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Human aerobic performance: too much ado about limits to $\dot{V}_{O_2}$

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Summary

Human endurance performance is often evaluated on the basis of the maximal rate of oxygen uptake during exercise ($\dot{V}_{O_2max}$). Methods for overcoming limits to $\dot{V}_{O_2max}$ are touted as means for increasing athletic endurance performance. Here, we argue that the respiratory system is well designed for delivering O_2 to meet O_2 demands and that no single factor is rate-determining for O_2 uptake. We show that $\dot{V}_{O_2max}$ can vary 5000-fold among mammals, while any limitation to O_2 delivery by a single component of the respiratory system affects $\dot{V}_{O_2max}$ by 10 % or less. Attempts to increase O_2 delivery by enhancing one step in the respiratory system are shown to have little effect. Blood doping, hyperoxia and O_2 supplementation of high-altitude natives all raise O_2 availability substantially to the working muscles, but these treatments increase $\dot{V}_{O_2max}$ only minimally. Finally, we argue that O_2 uptake is only one of a number of properties important to human aerobic performance.

Key words: oxygen delivery, oxygen transport cascade, $\dot{V}_{O_2max}$, human, aerobic performance, endurance

Introduction

There has been a long history of papers devoted to examining the factor or factors that conspire to limit maximum oxygen uptake. These usually focus on single species in an attempt to ascertain which functional 'bottleneck' is likely to set the upper limit to oxygen flow. In general, these fall into two categories, both of which have greatly increased our understanding of the mammalian respiratory system. First, because oxygen flows through structures in series (Fig. 1), (1) O_2 uptake by the mitochondria, (2) O_2 delivery by the circulation or (3) O_2 uptake by the lungs, the relative resistance (conductance) of each of these can be estimated and its contribution to the overall 'limit' approximated (di Prampero, 1985; di Prampero and Ferretti, 1990; Ferretti and di Prampero, 1995). However, this approach is complicated by the fact that some resistances are fixed and others variable, for example in response to training, and remain 'tuned' to demand (Lindstedt et al., 1988). In contrast, another approach has been to focus on one step and detail how this single step may be rate-limiting (Saltin and Strange, 1992; Wagner, 1992). One problem with this view is that this single-step 'limitation' has been ascribed to a number of different components in the cascade (Rowell, 1993; Wagner, 2000). The absence of consensus on where the 'limitation' lies may indicate that no single 'limitation' exists. Both these approaches have usually focused on relatively small changes (10–15 %) in the maximum rate of oxygen uptake, and usually in humans.

Our intention here is to take a slightly different approach, one that is also intended to provide insight into the design of the respiratory system. Rather than focus on small increases or decreases in rates of oxygen uptake, we hope to demonstrate that a broadly comparative picture yields distinct insights. We analyze this problem in three steps. First, we ask how the mammalian respiratory system is designed to match O_2 delivery to O_2 demand over a 5000-fold range of $\dot{V}_{O_2max}$. Second, we ask how the human system is designed to meet the twofold range of $\dot{V}_{O_2max}$ found among individuals. Third, we evaluate adjustments of steps in the O_2 cascade (such as blood doping, supplemental O_2, etc.) to evaluate whether a single 'limitation' dominates maximal O_2 flux. Through these comparisons, we seek to identify how the respiratory system is designed to match oxygen supply with oxygen demand. This comparative approach gives new insights and may change the nature of the question asked concerning how the respiratory system is designed to deliver O_2 to meet demand.

Underlying this approach is our belief that no single step in the O_2 delivery cascade dictates total flux but rather that each step contributes to flux. This notion of shared flux control is common to current thinking in biochemical pathways (Fell and Thomas, 1995; Kascar and Burns, 1973), the concept of symmorphosis (Weibel and Taylor, 1981; Weibel et al., 1991) and a recent physical analysis of the cardiovascular system (West et al., 1999).

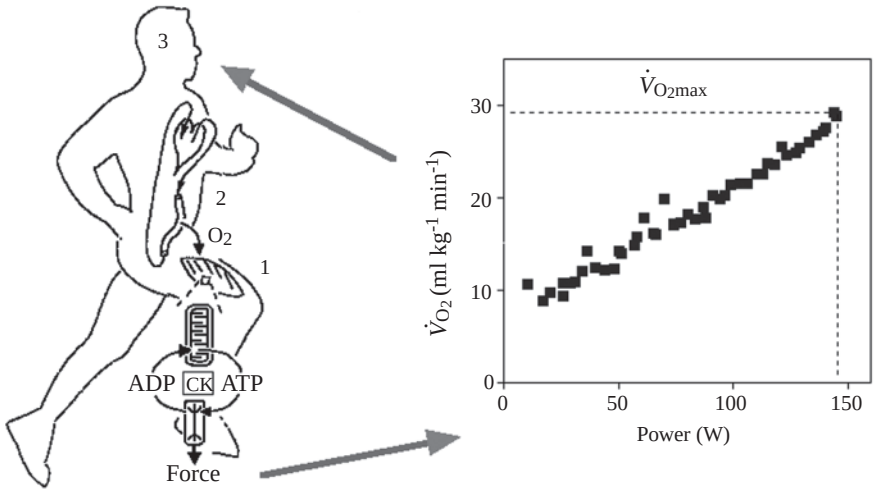

Fig. 1. (A) Diagram of the human respiratory–locomotory system showing the three stages governing O_2 uptake at the lungs (3), O_2 delivery by the cardiovascular system (2) and O_2 diffusion through the muscle and consumption by the mitochondria (1). (B) Plot of rate of O_2 uptake ($\dot{V}_{O_2}$) as a function of leg power output from rest to the aerobic capacity ($\dot{V}_{O_2max}$) in an exercising human. CK, creatine kinase.

Insights from the animal world

The quantitative analysis accomplished on the mammalian respiratory system may offer insight into the design of the human system. Our first question is how the range of $\dot{V}_{O_2max}$ of over 5000-fold (0.03 *versus* 169 ml s^{-1}; Seeherman et al., 1981) is achieved among all mammals. Let us start at the muscle, where the energy cost of locomotion determines the maximum O_2 demand. The two structures key to O_2 delivery and uptake are the mitochondria using O_2 and the capillaries delivering O_2. Fig. 2 shows that the volume of capillaries that deliver blood and the volume of mitochondria that use O_2 are directly proportional to $\dot{V}_{O_2max}$. The result is that the higher $\dot{V}_{O_2max}$ of larger animals corresponds with proportional increases in the muscle capillary capacity for O_2 delivery and the muscle mitochondrial capacity for O_2 uptake. The proportionality between structure and flux is demonstrated by the constancy of $\dot{V}_{O_2max}$ per mitochondrial volume despite a 5000-fold range in total flux between mouse and steer (Hoppeler, 1990).

A similar proportionality between O_2 delivery capacity and $\dot{V}_{O_2max}$ is found at the next step of the cascade, the cardiovascular system. Cardiac output and O_2 delivery both increase in proportion to maximal flux (Kayar et al., 1994). The structures of the pulmonary system also vary directly with $\dot{V}_{O_2max}$, but there is an apparent excess of O_2-diffusing capacity in all mammals (Weibel and Taylor, 1981). The end result is (i) that the structures of each step of the respiratory system scale in proportion to or in excess of $\dot{V}_{O_2max}$ (Weibel and Taylor, 1981), (ii) that each step in the system appears to operate at or near its maximum at $\dot{V}_{O_2max}$ and, as a result, (iii) that the O_2 flux per mitochondrial volume is nearly constant (Hoppeler, 1990). Clearly, a single step does not determine flux, but rather the structural and functional capacities of each step of the cascade increase almost in proportion to achieve the extraordinary range of $\dot{V}_{O_2max}$ found with body size in mammals.

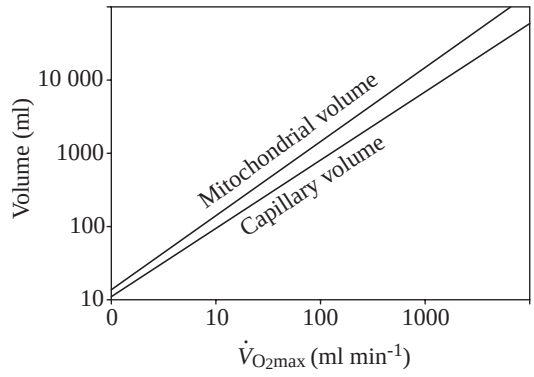

Fig. 2. The total volume of skeletal muscle capillaries and mitochondria plotted against maximum rate of oxygen consumption ($\dot{V}_{O_2max}$) for a wide variety of mammals. Both volumes are directly proportional to $\dot{V}_{O_2max}$ (data from Weibel and Taylor, 1981).

The human system is unique

Humans differ from most mammals in one important respect relevant to $\dot{V}_{O_2max}$: exercise involves bipedal rather than quadrupedal locomotion. This use of two rather than four limbs means that the whole musculature is not used to achieve $\dot{V}_{O_2max}$. Thus, defining the active muscle mass in humans is a critical problem, with differences in $\dot{V}_{O_2max}$ occurring between exercise modes such as running and cycling. For this analysis, we focus on cycling exercise, which evokes a nearly twofold range in $\dot{V}_{O_2max}$ between sedentary and well-trained athletes (Hoppeler et al., 1973) or between young and old subjects (Conley et al., 2000). Is this range of $\dot{V}_{O_2max}$ in humans accompanied by a proportional range in the capacities for O_2 uptake, delivery and use or does a single step dictate flux?

$\dot{V}_{O_2max}$ varies with mitochondrial content

An early study of muscle properties and $\dot{V}_{O_2max}$ showed that mitochondrial volume density, Vv(mt,f), was proportional to $\dot{V}_{O_2max}$ from sedentary humans to athletes (Hoppeler et al., 1973). Exercise training studies seemed to contradict this proportionality by showing a 40% increase in quadriceps Vv(mt,f) but only a 15% increase in whole-body $\dot{V}_{O_2max}$ (Hoppeler et al., 1985). However, a quantitative comparison of

the expected change in muscle *versus* whole-organism $\dot{V}_{O_2max}$ revealed the problem with this comparison of relative changes at the whole-body and muscle levels. The first step was to compare the changes that occurred at the level of the leg. This comparison showed that the increase in muscle power output agreed closely with the increase in muscle *V*v(mt,f) with training. Thus, ATP use, as measured by leg power output, increased in proportion to the mitochondrial capacity for O_2 uptake and ATP supply. The mitochondrial volume in the muscle increased as would be expected on the basis of the increased O_2 demand for muscle power output. The second step was to compare O_2 uptake estimated for the leg with whole-body $\dot{V}_{O_2}$. This comparison revealed that the $\dot{V}_{O_2}$ needed for this increase in power was close to the whole-body increase in $\dot{V}_{O_2max}$ that occurred with training. Thus, no discrepancy existed between changes at the level of the leg or between the leg and whole-body levels when the estimated change in $\dot{V}_{O_2}$ at the leg was compared directly with the whole-body $\dot{V}_{O_2}$ changes after training. This quantitative approach revealed that muscle mitochondrial volume, the estimated rate of O_2 consumption and the actual rate of O_2 uptake all increased proportionately with training. These results, and recent studies of sedentary subjects showing no increase in $\dot{V}_{O_2max}$ after breathing supplemental O_2 (Cardus et al., 1998), suggest that $\dot{V}_{O_2max}$ reflects the muscle oxidative capacity recruited during exercise, as it does in quadrupedal mammals.

A quantitative approach also helps us understand the factors responsible for the decline in $\dot{V}_{O_2max}$ with age. Elderly subjects show a large decline in $\dot{V}_{O_2max}$ relative to the young. A recent study showed that this decline in $\dot{V}_{O_2max}$ was accompanied by parallel changes in the oxidative capacity of the quadriceps muscle group with age (Conley et al., 2000). The end result was that a significant fraction of the decline in $\dot{V}_{O_2max}$ could be accounted for by the age-related change in the oxidative capacity of the quadriceps. In both adult and elderly subjects, the oxidative capacity of the quadriceps accounted for 30 % of the whole-body rate of O_2 uptake in accord with the fraction of quadriceps *versus* whole-limb power output during cycling. The implication of this study is clear: the drop in $\dot{V}_{O_2max}$ with age reflects the loss of O_2-consuming muscle. This study demonstrates that the kind of quantitative O_2 balance studies that have been accomplished in quadrupedal animals are also possible in humans even with the limitations of the bipedal gait. The result of this analysis in humans is the same as in quadrupeds: the range of $\dot{V}_{O_2max}$ corresponds quantitatively with the range of the oxidative capacity of muscle involved in exercise.

$\dot{V}_{O_2max}$ *varies with cardiovascular* O_2 *delivery*

Meeting the muscle O_2 demand is the cardiovascular capacity for O_2 delivery, which is determined by the product of cardiac output and O_2 extraction. Both normally active and athletic subjects have similar and high (up to 90 %) O_2 extractions at $\dot{V}_{O_2max}$, and the increase in O_2 delivery that underlies the twofold increase in $\dot{V}_{O_2max}$ results from an increase in cardiac output (see fig. 5.2 in Rowell, 1993). This difference in cardiac output is due to a higher stroke volume in athletes in accord with the larger heart of endurance-trained athletes. These findings indicate that a twofold difference in cardiovascular O_2 delivery capacity underlies the twofold difference in $\dot{V}_{O_2max}$ between sedentary and athletic subjects.

Finally, sufficient oxygen must be provided to the lungs, *via* ventilation, and to the blood, *via* diffusion through the lungs, to satisfy the demand of exercising muscles. There is no evidence for these structures being able to adapt, during an animal's lifetime. Lacking the plasticity that characterizes the other structures of the respiratory system, it is not surprising that the capacity of the lung for oxygen uptake exceeds the normal demand, suggesting to some that the lung may be 'built in excess' (Weibel et al., 1991). However, when we examine these structures across the full range of $\dot{V}_{O_2max}$ from a 5 g mouse to a 500 kg horse, we see that all structures vary proportionately (Weibel et al., 1991). For example, the cross-sectional area of the trachea varies directly with $\dot{V}_{O_2max}$ among mammals. Hence, it would appear that all mammals have a 'reserve capacity' to accommodate to, for example, high-altitude hypoxia or use or training-induced increases in the aerobic capacity of the muscles. Thus, the maximum ventilatory capacity may be fully exploited in humans only in the most elite endurance athletes (Lindstedt et al., 1994); for all others, capacity is excessive.

Limiting factors

Capacities versus *limitations as determinants of* $\dot{V}_{O_2max}$

What determines $\dot{V}_{O_2max}$, the capacities for O_2 delivery and uptake or the limitations to O_2 flux? To answer this question, let us examine the effect of varying single steps in the O_2 delivery cascade.

Does oxygen delivery limit oxygen uptake or is it adequate to meet oxygen uptake?

Cardiovascular O_2 delivery is the single identifiable factor most often implicated as the limit to oxygen uptake. Consequently, most of the recent drug scandals in endurance sports, starting with blood doping in the 1984 US Olympic cycling team, are designed to increase oxygen delivery. The current drug of choice, erythropoietin, can boost hematocrit dramatically and, until only recently, exogenous erythropoietin has been undetectable. This focus on boosting O_2 delivery seems to assume that humans do not conform to the general pattern of balance among respiratory system capacities. It also begs the question of what is responsible for the remaining respiratory structures being over-built (i.e. possessing capacity in excess of need or demand) if cardiovascular O_2 delivery is a single rate-limiting step.

One explanation for why cardiovascular O_2 delivery is thought to limit $\dot{V}_{O_2max}$ is that this step is the simplest to manipulate experimentally. Resultant correlations between rates of O_2 delivery and $\dot{V}_{O_2max}$ have been interpreted as demonstrating a rate-limiting role of oxygen delivery. On the surface, the evidence supports this concept. For example, when

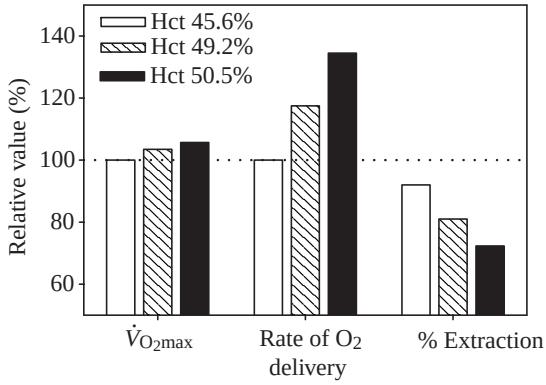

Fig. 3. $\dot{V}_{O_2max}$, rate of oxygen delivery (arterial O_2 content times cardiac output) and O_2 extraction for elite athletes receiving supplemental blood as the mean hematocrit (Hct) is increased from 45.6 to 50.5 %. $\dot{V}_{O_2max}$ and O_2 delivery are shown relative to their control (not blood-doped) values. Oxygen extraction is depicted as the actual percentage O_2 extraction. A 29 % increase in O_2 delivery to the muscles resulted in a 6.7 % increase in $\dot{V}_{O_2max}$; hence, O_2 extraction dropped from >90 % to <75 % (data from Spriet et al., 1986).

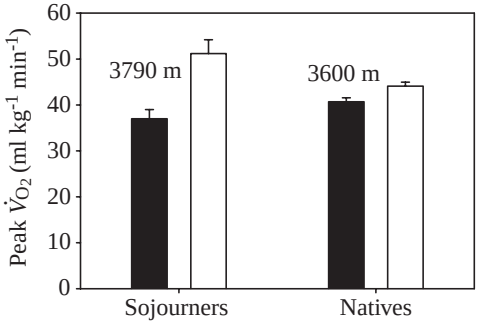

Fig. 4. $\dot{V}_{O_2max}$ at high altitude drops considerably in response to reduced arterial oxygen content. Here, $\dot{V}_{O_2max}$ is shown for sea-level sojourners at 3790 m altitude and for high-altitude natives at 3600 m (filled columns). $\dot{V}_{O_2max}$ increases in both groups of subjects when they are given supplemental O_2 equal to sea-level normoxia levels (open columns). However, the increase in sojourners (38 %) is over four times that of the high-altitude natives (8 %) (data from Cymerman et al., 1989; Favier et al., 1995). Values are means + S.E.M., N=8 (Cymerman), N=11 (Favier).

O_2 delivery is diminished, either by the withdrawal of erythrocytes or by the imposition of hypoxia, the rate of oxygen uptake is nearly always reduced in direct proportion. However, these results do not exclude the alternative interpretation that delivery is merely adequate (rather than limiting). How strong is the evidence supporting this single-step limitation to $\dot{V}_{O_2max}$?

Arterial oxygen content can be easily manipulated by changing the concentration of inspired oxygen or by the withdrawal or addition of red blood cells to alter hematocrit. In all cases, oxygen delivery varies with arterial oxygen content. In fact, when delivery is reduced by anemia or hypoxia, the oxygen extraction remains high (90 %) and $\dot{V}_{O_2max}$ declines in direct proportion to O_2 delivery (Lindstedt et al., 1988). However, when delivery is enhanced rather than reduced, a very different pattern emerges. A meticulous study (Spriet et al., 1986) measured arterial oxygen content, cardiac output and $\dot{V}_{O_2max}$ in very highly trained endurance runners (mean $\dot{V}_{O_2max}$ 77.5 ml O_2 kg^{-1} min^{-1}) given up to three units (500 ml each) of additional blood. They reported that a large increase in O_2 delivery (up to 30 %) was accompanied by a slight increase (<7 %) in $\dot{V}_{O_2max}$. As a consequence, O_2 extraction dropped from over 90 % to under 75 % (Fig. 3). The simple interpretation of these data is that oxygen delivery exceeded the capacity of the oxygen sink (mitochondria) in the exercising muscles and, hence, that muscle power output was unable to profit from the available oxygen.

Aerobic performance is limited at high altitude by the low O_2 partial pressure and resultant hypoxia. However, when exercising at high altitude, it is possible to supplement O_2 in the inspired air to return the subject functionally to 'sea-level' values of $\dot{V}_{O_2max}$ (hypobaric normoxia). Thus, when sojourners go to high altitude and are provided with additional oxygen, the consequence is an increase in the rate of oxygen consumption in direct proportion to the increase in arterial oxygen content and, hence, oxygen delivery. On the surface, these results seem to support a single cardiovascular limitation to $\dot{V}_{O_2}$. However, once again, a different pattern emerges when high-altitude natives, rather than sojourners, perform the same experiment. Comparing individuals from two different studies, at nearly the same altitude (3600 m altitude residents, 3790 m altitude sojourners), the two groups have a similar peak $\dot{V}_{O_2}$ (Cymerman et al., 1989; Favier et al., 1995). However, in contrast to the sojourners, when the high-altitude natives are given the sea-level-equivalent inspired oxygen partial pressure, the increase in $\dot{V}_{O_2max}$ (8 %) is much smaller than that of the sea-level sojourners (38 %) (Fig. 4). It seems that living at high altitude, where chronic hypoxia necessarily limits one's aerobic activity, the muscles collectively have a much lower aerobic capacity. Apparently, there is no stimulus to maintain the aerobic capacity of the muscles at a level beyond that which can be supplied *via* cardiovascular delivery. Thus, when the muscles are flooded with the equivalent of sea-level oxygen delivery, they simply have no aerobic machinery to utilize all that oxygen.

Finally, Richardson et al. (Richardson et al., 1999) have elegantly shown that intracellular (myoglobin-associated) P_{O_2} can also be manipulated by changing the fractional O_2 content of the inspired air (F_{IO_2}) from 0.12 (hypoxia) to 0.21 (normoxia) and 1.0 (hyperoxia). The drop in the mitochondrial rate of O_2 uptake in hypoxia (30 %) is identical to the drop in intracellular P_{O_2} (30 %). In contrast, a 65 % increase in intracellular P_{O_2} yields only an 11 % increase in mitochondrial $\dot{V}_{O_2}$. Once again, we see that, when delivery is reduced, $\dot{V}_{O_2}$ drops accordingly. However, when delivery is increased, more oxygen is apparently available to the mitochondria than can be utilized (Fig. 5).

Taken together, these data demonstrate using three different model systems that $\dot{V}_{O_2}$ does track O_2 delivery, but only when

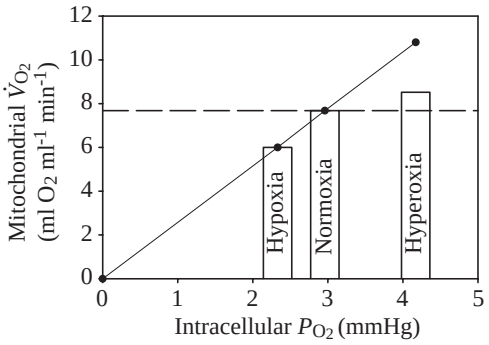

Fig. 5. Mitochondrial $\dot{V}_{O_2}$ increases linearly with intracellular P_{O_2} but only under conditions of hypoxia. When O_2 is increased (hyperoxia), the increase in mitochondrial $\dot{V}_{O_2}$ falls considerably below the predicted value (the line on the graph) (data from Richardson et al., 1999). 1 mmHg=0.133 kPa

delivery is reduced not when delivery is supplemented. This suggests to us that delivery is apparently rarely excessive. However, the fact that $\dot{V}_{O_2}$ does increase somewhat in response to increased O_2 delivery also argues against some other single rate-limiting step in the cascade. In other words, just as we see a structural balance accompanying the greatly varying $\dot{V}_{O_2}$ among mammals, so too within humans there is more evidence for a balance of structures and shared limitation than there is for a single-step limitation. When delivery is enhanced, unless there is a concomitant increase in the aerobic capacity of the muscles, little gain in $\dot{V}_{O_2max}$ is realized.

Are there general 'rules' that apply to human endurance performance?

By expanding our comparisons from within humans to among all mammals, there is a huge ratio of signal to noise such that $\dot{V}_{O_2max}$ varies by many orders of magnitude, not just a few per cent. What emerges is a consistent pattern of oxygen balance – structures ensuring supply are adequate to supply and utilize the oxygen required to meet the locomotor costs. Furthermore, those structures with the greatest plasticity will vary in proportion to oxygen uptake. These structures seem to be muscle mitochondrial volume and capillary density, cardiac output and hemoglobin concentration. In contrast, structures lacking plasticity (trachea, lungs) must be built with sufficient capacity to accommodate use-induced increases in oxygen demand during an animal's lifetime. There is no consistent evidence for a single rate-limiting step across the 5000-fold range of $\dot{V}_{O_2}$ among mammals, including humans. Finally, $\dot{V}_{O_2max}$ is just one of many interacting factors that collectively conspire to set the upper limits of human endurance performance.

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