TOPICAL REVIEW

$\dot{V}_{O_2,max}$: what do we know, and what do we still need to know?

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Maximal oxygen uptake ($\dot{V}_{O_2,max}$) is a physiological characteristic bounded by the parametric limits of the Fick equation: (left ventricular (LV) end-diastolic volume − LV end-systolic volume) × heart rate × arterio-venous oxygen difference. 'Classical' views of $\dot{V}_{O_2,max}$ emphasize its critical dependence on convective oxygen transport to working skeletal muscle, and recent data are dispositive, proving convincingly that such limits must and do exist. 'Contemporary' investigations into the mechanisms underlying peripheral muscle fatigue due to energetic supply/demand mismatch are clarifying the local mediators of fatigue at the skeletal muscle level, though the afferent signalling pathways that communicate these environmental conditions to the brain and the sites of central integration of cardiovascular and neuromotor control are still being worked out. Elite endurance athletes have a high $\dot{V}_{O_2,max}$ due primarily to a high cardiac output from a large compliant cardiac chamber (including the myocardium and pericardium) which relaxes quickly and fills to a large end-diastolic volume. This large capacity for LV filling and ejection allows preservation of blood pressure during extraordinary rates of muscle blood flow and oxygen transport which support high rates of sustained oxidative metabolism. The magnitude and mechanisms of cardiac phenotype plasticity remain uncertain and probably involve underlying genetic factors, as well as the length, duration, type, intensity and age of initiation of the training stimulus

(Received 1 November 2007; accepted after revision 2 November 2007; first published online 15 November 2007)
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All that is gold does not glitter,
Not all those who wander are lost.
The old that is strong does not wither,
Deep roots are not reached by the frost.

(J. R. R. Tolkein, 1955)

Maximal oxygen uptake ($\dot{V}_{O_2,max}$) is one of the most ubiquitous measurements in all of exercise science. The concept that there exists a finite rate of maximal oxygen transport from the environment to the mitochondria to support oxidative production of ATP to do physical work began with A.V. Hill (Hill & Lupton, 1923), and has been used diversely in clinical science as a measure of exercise performance (Mitchell *et al*. 1958; Levine & Stray-Gundersen, 1997; Hoppeler & Weibel, 2000; di Prampero, 2003), a marker of population-based fitness and cardiovascular disease (Blair *et al.* 1996; LaMonte *et al.* 2006), and even as a signal that patients with heart failure are on the verge of decompensation and should be referred for heart transplantation (Weber *et al*. 1987).

$\dot{V}_{O_2,max}$; the classical view

The 'classical' view of maximal oxygen uptake is that maximal rates of oxygen utilization (and sustainable rates of oxidative ATP production) in skeletal muscle are limited under most circumstances by the ability of the heart to deliver oxygen to and be accommodated by the working muscle (Saltin & Strange, 1992; Bassett & Howley, 1997). In some sense, this construct must be true as $\dot{V}_{O_2,max}$ is easily altered by manipulations that increase ((Ekblom *et al.* 1972; Buick *et al.* 1980; Ekblom & Berglund, 1991) or decrease (Ekblom *et al.* 1972; Jilka *et al.* 1988; Pawelczyk *et al.* 1992; Levine *et al.* 1996) peripheral oxygen delivery without altering arterial P_{O_2}; and the maximal vasodilatory capacity of skeletal muscle clearly exceeds the ability of the heart to deliver blood and still maintain adequate arterial

 DOI: 10.1113/jphysiol.2007.147629

perfusion pressure (Secher *et al.* 1977; Richardson *et al.* 1999).

Does a true $\dot{V}_{O_2,max}$ exist and can we measure it?

Some investigators have contended recently though that the absence of a clear and consistent plateau in $\dot{V}_{O_2}$ with increasing running speed in the early Hill experiments argues that the concept of $\dot{V}_{O_2,max}$ is not valid (Noakes, 1997). A number of scholarly reviews and rebuttals have been written about this issue (Saltin & Strange, 1992; Bassett & Howley, 1997, 2000; Bergh *et al.* 2000; Saltin & Calbet, 2006; Wagner, 2006) and these arguments will not be repeated here. To help answer this particular question and avoid the details of the 'what limits $\dot{V}_{O_2,max}$' debate for the moment, let's assume that there are 'upstream' and 'downstream' factors that provide oxygen to exercising skeletal muscle and then use it for physical work. The 'upstream' factors include all the physiological pathways that transfer O_2 from the environment to the blood, pump it to the periphery, and distribute it to and then inside the muscle cells. The 'downstream' factors include all the intracellular processes that occur once the O_2 molecule is transferred to the inside of the cell for oxidative production of ATP, and the neuromotor events that create calcium influx and muscle contraction.

A large part of the debate instigated by Noakes hinges on whether downstream factors, predominantly muscle motor recruitment, alone drive $\dot{V}_{O_2,max}$, or whether $\dot{V}_{O_2,max}$ has upstream limits independent of muscle motor recruitment. Indeed, Noakes has articulated what he considers a 'new model' of integrated performance physiology, which he has called The Central Governor Model (Noakes, 1997; Noakes *et al.* 2001, 2004*a*; Noakes & St Clair Gibson, 2004). In this formulation, a 'central governor' shuts down the body by putting a brake on muscle motor recruitment at very high work rates to avoid a 'disturbance of homeostasis'. So, during an incremental exercise test, the highest $\dot{V}_{O_2}$ that is achieved doesn't really reflect a true maximal ability to transport oxygen to the tissues and use it to make ATP to do physical work, because there remains lots of reserve that subjects don't 'choose' to evoke.

For the purposes of framing the debate, Dr Noakes frequently likes to place investigators into two camps: those who believe the brain plays a role in exercise performance, and those who do not (Noakes *et al.* 2004*b*). However this straw man is specious. No one disputes that 'the brain' is required to recruit motor units – for example, spinal cord-injured patients can't run. There is no doubt that motivation is necessary to achieve $\dot{V}_{O_2,max}$. A subject can elect to simply stop exercising on the treadmill while walking slowly because they don't want to continue; no mystical 'central governor' is required to hypothesize or predict a $\dot{V}_{O_2}$ below maximal achievable oxygen transport in this case.

For more than a century, cardiovascular scientists have appreciated that that 'central command' initiates the cardiovascular response to exercise and plays a critical role in the exercise pressor reflex (Mitchell *et al.* 1983; Mitchell & Victor, 1996; Williamson *et al.* 2006). This is especially true for the regulation of heart rate; for example, when voluntary effort ceases at the end of exercise, heart rate rapidly returns to normal, even if metabolic signals are trapped within skeletal muscle by vascular occlusion (Alam & Smirk, 1937). When skeletal muscle motor units are inhibited by curare, thus weakening the muscle contraction, the heart rate response to exercise is augmented (Leonard *et al.* 1985; Mitchell *et al.* 1989) as a function of increasing central command. Feedback to the brain from mechanically and metabolically sensitive skeletal muscle afferents also plays an essential role in increasing sympathetic nervous system outflow (Mitchell & Victor, 1996), as well as regulating the augmentation in cardiac output and the distribution of muscle blood flow – a response that is extremely tightly regulated with little effect of age, sex or fitness (McGuire *et al.* 2001; Fu & Levine, 2005). Indeed, when such signals are deranged, the cardiovascular response to exercise is dramatically altered, for example in patients with muscle metabolic disorders who may have 3–5 or, in extraordinary cases, more than 10 times the increase in cardiac output normally seen for a given increase in oxygen uptake (Lewis *et al.* 1984; Haller *et al.* 1991; Taivassalo *et al.* 2003). There are hundreds if not thousands of papers on animals and humans on the topic of cardiovascular regulation in healthy and patient populations, demonstrating the intimate connection between skeletal muscle and the CNS. These were reviewed thoroughly in a recent 'themed issue' of *Experimental Physiology* (Raven, 2006).

So why the 'controversy'?

One obvious reason is that a clear and unequivocal 'plateau' in oxygen uptake with increasing work may be difficult to demonstrate during incremental tests to exhaustion in different populations. The classic strategy to overcome this limitation is to continue to repeat tests using increasing work rates, even if this requires discontinuous exercise, until the rise in $\dot{V}_{O_2}$ is smaller by some fraction than that expected from the change in external work (Taylor *et al.* 1955). The most comprehensive study in this regard was that by Taylor *et al.* (1955). They studied over 100 healthy young subjects and repeated exercise tests near maximal work capacity daily, increasing the treadmill grade until the increase in $\dot{V}_{O_2}$ was less than half to one-third that which was observed at submaximal workrates. Only 7 of 115 subjects failed to achieve this criterion, thus firmly establishing the concept of $\dot{V}_{O_2,max}$ as a measure of cardiorespiratory performance. However it must be acknowledged that this actual finite point can

be challenging to demonstrate with small increments in external work. This is especially true in subjects with relatively small anaerobic capacities, who are unable to sustain the high work rates long enough for oxygen uptake to stabilize, and for whom the difference between expected and measured changes in $\dot{V}_{O_2}$ is within the experimental noise of the technique.

Fortunately this issue was put to rest recently by a study which provides unequivocal experimental evidence validating the concept of $\dot{V}_{O_2,max}$ – that is, that there exists a finite rate of oxygen uptake of a given organism (at a particular fraction of inspired oxygen (F_{IO_2}) and fitness level), beyond which increasing the work rate does not lead to more oxygen uptake (Hawkins *et al.* 2007). In this study by Hawkins *et al.* (2007), a group of well-trained collegiate middle-distance runners performed an incremental exercise test, followed the next day by a 'supramaximal' test designed to determine anaerobic capacity from the accumulated oxygen deficit (Medbo *et al.* 1988). In this study, which included 156 pairs of incremental and supramaximal tests, the subjects were able to accomplish and sustain a *very large* amount of extra work – more than 30% greater than would be required to support such work rates oxidatively – using great motivation (and pain tolerance) and large amounts of muscle motor recruitment, and making energy for that work by high rates of glycolysis and substrate level phosphorylation; yet $\dot{V}_{O_2,max}$ was rarely higher, and *never* substantively so, than on the incremental test. Most importantly, it *never* even came close to the oxidative requirements of the higher workload, despite the clear documentation of a levelling off of oxygen uptake in response to the acute initiation of the very intense work rate. The central figure from this study is reproduced as Fig. 1. Thus it cannot be argued that during the incremental test to $\dot{V}_{O_2,max}$, a 'central governor' stopped the test before an actual $\dot{V}_{O_2,max}$ to avoid ischaemia or other disturbance, because the subjects were quite capable of exercising on a separate effort at a *much* higher external work rate yet no such ischaemia occurred. Others have reported similar data recently including reasonable estimates of myocardial work (Brink-Elfegoun *et al.* 2007). Finally, it is worth emphasizing that patients with coronary heart disease are regularly stressed beyond the point of myocardial ischaemia, which does not prevent them from continuing to exercise (Chaitman, 2005) – their 'central governors' must fail them all the time!

If $\dot{V}_{O_2,max}$ exists, why is it so large in endurance athletes?

It should be emphasized that $\dot{V}_{O_2,max}$ is not equivalent to sport performance, by which I mean the time it takes to cover a specific distance under competitive circumstances, or scoring more points then an opponent in a team or individual game sport. Rather it is a physiological characteristic bounded by the parametric limits of the Fick equation:

left ventricular (LV) end − diastolic volume − LV end−systolic volume) × heart rate × arteriovenous oxygen difference.

Some simple calculations help to highlight these boundaries. First, let's assume a maximum haemoglobin concentration for competitive athletes of 17 g dl^{-1} for men, the upper limit established by the Federation Internationale de Ski (FIS) for allowing athletes to begin a race. If we assume 100% arterial oxygen saturation (i.e. no diffusion limitation or ventilation/perfusion ($\dot{V}/Q$) mismatch, certainly an overestimation in competitive athletes), and the lowest mixed venous oxygen saturations measured – 14% near the summit of Mount Everest (Sutton *et al.* 1988*b*), then the largest *possible* arteriovenous (a–v)

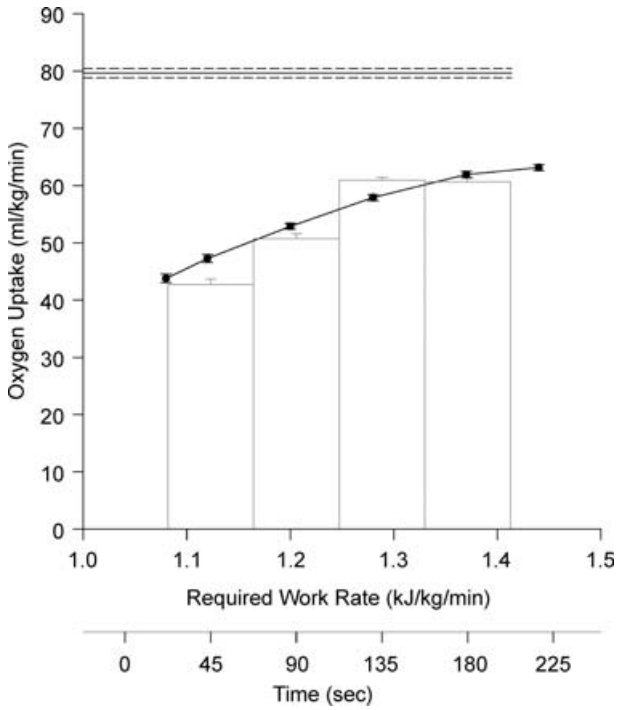

Figure 1. Maximal O_2 uptake during incremental and supramaximal excercise (N = 156)
Filled circles connected by lines represent Douglas bags obtained during the second minute of each 2 min stage run at a fixed speed with an increase in grade by 2% every 2 min. The last bag at the highest work rate was occasionally obtained earlier in the stage to accommodate subject exhaustion. Required work rate (dark abscissa) calculated directly from treadmill speed and grade. Open bars represent the last four 45 s Douglas bags collected continuously during the supramaximal test. The light abscissa reflects the time the bags were collected during the supramaximal test. Based on running economy determined individually at this grade (8%), the oxygen uptake required to perform this amount of work aerobically was calculated and shown as a solid line with 95% confidence limits (dashed line). From Hawkins *et al.* (2007) with permission from Lippincott Williams & Wilkins.

O_2 difference would be 200 ml l^{-1} (20 vol percentage). This value is within 10–20% or so of the values that have been reported in elite athletes (Ekblom & Hermansen, 1968). Notably, peak a–v O_2 differences in non-athletes are not much below the values observed in elite athletes (Sutton *et al.* 1988*a*, 1992; Hagberg *et al.* 1985), arguing that the major factor underlying the large $\dot{V}_{O_2,max}$ of endurance athletes is a large cardiac output. This contention is buttressed by the observations made by Mitchell *et al.* (1958), now half a century ago, that the levelling off of $\dot{V}_{O_2}$ with increasing workrate at $\dot{V}_{O_2,max}$ was associated with a clear levelling off of cardiac output.

Since maximum heart rate of athletes is, if anything, lower than that of non-athletes (Rowell, 1986), it follows that the primary distinguishing feature of athletes is their large stroke volume. Since end-systolic volume has never been reported to be smaller in athletes than non-athletes, the single most important factor allowing this large stroke volume is a large end-diastolic volume.

Work in our laboratory more than 15 years ago demonstrated the mechanism for this unique characteristic (Levine *et al.* 1991), using direct invasive techniques. Endurance athletes have a markedly greater ability to use the Starling mechanism to increase stroke volume. Contractility was not different between athletes and non-athletes, so virtually all the difference in stroke volume was due to a large end-diastolic volume. Athletes were able to achieve such a large end-diastolic volume by virtue of markedly enhanced cardiac chamber compliance (Fig. 2). Both static compliance determined from pressure (P)–volume (V) curves, and operational compliance determined from dV/dP of the P–V curve were substantially larger in the endurance athletes (Levine *et al.* 1991). In these studies, the largest hearts for male athletes showed an end-diastolic volume in the supine position during volume infusion of around 250 ml, which generated a stroke volume of around 130–150 ml; for peak heart rate of 200 beats min^{-1}; this gives a peak cardiac output of about 30 l; Assuming maximal possible a–v O_2 difference, these characteristics would give a $\dot{V}_{O_2,max}$ of about 6–7 l min^{-1} as seen in large, elite skiers or rowers (Ekblom *et al.* 1968; Jensen *et al.* 2001). To the best of my knowledge, the largest published cardiac output during exercise along with the largest stroke volume may be those reported in a world-class orienteer of 42.3 l min^{-1} and world champion cyclist of 212 ml (Ekblom *et al.* 1968) respectively, though anecdotal unpublished comments have suggested the possibility of higher values (http://indurain.chez-alice.fr/). The highest reported $\dot{V}_{O_2,max}$ of which I am aware is 7.48 l min^{-1} in a large, elite skier (Saltin, 1996). Studies in dogs (Stray-Gundersen *et al.* 1986) and pigs (Hammond *et al.* 1992) provide evidence that the pericardium provides a critical restraint to maximal LV filling. When the pericardium was removed in these studies, maximal LV end-diastolic volume was significantly increased, leading to increased cardiac output and $\dot{V}_{O_2,max}$. Thus the key distinguishing characteristic of elite endurance athletes is a large end-diastolic volume due to compliant heart and a distensible pericardium.

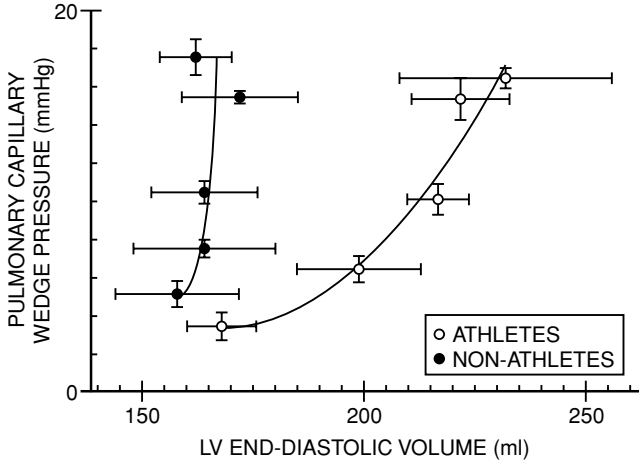

Figure 2. Directly measured cardiac pressure–volume curves for athletes and non-athletic controls
Note the marked improvement in both static and dynamic compliance in the endurance athletes. From Levine *et al.* (1991). Reproduced with permission.

Not only must the heart be compliant, but in order to fill to these large end-diastolic volumes during maximal exercise with very high heart rates, it must have very rapid diastolic relaxation with vigorous suction. Work by Ferguson *et al.* (2001) has shown that athletes do indeed have hearts that fill more rapidly at high levels of exercise intensity, which allows endurance athletes to continue to increase stroke volume at all levels of exercise (Gonzalez-Alonso *et al.* 2007). Diastolic suction develops because the remodelling of the athlete's heart (Pelliccia *et al.* 1999) increases the equilibrium volume of the left ventricle, which is the volume in the heart when transmural filling pressure is 0 mmHg (Nikolic *et al.* 1988; Yellin *et al.* 1990). When the heart contracts below the equilibrium volume in systole, it engages mechanical restorative forces which markedly augment the transmitral intraventricular pressure gradients that literally 'suck' blood from the left atrium across the mitral valve into the apex of the left ventricle (Yellin *et al.* 1990). This active process is particularly important during upright exercise when gravitational gradients must also be overcome to maximize venous return (Levine *et al.* 1997).

The point of going through these calculations is that there *must* be finite and fixed limitations to all the components of the Fick equation, thus providing absolute upper boundaries on maximum oxygen transport in humans (despite extraordinary rates of voluntary motor recruitment!). Assuming maximal possible a–v O_2 difference, and the highest reported exercise cardiac output, this absolute upper limit for $\dot{V}_{O_2,max}$ is about

8 l min^{-1} (and almost certainly lower due to the low likelihood of matching maximal possible a–v O_2 difference with maximal cardiac output in the same athlete at the same time, due at least in part to ventilatory limitations which are prominent in endurance athletes (Dempsey & Wagner, 1999). Ultimately then, it is the broad concept of $\dot{V}_{O_2,max}$ that is important for this discussion, not the fine distinction of the specific limitations which may change under different circumstances. Moreover, it doesn't matter at all whether Hill did or did not actually 'prove' a plateau in $\dot{V}_{O_2,max}$ in 1923 – it is the concept that these parametric limits exist that is important for understanding exercise performance.

Of course the factors determining oxygen uptake are not independent, and where the 'limits' to $\dot{V}_{O_2,max}$ lie depends on the nuance of how the question is asked (Wagner, 2006). Thus, increasing cardiac output by itself may increase diffusion limitation at the lung or at the skeletal muscle and therefore not buy more oxygen transport; this problem is especially true at high altitude where the gradients driving diffusion of oxygen from the alveoli into the pulmonary capillary are greatly reduced (Johnson, 1967; Wagner, 1993, 1996*b*). Indeed maximal rates of diffusion in the periphery are so limited at high altitude that even increasing oxygen content of the blood by transfusion (Young *et al.* 1996) or erythropoietin (Lundby & Damsgaard, 2006) do not increase $\dot{V}_{O_2,max}$, even though increasing O_2 content by increasing F_{IO_2} – emphasizing the importance of the pressure gradient from blood to muscle cell – obviously does (Savard *et al.* 1995; Boushel *et al.* 2001). Many detailed and scholarly discussions of the limitations to $\dot{V}_{O_2,max}$ have been reported by others (Saltin & Strange, 1992; Wagner, 1996*a*, 2006; di Prampero, 2003; Saltin & Calbet, 2006) to name only a few.

So what? What is the relationship between $\dot{V}_{O_2,max}$ and performance?

Although $\dot{V}_{O_2,max}$ is not performance, it clearly is one of the major characteristics that determine performance in endurance sport (Peronnet *et al.* 1991; di Prampero, 2003). Sometimes this relationship may be obscure when only elite athletes with similar $\dot{V}_{O_2,max}$ values are considered (Noakes, 1997, 1998; Bergh *et al.* 2000). However, an elite athlete with a $\dot{V}_{O_2,max}$ of 80 ml kg^{-1} min^{-1} can surely run 5000 m faster than a recreational athlete with a $\dot{V}_{O_2,max}$ of 40 ml kg^{-1} min^{-1} can, so this characteristic is clearly closely tied to endurance performance (Bergh *et al.* 2000; di Prampero, 2003). Of course, it depends on the distance being covered, which determines the rate of optimal/possible energy utilization and the substrate used to produce ATP, how much $\dot{V}_{O_2,max}$ contributes to performance (Peronnet *et al.* 1991; di Prampero, 2003; Joyner & Coyle, 2007).

Moreover, it has been widely recognized for decades that $\dot{V}_{O_2,max}$ is not the only characteristic that determines how fast an athlete can travel, especially as the differences in outcome at a world-class level are measured in fractions of a second. Other traits such as sport-specific economy, anaerobic capacity and, for longer distances, fuel utilization and the speed or oxygen uptake at the maximal steady state will all contribute to the final count on the stop watch (Joyner, 1991; Peronnet *et al.* 1991; di Prampero, 2003; Joyner & Coyle, 2007). Since maximal oxygen delivery has little to do with most of these factors, it should not surprise anyone that athletes can perform at work rates higher than $\dot{V}_{O_2,max}$ for brief periods of time, even if $\dot{V}_{O_2,max}$ is indeed limited by cardiovascular performance. Every sprinter knows this fact – but no amount of voluntary motor recruitment can allow an athlete to run at a rate of 10 m s^{-1} for the distance of a marathon. Why is this? Is it because humans do not have the motivation to sustain such high rates of muscle contraction for more than 10 s or so? Because a 'central governor' knows that it is dangerous to do so for more than 100 m? Or is it because human skeletal muscle cannot produce enough ATP at a high enough rate for a sustained period of time (or regenerate it on a sustained basis via oxidative metabolism) to support this kind of external work? It seems clear that the muscle (not the brain) is fatiguing over these brief bursts of extremely high levels of motor recruitment, though of course such local signals are communicated to the brain and influence the athlete's sense of how fast they can continue to run. Such sprint athletes are able to generate so much force from such intense motor recruitment that they rip their muscles apart (Thelen *et al.* 2006), yet they don't stop sprinting because of inadequate central drive or myocardial ischaemia. No one disputes the fact that motivation and voluntary motor recruitment influenced by sensations coming from skeletal muscle (not the vague action of a 'central governor') play a role in exercise performance, and in no way does this reality violate any tenet of the concept of $\dot{V}_{O_2,max}$ and cardiovascular performance.

It may be instructive to examine how $\dot{V}_{O_2,max}$ changes with hypoxia at altitude, to demonstrate the tight relationship between $\dot{V}_{O_2,max}$ and performance, even in athletes with relatively uniform $\dot{V}_{O_2,max}$. It has long been known that $\dot{V}_{O_2,max}$ decreases with high-altitude exposure or hypoxia (for review, see Fulco *et al.* 1998), and that in athletes, this decrease is evident at altitudes as low as a few hundred metres (Terrados *et al.* 1985; Lawler *et al.* 1988; Gore *et al.* 1996; Wehrlin & Hallen, 2006). The mechanism for this reduction is related to diffusion limitation in the lung, which is exaggerated in athletes with high pulmonary blood flows (Johnson, 1967; Torre-Bueno *et al.* 1985; Levine & Stray-Gundersen, 1999) and who may develop exercise-induced hypoxaemia even at sea level (Dempsey & Wagner, 1999) (*see* Fig. 3).

Not only does $\dot{V}_{O_2,max}$ decrease, but exercise performance at altitude clearly deteriorates at all running distances greater than 800 m (events lasting longer than 2 min (Peronnet *et al.* 1991). Noakes *et al.* (2001) have suggested that this decrease in $\dot{V}_{O_2,max}$ and performance is a function of reduced motor recruitment, and argue that it provides evidence in support of the central governor model. However, this speculation has recently been proved convincingly to be incorrect.

Some insight can be obtained from an early study by Medbo *et al.* (1988), who elaborated on the Krogh and Lindhard concept of the accumulated oxygen deficit as a measure of anaerobic capacity. In this study the investigators performed supramaximal exercise on a treadmill after careful assessment of individual running economy. During the uphill run, the total energy expended during the test was divided into aerobic and anaerobic components, and the anaerobic capacity was defined as the difference between the predicted cost of the total work if all energy had been derived from oxidative sources, and the directly measured accumulated oxygen uptake. Central to the proof that this measure is truly representative of anaerobic capacity is the demonstration that it is independent of oxygen uptake, and unaffected by hypoxia. Consistent with this hypothesis, the data showed that there was no difference in the anaerobic capacity measured under normoxic and hypoxic conditions, equivalent to an altitude of 3500 m; 100% of the reduction in performance (slower speed, lower grade) was due to a reduction in accumulated oxygen uptake. However, in order to keep the duration of the test constant in normoxia and hypoxia, the speed and grade of the treadmill had to be reduced.

More recently, Wehrlin & Hallen, (2006) extended this work by performing repeated supramaximal running tests in a group of trained athletes at multiple low to moderate altitudes from 300 m to 2800 m. In order to ensure that motor recruitment and power output were the same in all tests, each supramaximal test was performed at exactly the same speed, at 107% normoxic velocity at $\dot{V}_{O_2,max}$. Despite keeping the speed absolutely constant at all altitudes, $\dot{V}_{O_2,max}$ was reduced progressively and linearly by 0.6% per 100 m altitude, in direct proportion to the reduction in oxygen saturation (S_{pO_2}) (Wehrlin & Hallen, 2006); performance was reduced by 1.4% per 100 m altitude in direct proportion to the decrease in $\dot{V}_{O_2,max}$. This study provides strong evidence that: (a) $\dot{V}_{O_2,max}$ is closely tied to oxygen transport, even when the differences are quite small, especially in well-trained endurance athletes; and (b) the reduction in $\dot{V}_{O_2,max}$ at altitude is not likely to be due to decreased motor unit recruitment since running speed was constant at all altitudes studied.

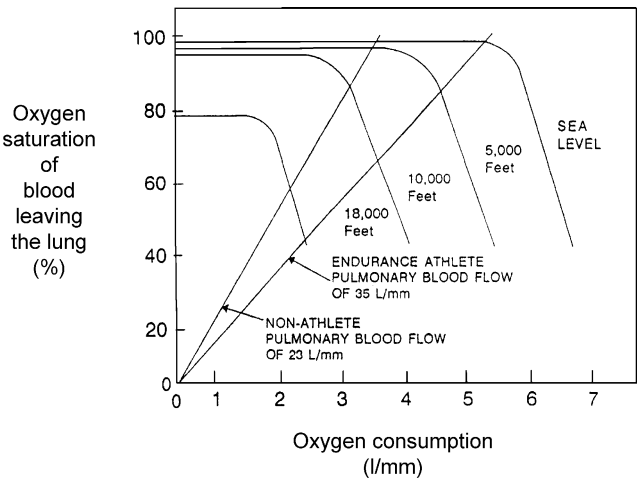

Figure 3. Effect of different pulmonary blood flows (i.e. cardiac output) on oxygen saturation at different altitudes
Note that a non-athlete with a peak pulmonary blood flow of 23 l min^{-1} would be well saturated at sea level and low altitude up to 5000 feet. (1500 m); however, an endurance athlete with a peak pulmonary blood flow of 35 l min^{-1} would be barely compensated at sea level and would have clear desaturation even at low altitude. From Levine & Stray Gundersen (1999) as modified from Johnson (1967). Reproduced with permission (© Elsevier 1999).

What next?

So why do athletes stop exercising at $\dot{V}_{O_2,max}$? This is a complex question that is beyond the scope of this essay, and the answer unquestionably varies depending on the circumstances of the exercise effort. Certainly, oxygen-dependent pathways are involved in energetic failure (Kindig *et al.* 2005), though these may be more important in muscle fibres that are less rather than more oxidative (Howlett & Hogan, 2007). A very recent series of 'mini-reviews' summarizes the state of the art in this field (McKenna & Hargreaves, 2007) and emphasizes that there is a multiplicity of factors responsible for inducing local muscle fatigue, including failure of sarcoplasmic reticulum calcium release (Allen *et al.* 2007), impaired sodium/potassium pump activity (McKenna *et al.* 2007), and slowed cross-bridge cycling (Fitts, 2008) due to a variety of metabolic mediators including reactive oxygen species (Ferriera & Reid, 2008). It is also clear that these muscle factors stimulate a number of neural pathways (Todd *et al.* 2007) that ultimately lead to reduced central motor drive and neural activation (Amann & Calbet, 2007; Amann *et al.* 2006). Under certain conditions such as severe acute hypoxia, central fatigue may be quite prominent and cause exercise effort to be compromised even before peripheral fatigue develops (Amann *et al.* 2007). It is highly likely that many of these factors are redundant, and may be more or less prominent in leading to cessation of effort under different circumstances. Defining the link between metabolic demand, cardiovascular control (including the regulation of cardiac output and local

muscle blood flow), and fatiguing exercise including the afferent receptors, neural pathways and central integration will be an important direction for future research.

Lastly, it is intuitively obvious to anyone who has grown up on a playground that some individuals are more gifted athletically than others. Not only are there those that are bigger, stronger and faster, but also those with more endurance. Recent evidence suggests that at least some amount of $\dot{V}_{O_2,max}$ is heritable (Bouchard *et al.* 1998; Hagberg *et al.* 2001), though identification of specific genes has been less convincing. For example, despite the early enthusiasm for genes that govern the angiotensin converting enzyme (Myerson *et al.* 1999; Gayagay *et al.* 1998), it is quite clear that large numbers of successful endurance athletes do not have the 'endurance genotype' (Gayagay *et al.* 1998; Woods *et al.* 2001; Tsianos *et al.* 2004; Lucia *et al.* 2005; Scott *et al.* 2005). How much does this have to do with differences in underlying genotype or, more importantly, gene–environment interactions? What are the limits of phenotypic plasticity in response to training? For example, training studies in our lab show the ability to achieve the same LV mass as elite endurance athletes with 1 year of training (Morrow *et al.* 1997, 1998; Levine *et al.* 1998). However, LV end-diastolic volume and compliance remain much lower than we have previously reported in cross-sectional studies of endurance athletes (Levine *et al.* 1991). Is this a function of pericardial constraint which needs more than 1 year to dilate? Do we just need many more years of training? Or rather is it more important that training occurs during growth and development to achieve optimal cardiac size and compliance (Saltin *et al.* 1995)?

In conclusion, the key take home messages from this essay are: (1) $\dot{V}_{O_2,max}$ is an important determinant of endurance performance which represents a true parametric measure of cardiorespiratory capacity for an individual at a given degree of fitness and oxygen availability; (2) the primary distinguishing characteristic of elite endurance athletes that allows them to run fast over prolonged periods of time is a large, compliant heart with a compliant pericardium that can accommodate a lot of blood, very fast, to take maximal advantage of the Starling mechanism to generate a large stroke volume; (3) athletes stop exercising at $\dot{V}_{O_2,max}$ because of severe functional alterations at the local muscle level due to what is ultimately a limitation in convective oxygen transport, which activates muscle afferents leading to cessation of central motor drive and voluntary effort.

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