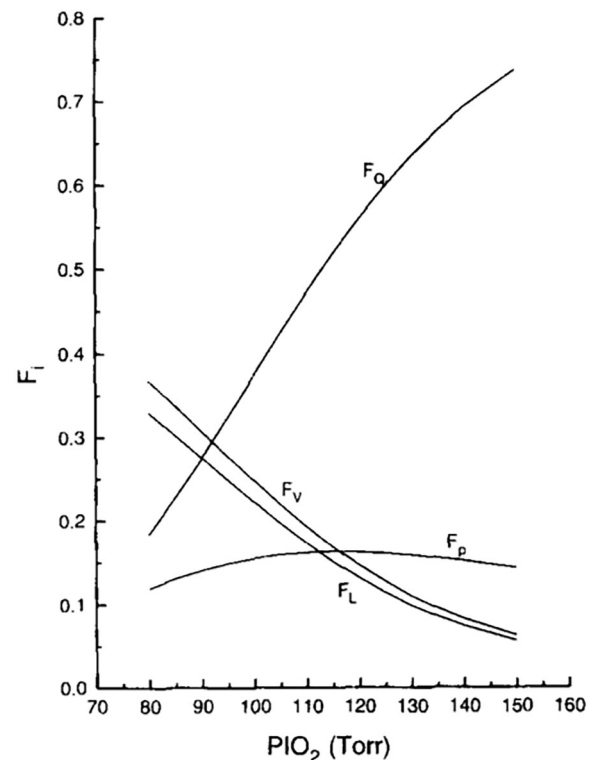


Figure 8. Fractional limitation of maximal oxygen consumption ($\dot{V}_{O_2\max}$) imposed by the *i*th resistance to oxygen flow (F_i) as a function of inspired oxygen pressure (P_{IO_2})

A 25% reduction of the ventilatory resistance (R_V) was assumed. Curves referring to the fractional limitation of $\dot{V}_{O_2\max}$ imposed by alveolar ventilation (F_V), pulmonary oxygen transfer (F_L) cardiovascular oxygen transport (F_Q), and peripheral oxygen transfer (F_p) are shown. From Elsevier Ferretti & di Prampero (1995).

Table 1. Maximal oxygen consumption limitation on top of Mount Everest

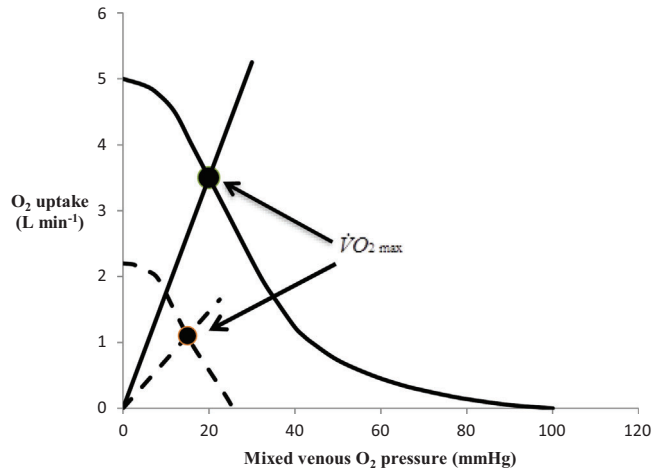
Characteristic variables							
P_{IO_2}	P_{AO_2}	P_{aO_2}	P_{VO_2}	P_{mO_2}	\dot{V}_{O_2max}	[Hb]	S_{aO_2}
mmHg	mmHg	mmHg	mmHg	mmHg	$l \text{ min}^{-1}$	$g \text{ l}^{-1}$	
43	36	25	15	0	1.07	188	0.54
Oxygen gradients (mmHg)							
$P_{IO_2} - P_{AO_2}$	$P_{AO_2} - P_{aO_2}$	$P_{aO_2} - P_{VO_2}$	$P_{VO_2} - P_{mO_2}$	$P_{IO_2} - P_{mO_2}$			
7	11	10	15	43			
Resistance to oxygen flow ($mmHg \text{ min}^{-1}$)							
R_V	R_L	R_Q	R_p	R_T			
6.54	10.28	9.35	14.02	40.19			
Fractional limitation of \dot{V}_{O_2max}							
F_V	F_L	F_Q	F_p				
0.16	0.26	0.23	0.35				

P_{IO_2} , oxygen partial pressure in inspired air; P_{AO_2} , oxygen partial pressure in alveolar air; P_{aO_2} , oxygen partial pressure in arterial blood; P_{VO_2} , oxygen partial pressure in mixed venous blood; P_{mO_2} , oxygen partial pressure in the mitochondria, after oxygen has been consumed; \dot{V}_{O_2max} , maximal oxygen consumption; [Hb], blood haemoglobin concentration; S_{aO_2} , arterial oxygen saturation at maximal exercise; R_V , R_L , R_Q , R_p and R_T are the ventilatory, pulmonary, cardiovascular, peripheral and total (sum of the preceding four resistances) resistance to oxygen flow, respectively. F_V , F_L , F_Q and F_p are the corresponding fractions of \dot{V}_{O_2max} limitation (di Prampero & Ferretti, 1990). Data are mean values from the American Medical Research Expedition to Everest (West, Boyer et al, 1983). Data in italic are estimates. To calculate P_{VO_2} , we assumed a cardiac output at maximal exercise of 15 litres min^{-1} and a mean P_{50} of capillary blood of 23 mmHg. The assumption of a linear behaviour of the respiratory system was made.

limitation of \dot{V}_{O_2max} on top of Mount Everest, which we estimated on the assumption of a linear behaviour of the respiratory system, is reported in Table 1.

In Wagner's model of \dot{V}_{O_2max} limitation (Wagner, 1993), hypoxia implies a displacement downward and leftward of the convective curve (Fig. 9). The curve covers only the steep part of the OEC, becomes practically linear and intercepts the x-axis at a low P_{VO_2} value. Using data from Operation Everest II, Wagner (1996b) demonstrated the linearity of the OEC in deep hypoxia. Similar conclusions can be drawn from data in acute hypoxia (Roca et al., 1989).

Thus, at extreme altitude, β_b becomes invariant and the oxygen conductance equation takes a linear solution. The

**Figure 9. Graphical representation of Wagner's model in hypoxia**

As in Fig. 5, oxygen uptake (\dot{V}_{O_2}) is plotted as a function of mixed venous oxygen pressure (P_{VO_2}). Continuous lines represent Wagner's convective curve and diffusion line. Dashed lines are the convective curve and the diffusion line in hypoxia. Concerning the former, it lacks the flattening part at high P_{VO_2} values, because we operate exclusively at the steep part of the oxygen equilibrium curve. The diffusion line in hypoxia shows the decrease in peripheral conductance to oxygen flow. In normoxia, arterial oxygen partial pressure was assumed equal to 100 mmHg, and P_{VO_2} was assumed equal to 20 mmHg. The data of Operation Everest II were used in hypoxia (Wagner, 2010). From *Springer-Nature* Ferretti (2014).

effective oxygen pressure gradient becomes equal to P_{IO_2} instead of P_{aO_2} , so that we can write:

$$F_Q = \frac{\dot{V}_{O_2max}}{\dot{Q}_{aO_2max}} \cdot \frac{P_{aO_2}}{P_{IO_2}} \quad (12)$$

where \dot{Q}_{aO_2max} is the oxygen flow in arterial blood (y-axis intercept of Wagner's convective curve). If we solve Equation (12) using the data of Operation Everest II, we would obtain $F_Q = 0.19$, very close to the theoretical value of 0.20 reported by Ferretti & di Prampero (1995). If we look instead at the fractional limitation to \dot{V}_{O_2max} imposed by the peripheral factors (F_p), we have:

$$F_p = \left(1 - \frac{\dot{V}_{O_2max}}{\dot{Q}_{aO_2max}} \right) \cdot \frac{P_{aO_2}}{P_{IO_2}} \quad (13)$$

whence, again from the data of Operation Everest II, $F_p = 0.22$.

Conclusions

This analysis explains why Messner was right in his belief and why Oelz and he had a visionary intuition, although they could not know it in 1978. There is no need for a high \dot{V}_{O_2max} to climb to the top of Mount

Everest without supplementary oxygen, and $\dot{V}_{O_2\max}$ on top is high enough to allow exercise performance at low powers. Hunt and Pugh did not know this either, of course, and thus they, who had not the romantic attitude of Messner and Oelz, but were pragmatically wise, took a safe decision in sending Hillary and Norgay to the summit with supplementary oxygen in 1953.

In sum, in this celebrative article, we have discussed specifically the effects of non-linearity in the respiratory system on $\dot{V}_{O_2\max}$ limitation at altitude. The application of an analogue of Hill's model to the non-linear decrease of $\dot{V}_{O_2\max}$ at altitude has led to the line reported in Fig. 7, the slope of which is independent of the individual $\dot{V}_{O_2\max}$ at sea level. As such, this article does not exhaust the subject of $\dot{V}_{O_2\max}$ limitation: in fact, all variables and concepts that are included in a conductance term along the oxygen cascade from ambient air to mitochondria (ventilation, lung diffusing capacity, ventilation/perfusion heterogeneity, cardiac output, muscle diffusing capacity, muscle oxidative capacity) contribute to $\dot{V}_{O_2\max}$ limitation in various degrees, depending on altitude. Nevertheless, the concept that $\dot{V}_{O_2\max}$ limitation is mainly imposed by cardiovascular oxygen transport, as at sea level, is questionable at extreme altitude, where the fractional limitation of $\dot{V}_{O_2\max}$ imposed by the lungs becomes important.

References

- Åstrand, P. (1954). The respiratory activity in man exposed to prolonged hypoxia. *Acta Physiologica Scandinavica*, **30**(4), 343–368.
- Benoit, H., Busso, T., Castells, J., Denis, C., & Geysant, A. (1995). Influence of hypoxic ventilatory response on arterial O_2 saturation during maximal exercise in acute hypoxia. *European Journal of Applied Physiology*, **72**(1–2), 101–105.
- Cerretelli, P. (1976). Limiting factors to oxygen transport on Mount Everest. *Journal of Applied Physiology*, **40**(5), 658–667.
- Cerretelli, P. (1980). Gas exchange at high altitude. In: West JB (ed). *Pulmonary gas exchange*, vol II. Academic Press, New York, pp 97–147.
- Cerretelli, P., & di Prampero, P. E. (1987). Gas exchange at exercise. In: Farhi LE, Tenney SM (eds). *Handbook of physiology, the respiratory system*, vol. IV. Gas Exchange. American Physiological Society, Bethesda MD, sect. 3, pp 555–632.
- Cerretelli, P., & Hoppeler, H. (1996). Morphologic and metabolic response to chronic hypoxia. In: *Handbook of physiology. Environmental physiology*. Fregly MJ, Blatteis CM eds. Oxford University Press, New York, sect. 4, vol. II, pp. 1155–1181.
- Cerretelli, P., & Margaria, R. (1961). Maximum oxygen consumption at altitude. *Internationale Zeitschrift Fur Angewandte Physiologie Einschliesslich Arbeitsphysiologie*, **18**, 460–464.
- Christensen, E. H. (1937). Sauerstoffaufnahme und respiratorische Funktionen in grossen Höhen. *Skand Arch Physiol*, **76**(1–2), 88–101.
- Cotes, J. E. (1954). The open-circuit oxygen equipment used by the British Mount Everest Expedition. *The Journal of Physiology*, **123**(2), 24P–25P.
- Dempsey, J. A., Hanson, P. G., & Henderson, K. S. (1984). Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *The Journal of Physiology*, **355**(1), 161–175.
- Di Prampero, P. E. (1985). Metabolic and circulatory limitations to $V_{O_2\max}$ at the whole animal level. *Journal of Experimental Biology*, **115**(1), 319–331.
- Di Prampero, P. E., & Ferretti, G. (1990). Factors limiting maximal oxygen consumption in humans. *Respiration Physiology*, **80**(2–3), 113–128.
- Downey, A. E., Chenoweth, L. M., Townsend, D. K., Ranum, J. D., Ferguson, C. S., & Harms, C. A. (2007). Effects of inspiratory muscle training on exercise responses in normoxia and hypoxia. *Respiratory Physiology & Neurobiology*, **156**(2), 137–146.
- Esposito, F., & Ferretti, G. (1997). The effects of breathing He– O_2 mixtures on maximal oxygen consumption in normoxic and hypoxic men. *The Journal of Physiology*, **503**(1), 215–221.
- Esposito, F., Limonta, E., Alberti, G., Veicsteinas, A., & Ferretti, G. (2010). Effect of respiratory muscle training on maximum aerobic power in normoxia and hypoxia. *Respiratory Physiology & Neurobiology*, **170**(3), 268–272.
- Ferretti, G. (2014). Maximal oxygen consumption in healthy humans: Theories and facts. *European Journal of Applied Physiology*, **114**(10), 2007–2036.
- Ferretti, G., & Di Prampero, P. E. (1995). Factors limiting maximal O_2 consumption: Effects of acute changes in ventilation. *Respiration Physiology*, **99**(2), 259–271.
- Ferretti, G., Fagoni, N., Taboni, A., Vinetti, G., & Di Prampero, P. E. (2022). A century of exercise physiology. Key concepts on coupling respiratory oxygen flow to muscle energy demand during exercise. *European Journal of Applied Physiology*, **122**(6), 1317–1365.
- Ferretti, G., & Miserocchi, G. (2023). A School goes to altitude. In: Ferretti G (ed). *Exercise, respiratory and environmental Physiology: A tribute from the School of Milano*. Springer, Cham, Switzerland and American Physiological Society.
- Ferretti, G., Moia, C., Thomet, J. M., & Kayser, B. (1997). The decrease of maximal oxygen consumption during hypoxia in man: A mirror image of the oxygen equilibrium curve. *The Journal of Physiology*, **498**(1), 231–237.
- FitzGerald, M. P. (1913). The changes in the breathing and the blood at various high altitudes. *Philosophical Transactions of the Royal Society*, **203**, 351–371.
- Gavin, T. P., Derchak, P. A., & Stager, J. M. (1998). Ventilation's role in the decline in $VO_2\max$ and SAO_2 in acute hypoxic exercise. *Medicine and Science in Sports and Exercise*, **30**(2), 195–199.
- Giesbrecht, G. G., Puddy, A., Ahmed, M., Younes, M., & Anthonisen, N. R. (1991). Exercise endurance and arterial desaturation in normobaric hypoxia with increased chemosensitivity. *Journal of Applied Physiology*, **70**(4), 1770–1774.

- Greene, R. (1934). Observations on the composition of alveolar air on Everest, 1933. *The Journal of Physiology*, **82**(4), 481–485.
- Grocott, M. P. W., Martin, D. S., Levett, D. Z. H., Mcmorrow, R., Windsor, J., & Montgomery, H. E. (2009). Arterial blood gases and oxygen content in climbers on Mount Everest. *The New England Journal of Medicine*, **360**(2), 140–149.
- Grocott, M. P., Martin, D. S., Wilson, M. H., Mitchell, K., Dhillon, S., Mythen, M. G., Montgomery, H. E., & Levett, D. Z. (2007). Caudwell xtreme Everest expedition. *High Altitude Medicine & Biology*, **11**, 133–137.
- Harrop, G. A. (1919). The oxygen and carbon dioxide content of arterial and of venous blood in normal individuals and in patients with anaemia and heart disease. *Journal of Experimental Medicine*, **30**(3), 241–257.
- Hill, A. V. (1910). The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *The Journal of Physiology*, **40**, iv–vii.
- Hoppeler, H., Howald, H., Conley, K., Lindstedt, S. L., Claassen, H., Vock, P., & Weibel, E. R. (1985). Endurance training in humans: Aerobic capacity and structure of skeletal muscle. *Journal of Applied Physiology*, **59**(2), 320–327.
- Hoppeler, H., Kleinert, E., Schlegel, C., Claassen, H., Howald, H., Kayar, S., & Cerretelli, P. (1990). Morphological adaptations of human skeletal muscle to chronic hypoxia. *International Journal of Sports Medicine*, **11**(S 1) S3–S9.
- Houston, C. S., Sutton, J. R., Cymerman, A., & Reeves, J. T. (1987). Operation Everest II: Man at extreme altitude. *Journal of Applied Physiology*, **63**(2), 877–882.
- Hunt, J. (1953). *The Ascent of Everest*, Hodder & Stoughton, London.
- Kellas, A. M. (1917). A consideration of the possibility of ascending the loftier Himalaya. *The Geographical Journal*, **49**(1), 26–47, 1917.
- Kellas, A. M. (2001). A consideration of the possibility of ascending Mount Everest. *Reprinted by John West in High Altitude Medicine and Biology*, **2**(3), 431–461.
- Koistinen, P., Takala, T., Martikkala, V., & Leppäluoto, J. (1995). Aerobic fitness influences the response of maximal oxygen uptake and lactate threshold in acute hypobaric hypoxia. *International Journal of Sports Medicine*, **16**(02), 78–81.
- Marconi, C., Marzorati, M., Grassi, B., Basnyat, B., Colombini, A., Kayser, B., & Cerretelli, P. (2004). Second generation Tibetan lowlanders acclimatize to high altitude more quickly than Caucasians. *The Journal of Physiology*, **556**(2), 661–671.
- Margaria, R. (1929). Die Arbeitsfähigkeit des Menschen bei verminderten Luftdruck. *Arbeitsphysiol*, **2**, 261–272.
- Margaria, R. (1938). Sulla fisiologia e specialmente sul consumo energetico della marcia e della corsa a varia velocità ed inclinazione del terreno. *Atti R Accad Lincei*, **7**, 299–368.
- Minetti, A. E., Moia, C., Roi, G. S., Susta, D., & Ferretti, G. (2002). Energy cost of walking and running at extreme uphill and downhill slopes. *Journal of Applied Physiology*, **93**(3), 1039–1046.
- Ogawa, T., Calbet, J. A. L., Honda, Y., Fujii, N., & Nishiyasu, T. (2010). The effects of breathing a helium–oxygen gas mixture on maximal pulmonary ventilation and maximal oxygen consumption during exercise in acute moderate hypobaric hypoxia. *European Journal of Applied Physiology*, **110**(4), 853–861.
- Ogawa, T., Hayashi, K., Ichinose, M., & Nishiyasu, T. (2007). Relationship between rest ventilatory chemosensitivity and maximal oxygen uptake in moderate hypobaric hypoxia. *Journal of Applied Physiology*, **103**(4), 1221–1226.
- Oelz, O., Howald, H., Di Prampero, P. E., Hoppeler, H., Claassen, H., Jenni, R., Buhlmann, A., Ferretti, G., Bruckner, J. C., Veicsteinas, A., Gussoni, M., & Cerretelli, P. (1986). Physiological profile of world class high altitude climbers. *Journal of Applied Physiology*, **60**(5), 1734–1742.
- Perutz, M. F. (1970). Stereochemistry of cooperative effects in haemoglobin. *Nature*, **228**(5273), 726–734.
- Piiper, J., Meyer, M., & Scheid, P. (1984). Dual role of diffusion in tissue gas exchange: Blood-tissue equilibration and diffusion shunt. *Respiration Physiology*, **56**(2), 131–144.
- Piiper, J., & Scheid, P. (1981). Model for capillary-alveolar equilibration with special reference to O₂ uptake in hypoxia. *Respiration Physiology*, **46**(3), 193–208.
- Pugh, L. (1952). *Report on British Himalayan Expedition [to Cho Oyu]*. Medical Research Council, London.
- Pugh, L. G. C. E. (1954). Scientific aspects of the expedition to Mount Everest, 1953. *The Geographical Journal*, **120**(2), 183–192.
- Pugh, L. G. C. E. (1957). Resting ventilation and alveolar air on Mount Everest: With remarks on the relation of barometric pressure to altitude in mountains. *The Journal of Physiology*, **135**(3), 590–610.
- Pugh, L. G. C. E. (1958). Muscular exercise on Mount Everest. *The Journal of Physiology*, **141**(2), 233–261.
- Pugh, L. G. C. E., Gill, M. B., Lahiri, S., Milledge, J. S., Ward, M. P., & West, J. B. (1964). Maximal exercise at great altitudes. *Journal of Applied Physiology*, **19**(3), 431–440.
- Roca, J., Hogan, M. C., Story, D., Bebout, D. E., Haab, P., Gonzalez, R., Ueno, O., & Wagner, P. D. (1989). Evidence for tissue diffusion limitation of in normal humans. *Journal of Applied Physiology*, **67**(1), 291–299.
- Severinghaus, J. W. (1979). Simple, accurate expressions for human blood oxygen dissociation computations. *Journal of Applied Physiology*, **46**(3), 599–602.
- Shephard, R. J. (1969). A non-linear solution of the oxygen conductance equation: Applications to performance at sea level and at an altitude of 7,350 ft. *Internationale Zeitschrift Fur Angewandte Physiologie Einschliesslich Arbeitsphysiologie*, **27**(3), 212–225.
- Shipton, E. E. (1952). *The Mount Everest Reconnaissance Expedition 1951*. Hodder & Stoughton, London.
- Stembridge, M., Ainslie, P. N., & West, J. B. (2022). Elevating physiology: Griffith Pugh on the limits of human performance and survival. *The Journal of Physiology*, **600**(8), 1811–1813.

- Richard Taylor, C., & Weibel, E. R. (1981). Design of the mammalian respiratory system. I. Problem and strategy. *Respiration Physiology*, **44**(1), 1–10.
- Wagner, P. D. (1993). Algebraic analysis of the determinants of VO_2 max. *Respiration Physiology*, **93**(2), 221–237.
- Wagner, P. D. (1996a). Determinants of maximal oxygen transport and utilization. *Annual Review of Physiology*, **58**(1), 21–50.
- Wagner, P. D. (1996b). A theoretical analysis of factors determining VO_2 max at sea level and altitude. *Respiration Physiology*, **106**(3), 329–343.
- Wagner, P. D. (2010). Operation Everest II. *High Altitude Medicine & Biology*, **11**(2), 111–119.
- Ward, M. P. (2003). Everest 1953, First Ascent: A clinical record. *High Altitude Medicine & Biology*, **4**(1), 27–37.
- Wehrlin, J. P., & Hallén, J. (2006). Linear decrease in VO_2 max and performance with increasing altitude in endurance athletes. *European Journal of Applied Physiology*, **96**(4), 404–412.
- West, J. B. (1987). Alexander M. Kellas and the physiological challenge of Mt. Everest. *Journal of Applied Physiology*, **63**(1), 3–11.
- West, J. B. (1988). Rate of ventilatory acclimatization to extreme altitude. *Respiration Physiology*, **74**(3), 323–333.
- West, J. B., Boyer, S. J., Graber, D. J., Hackett, P. H., Maret, K. H., Milledge, J. S., Peters, R. M., Pizzo, C. J., Samaja, M., Sarnquist, F. H., Schoene R. B., & Winslow, R. M. (1983). Maximal exercise at extreme altitudes on Mount Everest. *Journal of Applied Physiology*, **55**(3), 688–698.
- West, J. B., Hackett, P. H., Maret, K. H., Milledge, J. S., Peters, R. M., Pizzo, C. J., & Winslow, R. M. (1983). Pulmonary gas exchange on the summit of Mount Everest. *Journal of Applied Physiology*, **55**(3), 678–687.
- West JB, Lahiri S (eds.) (1984). High altitude and man. *Clinical Physiology Series*, American Physiological Society.
- West, J. B., Lahiri, S., Maret, K. H., Peters, R. M., & Pizzo, C. J. (1983). Barometric pressure at extreme altitudes on Mount Everest: Physiological significance. *Journal of Applied Physiology*, **54**(5), 1188–1194.
- Winslow, R. M., Samaja, M., & West, J. B. (1984). Red cell function at extreme altitude on Mount Everest. *Journal of Applied Physiology*, **56**(1), 109–116.
- Zuntz, N., Loewy, A., Müller, F., & Caspari, W. (1906). *Höhenklima und Bergwanderungen*. Deutsches Verlagshaus, Berlin.

Additional information

Competing interests

The authors declare that they have neither competing interests nor conflicts of interest.

Author contribution

G.F. conceived and designed the review and drafted the first version. G.S. revised it critically and completed some parts. G.F. and G.S. prepared the final version together. They both approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

There were no specific grants supporting this study. Only institutional funds were used.

Acknowledgements

This is a review article, which relies on previous publications. Fig. 7 is novel. The data are from Ferretti et al. (1997), Pugh (1958) and West, Boyer et al. (1983). Therefore, no new data have been uploaded to a repository. The authors thank the Department of Innovation, Research, University and Museums of the Autonomous Province of Bozen/Bolzano for covering the Open Access publication costs.

Keywords

altitude, exercise, hypoxia, maximal oxygen consumption

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History