Oxygen uptake (VO₂) kinetics in different species: a brief review

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Submitted 3 September 2004: Accepted 29 October 2004

Abstract

When a human begins to move or locomote, the energetic demands of its skeletal muscles increase abruptly and the oxygen (O₂) transport system responds to deliver increased amounts of O₂ to the respiring mitochondria. It is intuitively reasonable that the rapidity with which O₂ transport can be increased to and utilized by (VO₂) the contracting muscles would be greater in those species with a higher maximal VO₂ capacity (i.e., VO₂max). This review explores the relationship between VO₂max and VO₂ dynamics or kinetics at across a range of species selected, in part, for their disparate VO₂max capacities. In healthy humans there is compelling evidence that the speed of the VO₂ kinetics at the onset of exercise is limited by an oxidative enzyme inertia within the exercising muscles rather than by O₂ delivery to those muscles. This appears true also for the horse and dog but possibly not for a certain species of frog. Whereas there is a significant correlation between VO₂max and the speed of VO₂ kinetics among different species, it is possible to identify species or individuals within a species that exhibit widely disparate mass-specific VO₂max capacities but similar VO₂ kinetics (i.e., superlative human athlete and horse).

Keywords: maximal oxygen uptake; oxygen uptake dynamics; exercise; muscle contractions

Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>amplitude of VO₂ response</td>
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<tr>
<td>CP</td>
<td>critical power</td>
</tr>
<tr>
<td>DO₂</td>
<td>diffusive O₂ conductance</td>
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<tr>
<td>LT</td>
<td>lactate threshold</td>
</tr>
<tr>
<td>MRT</td>
<td>mean response time (time delay + time constant; denotes time to 63% of final response)</td>
</tr>
<tr>
<td>l-NAME</td>
<td>L-nitro-arginine methyl ester (inhibits NOS)</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>NOS</td>
<td>nitric oxide synthesis</td>
</tr>
<tr>
<td>PCR</td>
<td>phosphocreatine</td>
</tr>
<tr>
<td>Phase I</td>
<td>initial increase in VO₂ at exercise onset caused by elevated pulmonary blood flow (also called the cardiodynamic phase)</td>
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<tr>
<td>Phase II</td>
<td>exponential increase in VO₂ that is initiated when venous blood from the exercising muscles arrives at the lungs. Corresponds closely with muscle VO₂ dynamics</td>
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<tr>
<td>Phase III</td>
<td>steady-state VO₂ response present for moderate and heavy, but not severe, exercise</td>
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<tr>
<td>PO₂</td>
<td>partial pressure of O₂</td>
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<tr>
<td>RBC</td>
<td>red blood cell</td>
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<tr>
<td>TD</td>
<td>time delay</td>
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<tr>
<td>t</td>
<td>time</td>
</tr>
<tr>
<td>τ</td>
<td>time constant; time to 63% of final response</td>
</tr>
<tr>
<td>t½</td>
<td>half time; time to 50% of final response</td>
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Please note that, with the exception of the horse and human, kinetics data on the species presented herein have not been partitioned into a time delay and exponential components. Consequently, the overall response times are synonymous with MRT VO₂max.

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Introduction

This brief review adopts a comparative physiological approach to explore oxygen uptake (\(V\dot{O}_2\)) kinetics across extremely diverse species. The rate at which \(V\dot{O}_2\) adjusts to meet the new energy demand at the transition from one metabolic rate to another (i.e. \(V\dot{O}_2\) kinetics) in an individual or a given species represents a fundamental parameter of metabolic capacity and function that has an impact on exercise tolerance and performance. \(V\dot{O}_2\) kinetics are generally faster in fitter humans and animal species than in their sedentary or less fit counterparts as judged by their maximal \(V\dot{O}_2\) (\(V\dot{O}_2\)max). In humans, after exercise training, the speeding of \(V\dot{O}_2\) kinetics is usually associated with an increased \(V\dot{O}_2\)max. In contrast, decrements in \(V\dot{O}_2\)max that accompany chronic disease are typically associated with slowed \(V\dot{O}_2\) kinetics. Judicious selection of the poorly aerobic lungless salamander\(^1\) (\(V\dot{O}_2\)max < 10 ml min\(^{-1}\) kg\(^{-1}\)) and the Thoroughbred horse\(^2\) or deer mouse\(^3\) (\(V\dot{O}_2\)max = 160–220 ml min\(^{-1}\) kg\(^{-1}\)) permits analysis of the relationship between \(V\dot{O}_2\) kinetics and \(V\dot{O}_2\)max and the investigation of metabolic control over a much broader range of absolute and mass-specific \(V\dot{O}_2\)max values than possible within a single species (Figs 1–3). Given space restrictions, this review is not intended to encompass all species, but rather focuses on those that may best illustrate specific aspects of the physiological control of \(V\dot{O}_2\).

**What is \(\dot{V}O_2\) and what are \(\dot{V}O_2\) kinetics?**

The term ‘kinetics’ is defined as ‘the science of the action of force in producing or changing motion’ (Chambers English dictionary) and the study of \(\dot{V}O_2\) kinetics encompasses those physiological mechanisms responsible for the dynamic \(\dot{V}O_2\) response to exercise. The study of \(\dot{V}O_2\) and its regulation is important because oxidative metabolism is the principal means by which the human organism generates energy to do work in all but the most short-lived of activities. Factors such as the highest attainable \(\dot{V}O_2\) (\(\dot{V}O_2\)max), the \(\dot{V}O_2\) required to perform submaximal exercise (i.e. the economy or efficiency of exercise) and the rate at which \(\dot{V}O_2\) rises in the transition to an activity with a higher energetic requirement to reach the requisite steady-state or maximal level will all influence an individual’s tolerance to physical activity.

The body has an extraordinary capacity to increase its metabolic rate in response to energetic challenges. Other than when sleeping or being completely immobile, humans and animals are rarely in a metabolic steady state; rather, the individual shifts dynamically across a range of metabolic requirements. At the onset of movement or dynamic exercise such as running, the energetic requirements of the contracting muscles increase immediately with the first contraction in what has been termed a ‘stepwise’ fashion. However, as demonstrated in Fig. 1, the increase in

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**Subscripts**

- \(e\) extracellular
- \(i\) intracellular
- \(p\) primary component
- \(s\) slow component

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**Fig. 1** The dynamic profile of \(O_2\) uptake (\(\dot{V}O_2\)) in the Thoroughbred horse at the onset of heavy-intensity exercise. Time zero is exercise onset. The profile is very similar, albeit more rapid, than that of the human. Specifically, at exercise onset there is an initial cardiodynamic phase (Phase I) followed by the primary fast exponential increase (Phase II). \(A_c\), \(A_p\) and \(A_s\) denote the amplitudes of Phase I, Phase II and the slow component, respectively. \(TD_c\) and \(TD_s\) denote the time delays prior to the start of Phase II and the slow component, respectively. Adapted from Langsetmo et al.\(^4\)
pulmonary VO₂ does not follow a ‘stepwise’ response profile⁴. Rather, the response demonstrates considerable inertia and, depending on the health or fitness of the individual and the exercise intensity, may take from 2 to 15 min or more to achieve the steady-state value (Figs 1, 4 and 5). ‘Stepwise’ exercise tests, in which the running speed is increased abruptly from a baseline of rest or lighter exercise, allow the gathering of important information on the dynamic responses of pulmonary gas exchange to work-rate forcing functions. Measurement of VO₂ kinetics has become an important tool in evaluation of the extent of dysfunction and in some instances the mechanism behind that dysfunction in many major chronic disease conditions (e.g. heart failure, diabetes, emphysema)⁵.

The pulmonary VO₂ response following the onset of exercise has been well characterized⁶–⁸. At the onset of exercise, there is an early rapid increase that is typically initiated within the first breath (Phase I or cardiodynamic component, Fig. 1). This initial increase in Phase I has been characterized for modelling purposes as a delay (although there is an increased VO₂ within Phase I) that is followed by a rapid exponential increase in VO₂ (Phase II) with a time constant (τ) of some 20–45 s (in healthy humans) that drives VO₂ to the actual, or towards the initially anticipated, steady-state value (Phase III) within approximately 3 min. Phase I represents the O₂ exchange associated with the initial elevation of cardiac output and thus pulmonary blood flow. Phase II reflects the arrival at the lung of venous blood draining the exercising muscles (note that the Phase II VO₂ response is variously described as the ‘fast component’, the ‘primary component’ or the ‘fundamental component’ in the VO₂ kinetics literature). The pulmonary VO₂ kinetics in Phase II therefore largely reflects the kinetics of O₂ consumption in the exercising muscles, although there is a temporal lag between events at the muscle and those recorded at the lung⁹. For moderate-intensity exercise (i.e. below the lactate threshold, LT), the onset of Phase III corresponds to the point at which cardiac output plateaus and venous O₂ content reaches its nadir. At
higher exercise intensities, the attainment of a steady state might be delayed or absent.

In the transition from rest or unloaded exercise to a work rate with a \( \dot{V}O_2 \) requirement below that at the LT, the vertical distance between the actual \( \dot{V}O_2 \) at a given moment and that required in the steady state represents the energy requirement that must be met from energy stores within the muscle. These stores consist principally of energy released through phosphocreatine (PCr) hydrolysis and anaerobic glycolysis, with a small contribution from \( O_2 \) stores (myoglobin, venous blood). The total \( O_2 \) equivalent of the shaded area in Fig. 4 is termed the \( O_2 \) deficit. As can be appreciated in that figure, the absolute size of this deficit is the product of the increase in \( \dot{V}O_2 \) across the transient and the speed of the \( \dot{V}O_2 \) response denoted by the time constant \( \tau \) of the \( \dot{V}O_2 \) response from the onset of exercise: \( \text{O}_2 \text{ deficit} = \Delta \dot{V}O_2 \times \tau \), where \( \Delta \dot{V}O_2 \) is given in \( \text{L min}^{-1} \) and \( \tau \) in fractions of a minute. Thus, for a given \( \Delta \dot{V}O_2 \), the faster the \( \dot{V}O_2 \) response (smaller \( \tau \)), the smaller is the \( O_2 \) deficit that will be incurred. In contrast, extremely unfit or unhealthy individuals (i.e. poorly aerobic animal species or humans) will have a very slow response (larger \( \tau \)) and will incur a high \( O_2 \) deficit and thus exhibit a greater degree of intracellular perturbation (increased lactic acid production and PCr degradation, Fig. 4). Slow \( \dot{V}O_2 \) kinetics mandate a greater depletion of intramuscular [PCr] and a greater rate of glycogenolysis leading to greater accumulation of lactate and

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**FIG. 4** Schematic demonstration of the effect of altering the speed of \( \dot{V}O_2 \) kinetics \( (\tau) \) on the \( O_2 \) deficit. Time zero is exercise onset. The range of \( \tau \) values given represents those measures in a racehorse \((10 \text{s})\), sedentary human \((45 \text{s})\) and a cardiac patient \((90 \text{s})\). The shaded area represents the size of the \( O_2 \) deficit for \( \tau = 10 \text{s} \). Note that this area becomes systematically larger as \( \dot{V}O_2 \) kinetics become slower (increasing \( \tau \)).

**FIG. 5** Schematic representation of the \( \dot{V}O_2 \) response to constant work-rate exercise in the moderate (below the lactate threshold), heavy (above the lactate threshold) and severe (above the asymptote of the power–time relationship for high-intensity exercise or critical power) exercise domains. Time zero is exercise onset. For clarity, the \( \dot{V}O_2 \) response occurring at exercise onset (Phase I, see Fig. 1) has been omitted. Note that for moderate-intensity exercise, \( \dot{V}O_2 \) increases mono-exponentially (Phase II) to the steady state (plateau, Phase III), which in healthy subjects is achieved within 3 min. In contrast, for heavy- and severe-intensity exercise, the steady state is either delayed (heavy) or not achieved (severe) because of the slow component (shaded area) which occurs only above the lactate threshold. The slow component elevates \( \dot{V}O_2 \) above that predicted for the work rate. Within the severe exercise domain, \( \dot{V}O_2 \) achieves its maximum value \( (\dot{V}O_{2\text{max}}) \) at or before fatigue.
protons and a greater utilization of the finite intramuscular glycogen reserves, all factors which predispose the individual to a reduced exercise tolerance.

**Exercise intensity domains**

As intimated above, the metabolic and gas exchange responses to exercise can be defined in relation to a number of identifiable exercise intensity domains, namely: moderate, heavy, severe and extreme (Fig. 5).

**Moderate exercise** encompasses all work rates that are below the LT. For moderate-intensity exercise, blood lactate is not elevated and steady-state (Phase III) \( VO_2 \) increases in close proportion to the running speed or work rate. Within the moderate intensity domain, the speed of the Phase II \( VO_2 \) kinetics has been shown generally to be invariant with work rate, but is accelerated by exercise training and slowed by ageing, prolonged inactivity and/or chronic diseases.

**Heavy exercise** comprises those work rates lying between the LT and the asymptote of the power–duration curve for high-intensity exercise, i.e. the critical power (CP). Exercise in the heavy intensity domain results in an elevated but stable blood [lactate] over time such that there is a balance between the rate of appearance of lactate in the blood and the rate of its removal from the blood. The upper boundary for the heavy domain is defined as the highest \( VO_2 \) at which blood lactate (and \( VO_2 \)) can be stabilized and typically occurs mid-way between the speed or work rate that elicits LT and \( VO_{2\max} \) on a standard incremental test. There is some evidence that the Phase II \( VO_2 \) kinetics may be slowed at the onset of heavy-compared with moderate-intensity exercise, although the bulk of the available literature has not demonstrated a significant difference from the response to moderate-intensity exercise. Exercise in the heavy domain evidences a ‘slow component’ of the \( VO_2 \) kinetics that becomes apparent after approximately 2 min following exercise onset and is superimposed upon the primary \( VO_2 \) response (Figs 1 and 5). This slow component elevates the \( VO_2 \) above rather than towards the \( VO_2 \) that would be calculated for a particular running speed or work rate by extrapolation of the \( VO_2 \) response to moderate exercise. Depending on the characteristics of the slow component, achievement of the steady-state \( VO_2 \) may be delayed by 10-15 min or more.

**Severe exercise** comprises those work rates lying between CP and \( VO_{2\max} \) as assessed during an incremental exercise test in which fatigue is reached in ~10 min. In the severe domain, the slow component causes \( VO_2 \) to increase to its maximum and blood [lactate] rises inexorably until the exercise is terminated. For the very highest work rates in the severe domain, no slow component is evident and \( VO_2 \) may rise with a close to mono-exponential profile that is truncated at \( VO_{2\max} \). However, for all work rates in the severe domain, when exercise is continued to the point of exhaustion, \( VO_{2\max} \) is attained. Consequently, the severe intensity domain presents a broad range of running speed or work rate at which it is possible to attain \( VO_{2\max} \).

Given the finite kinetics of \( VO_2 \), it is inevitable that some work rates are so high that fatigue intervenes before \( VO_{2\max} \) can be achieved. This domain has recently been termed ‘extreme exercise’. Fitter individuals will exhibit faster \( VO_2 \) kinetics and it would therefore be expected that such individuals would require less time at these extreme work rates to reach \( VO_2s \), approaching their \( VO_{2\max} \).

**Model characterization of \( VO_2 \) kinetics**

It has been established that the \( VO_2 \) response in Phase II is essentially exponential in character. An exponential response of a system is consistent with the existence of an initial ‘error signal’ (i.e. a difference between the instantaneous and required value, in this case of \( VO_2 \)) and feedback control of the response until the error signal is eliminated. An exponential function has an amplitude and a time constant (\( \tau \)); the equivalent of the reciprocal of the rate constant, \( 1/\beta \) that reflects the time required for the attainment of 63% of the total amplitude. The exponential nature of the \( VO_2 \) response in Phase II can therefore be described with the following equation:

\[
\dot{VO}_2(t) = \dot{VO}_2(b) + A(1 - e^{-(t-TD)/\tau}),
\]

where \( \dot{VO}_2(t) \) is the \( VO_2 \) at any point in time, \( \dot{VO}_2(b) \) is the baseline \( VO_2 \) before the commencement of the square-wave transition to a higher work rate, \( A \) is the steady-state amplitude of the \( VO_2 \) response, and \( (1 - e^{-(t-TD)/\tau}) \) is the exponential function describing the rate at which \( VO_2 \) is rising towards the steady-state amplitude. In this exponential function, \( t \) is time, TD is the time delay before the start of the exponential term and \( \tau \) is the time constant. Therefore, for a \( \tau \) of 30 s: 63% of the response amplitude is attained after 30 s; 86% of the response amplitude is attained after 60 s (i.e. 2 \( \times \) \( \tau \)), 1.0 - 0.63 = 0.37; (0.37 \( \times \) 0.63) + 0.63 = 0.86; 95% of the response amplitude is attained after 90 s (3 \( \times \) \( \tau \)); 98% of the response amplitude is attained after 120 s (4 \( \times \) \( \tau \)); and >99% of the response amplitude is attained after 150 s (5 \( \times \) \( \tau \)). It is generally considered that the response is essentially complete after four time constants (4\( \tau \)) have elapsed.

The exponential increase of pulmonary \( VO_2 \) following the onset of muscular exercise is essentially a ‘mirror image’ of the exponential reduction of intramuscular [PCr], once the ‘muscle to mouth’ transport delay time has been accounted for. This strongly suggests that muscle \( VO_2 \) kinetics is principally
under feedback control from one or more of the products of high-energy phosphate splitting.

For heavy- and severe-intensity exercise, an additional exponential term is required for satisfactory fitting of the VO₂ on-response following the completion of Phase I:

\[ VO₂(t) = VO₂(b) + A_p(1 - e^{-(t-TD_p)/τ_p}) + A_s(1 - e^{-(t-TD_s)/τ_s}) \]

where \( A_p \) and \( A_s \) are the amplitudes of the VO₂ primary and slow components, respectively; \( TD_p \) and \( TD_s \) are the independent time delays before the commencement of the primary and slow components, respectively; and \( τ_p \) and \( τ_s \) are the time constants for the primary and slow components, respectively (see Fig. 1).

Application of rapidly responding gas analysers and development of high-capacity (\( \sim 10^4 \) min\(^{-1} \)) flow-by or bias-flow systems has facilitated resolution of VO₂ kinetics in the running horse with a fidelity approaching that possible in humans. The results of these experiments are detailed below and suggest that whilst the magnitude and speed of the VO₂ response are very different from those found in humans, there are substantial commonalities between these two species. These include the presence of:

1. a discernible Phase I (cardiodynamic) and Phase II (primary component) response and
2. a VO₂ slow component that arises within 1-2 min after increasing running speed within the heavy or severe exercise intensity domains.

A further surprising feature of the on-transient VO₂ response to moderate-intensity exercise in the horse is preservation of the mono-exponential kinetics. This response occurs despite the presence of a massive (\( \sim 14 \) kg) spleen that contracts at exercise onset, resulting in an almost doubling of arterial haemoglobin concentration and therefore arterial O₂-carrying capacity within 20-60 s.

It is beyond the scope of this review to detail the specific anatomy and physiology of O₂ transport among all species presented herein. However, where pertinent to the central issue of understanding the possible control mechanisms for VO₂ kinetics, discrete anatomical features will be explored briefly.

**Mammals**

**Equine**

The equine (Equus caballus, Fig. 2) athlete is distinctive in that it has been bred for its running performance for over 6000 years. This has ultimately resulted in an animal (horse and pony) with a remarkably high oxidative metabolic capacity. From several perspectives, the horse may well be the most impressive aerobic athlete on the planet. In concert with the relationship between mass-specific VO₂max and the speed of the VO₂ kinetics at exercise onset demonstrated in humans, the Thoroughbred horse is capable of achieving maximal VO₂ values near 200 ml min\(^{-1} \) kg\(^{-1} \) and the speed of the VO₂ kinetic response is correspondingly rapid (Figs 1 and 3). VO₂ kinetics were first measured in the pony in 1984 and subsequent investigations have studied VO₂ kinetics in Standardbred, Thoroughbred and Quarter horses. However, it was not until recently that a rigorous investigation was undertaken to formally characterize equine VO₂ kinetics.

**VO₂ kinetics in the horse**

While previous investigations had studied VO₂ kinetics in equids, prior to the work of Langsetmo et al. VO₂ was not measured rapidly enough to accurately assess VO₂ kinetics. By obtaining gas-exchange data on a second-by-second basis and studying VO₂ kinetics strictly within the moderate and heavy work domains while horses were run on a high-speed treadmill, several principal features of the response were defined (Fig. 1). First, in the moderate domain, VO₂ kinetics were well fit by a two-phase exponential model (cardiodynamic + primary phases), the primary phase of which was very rapid (\( τ \sim 10 \) s; see Figs 6 and 7 for horse and human comparison). Second, for heavy exercise, the primary-phase \( τ \) was still quite rapid (i.e. \( \sim 21 \) s) but markedly slowed compared with that during moderate running. Additionally, heavy exercise was attended (with one exception in that investigation) by a VO₂ slow component which occurred \( \sim 135 \) s after the onset of exercise.

The VO₂ kinetics reported by Langsetmo et al. have subsequently been replicated by Geor et al. In that investigation, in which Standardbred horses were transitioned almost instantaneously from a walk to the speed of the VO₂ kinetics at exercise onset demonstrated in humans, the Thoroughbred horse is capable of achieving maximal VO₂ values near 200 ml min\(^{-1} \) kg\(^{-1} \) and the speed of the VO₂ kinetic response is correspondingly rapid (Figs 1 and 3). VO₂ kinetics were first measured in the pony in 1984 and subsequent investigations have studied VO₂ kinetics in Standardbred, Thoroughbred and Quarter horses. However, it was not until recently that a rigorous investigation was undertaken to formally characterize equine VO₂ kinetics.

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As depicted in Fig. 7, VO₂ onset kinetics in the phases are similar between the horse and human. Features of the VO₂ on-kinetic response (i.e. three distinct human. Again, in the heavy domain (Fig. 7), key features of the VO₂ on-kinetic response to an elevation in metabolic demand are remarkably similar to that in man. It should be noted that exceptional human athletes such as the World record holder in the marathon, Paula Radcliffe, have VO₂ kinetics that may resemble those seen in Figs 6 and 7 for the horse.

Comparison of the horse and human

Despite the capacity to reach maximal relative VO₂ values two- to three-fold greater than humans, the rapidity with which the horse responds energetically at the transition to higher running speeds is generally far superior to that of its human counterpart (Figs 3, 6 and 7). Nevertheless, key underlying features of the equine VO₂ kinetic response to an elevation in metabolic demand are remarkably similar to that in man. It should be noted that exceptional human athletes such as the World record holder in the marathon, Paula Radcliffe, have VO₂ kinetics that may resemble those seen in Figs 6 and 7 for the horse.

Figure 6 demonstrates VO₂ kinetics normalized to end-exercise values in a typical running horse and a typical human performing cycle ergometer exercise across the transition to moderate-intensity exercise. While both the horse and human have proportionately sized cardiodynamic- and primary-phase amplitudes, the most striking feature is how much more rapid the rise in VO₂ is in the horse compared with the human. Again, in the heavy domain (Fig. 7), key features of the VO₂ on-kinetic response (i.e. three distinct phases) are similar between the horse and human. As depicted in Fig. 7, VO₂ onset kinetics in the Thoroughbred horse are significantly faster than those reported in man. However, Langsetmo et al. demonstrated a clear slowing of the equine VO₂ on-kinetic response when running at speeds in the heavy versus moderate domain. Whether this slowing of the VO₂ kinetics from moderate to heavy exercise occurs in humans is controversial. Specifically, many studies have demonstrated that the speed of the primary VO₂ amplitude rise is unchanged as work intensity increases from moderate to heavy in humans. In contrast, several investigations also studying human subjects have reported slowed VO₂ on-transient kinetics in response to heavy compared with moderate exercise. It is certainly possible that oxidative capacity and/or fitness level of the subjects may play an important role in these disparate findings. However, with respect to the horse, its reliance on a contractile spleen to increase O₂ delivery via an augmented influx of red blood cells (RBCs) during periods of increased metabolic demand may place a constraint on the speed of VO₂ kinetics in the heavy domain that is unique to this species. There may also be fibre-type recruitment profiles that may slow the VO₂ response to heavy exercise that cannot be discounted at the present time. As shown in Figs 1 and 7, a clear slow component is evidenced in the equine profile, the magnitude of which is proportionately similar to that seen in humans. Interestingly, Langsetmo et al. reported that one of the horses did not display a slow component during heavy-domain running. It is also true that some humans do not evidence a discernible slow component during heavy exercise.

Why are VO₂ kinetics so fast in the horse?

As mentioned previously, the Thoroughbred racehorse is a superlative model of mammalian oxidative function. The extraordinary capacity to deliver and utilize O₂ culminates, ultimately, in prodigious maximal VO₂ values and also brings the lungs to the point of failure (exercise-induced pulmonary haemorrhage and arterial hypoxaemia/hypercapnia). This demands a finely tuned integration of pulmonary, cardiovascular and muscle function. Specifically, the horse has a large heart-to-body ratio, which is capable of generating cardiac outputs in excess of 300 l min⁻¹ or 600 ml min⁻¹, kg⁻¹. To place this in perspective, one would be hard-pressed to get half this flow of water (let alone blood with a haematocrit of ~70%) out of a high-pressure hose with the diameter of an equine atrioventricular valve! Next, the pulmonary system must be capable of achieving alveolar ventilation rates that will facilitate oxygenation of the cardiac output in order to maintain arterial O₂ saturation. To this end, during strenuous exercise the horse is capable of total ventilations in excess of 1700 l min⁻¹ (estimated alveolar ventilation >1400 l min⁻¹). However, despite these ventilatory rates, severe arterial hypoxaemia nearing 60 mmHg
is incurred during intense running\textsuperscript{39,40}. In addition to the short RBC transit times in the pulmonary capillaries, one factor contributing to this hypoxaemia is the fact that the blood–gas barrier has to be thicker (\textasciitilde 1 \textmu m) than that of other mammals (\textasciitilde 0.3 \textmu m in man). This additional thickness helps protect against the very high pulmonary arterial pressures, which may reach values in excess of 120 mmHg during maximal exercise. However, despite the thicker blood–gas barrier that must impede gas exchange, racehorses do experience exercise-induced pulmonary haemorrhage at the gallop to an extent that exceeds that found in any other species. Thus, the blood–gas barrier is effectively thickened by plasma exudates and RBCs in the alveolar space. In addition and as mentioned above, the horse (as well as some canine breeds) has a contractile spleen that is capable of increasing the number of circulating RBCs and dramatically augmenting O\textsubscript{2}-carrying capacity\textsuperscript{23,41}. Finally, in the Thoroughbred racehorse muscle comprises \textasciitilde 50\% of the body mass and that muscle contains a dense capillary network and a correspondingly high mitochondrial volume density\textsuperscript{42,43}.

Applications

It is apparent that the racehorse has evolved into a muscle, heart and lung machine capable of performing athletically at the highest level. As the horse adapts well to treadmill running and can tolerate headgear necessary to gather gas-exchange data as well as arterial and venous lines even while running at speeds well in excess of 30 miles h\textsuperscript{-1}, the horse represents an excellent model to study control of VO\textsubscript{2} kinetics and provides insights germane to the understanding of metabolic control and performance in humans and other species.

For example, the horse was used recently to elucidate issues key to understanding the mechanistic bases of the metabolic inertia manifested at exercise onset. Horses performed heavy-intensity exercise on a treadmill under control and systemic nitric oxide synthase (NOS) inhibition conditions (L-nitro-arginine methyl ester \textit{L-NAME}). Whilst nitric oxide (NO) is necessary to attain peak cardiac outputs and systemic O\textsubscript{2} delivery in the horse\textsuperscript{39}, it also inhibits mitochondrial oxygen consumption by binding to cytochrome c oxidase. Kindig \textit{et al.}\textsuperscript{44} demonstrated, in the face of a reduced cardiac output and presumably muscle blood flow, that VO\textsubscript{2} kinetics was speeded significantly with NOS inhibition. Additionally, NOS inhibition resulted in an earlier onset of the slow component. These findings suggest that NO inhibition of the mitochondrial O\textsubscript{2} consumption may contribute importantly to the mitochondrial inertia seen at the transition to increased metabolic demands. Interestingly, at the onset of heavy exercise, NOS inhibition sped VO\textsubscript{2} kinetics to values close to those observed during moderate-intensity running. Subsequent research, shown in Fig. 8, demonstrated that NOS inhibition sped VO\textsubscript{2} kinetics \textasciitilde 30\% at the onset of moderate running (NOS inhibition \textit{t} = 12 s versus control \textit{t} = 18 s)\textsuperscript{45}. These findings have been confirmed in humans\textsuperscript{46,47} and collectively demonstrate that the rapidity of VO\textsubscript{2} kinetics at exercise onset can be enhanced by removing the NO brake on mitochondrial function.

Dog

The domestic dog (\textit{Canidae}), like the horse, represents another extreme athlete, with VO\textsubscript{2max} values almost double that of humans (i.e. \textasciitilde 100 ml O\textsubscript{2} min\textsuperscript{-1} kg\textsuperscript{-1})\textsuperscript{48}. In addition, the dog as an experimental modality has

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Fig_8}
\caption{Effect of L-nitro-arginine methyl ester (L-NAME; an inhibitor of nitric oxide synthase) administration on VO\textsubscript{2} kinetics. Time zero is exercise onset. L-NAME alleviates the NO inhibition of mitochondrial O\textsubscript{2} consumption, thereby reducing the metabolic inertia at exercise onset and speeding VO\textsubscript{2} kinetics. Adapted from Kindig \textit{et al.}\textsuperscript{45}}
\end{figure}
played a pivotal role in filling the void between isolated single-fibre (usually amphibian) and whole-organism (e.g. human) preparations. Specifically, canine VO₂ kinetics has been studied both within the whole body and in surgically isolated but otherwise intact isolated muscle groups. Whereas pulmonary and muscle VO₂ can be measured simultaneously in the human⁹,⁴⁹,⁵⁰, the experimental conditions (e.g. blood O₂ content, blood flow dynamics) can be controlled to a greater extent in dog preparations. Accordingly, a substantial portion of our understanding of the regulation of VO₂ kinetics has stemmed from research using the dog.

**Whole-body versus isolated muscle preparations**

VO₂ kinetics has been studied extensively in dog locomotory muscle groups⁵¹–⁵⁴. However, few studies have focused on quantifying pulmonary VO₂ kinetics in conscious, exercising dogs. One such study was performed by Marconi *et al.*⁵⁵ and was the first to quantify the VO₂ response at the onset of ‘square-wave’ exercise bouts in conscious dogs. With an experimental set-up similar to that used in humans (i.e. respiratory mask connected to a mass spectrometer), these researchers subjected dogs to different work intensities (constant-工作 intensity connected to a mass spectrometer), these researchers similar to that used in humans (i.e. respiratory mask connected to a mass spectrometer), these researchers subjected dogs to different work intensities (constant-工作 intensity connected to a mass spectrometer). These investigators demonstrated that the dog has extremely rapid VO₂ on-kinetics with τ ≈ 20 s, apparently independent of work load at least up to 12 km h⁻¹ on a 10% incline. Interestingly, there was no discernible slow component for any of the runs, even those presumed to be in the heavy/severe intensity domain. At similar relative exercise intensities, horses and humans demonstrate a pronounced slow component. One important finding in Marconi *et al.*’s investigation⁵⁵ was the similarity between whole-body pulmonary VO₂ on-kinetics and those found in the dog isolated gastrocnemius complex (pulmonary VO₂, τ ≈ 20 s⁵⁵; isolated gastrocnemius VO₂, τ = 15 – 17 s⁵¹), thereby substantiating that pulmonary VO₂ kinetics is an accurate representation of that occurring within the active musculature. This finding corroborated the work of Casaburi *et al.*⁵², who, by measuring concomitantly pulmonary and muscle VO₂ in anaesthetized dogs, demonstrated no difference in VO₂ on-kinetics between pulmonary and muscle (both ~17 s) during electrical stimulation.

**Dog isolated muscle VO₂ kinetics**

Individual surgically isolated canine muscles or muscle groups (e.g. gastrocnemius–plantaris complex) in the dog have been used to study muscle energetics since the early 20th century.⁵⁶ One particularly attractive feature of this experimental model is that it allows a rapid and precise control of the blood flow into the muscle and alteration of the physiological properties (e.g. gas contents) of that blood. Specifically, the investigator can manipulate O₂ delivery independently of O₂ uptake⁵³,⁵⁴ or vice versa (see Grassi *et al.*⁵⁷) to elucidate the mechanisms governing the rate of VO₂ increase. For example, using the dog isolated gastrocnemius complex (comprised of gastrocnemius–plantaris muscles) first described by Stainsby and Welch⁵⁸, Grassi *et al.* have demonstrated that muscle VO₂ on-kinetics for moderate-intensity contractions (yielding <60% VO₂max) are not affected by:

1. An increase in peripheral O₂ diffusion evoked via hyperoxia or hyperoxia concomitantly with a rightward shift of the haemoglobin–O₂ dissociation curve (via the drug RSR-13). Both of these paradigms act to increase the driving force for O₂ from the capillary to the myocyte, thus facilitating enhanced transcapillary O₂ flux. The VO₂ kinetics was not altered by these manipulations, with τ being 24–26 s under all conditions⁴⁴.

2. A faster adjustment of O₂ delivery at exercise onset evoked by setting the pre-contracting blood flow to the same values attained during steady-state contractions. VO₂ kinetics was unchanged at τ = 17 – 19 s for both a spontaneous and pre-adjusted increase in blood flow to the muscle⁵⁵.

As can be seen from these two latter series of experiments, dog muscle demonstrates rapid VO₂ kinetics that is not limited by O₂ delivery at least in the moderate intensity domain.

**Mechanisms responsible for rapid VO₂ on-kinetics in the dog**

There are many adaptations in the dog that contribute to rapid VO₂ kinetics. However, it is evident that the dog enjoys an extremely high mitochondrial volume density in most locomotory muscles⁵⁹. Moreover, the kinetics of blood (and therefore O₂ delivery to these muscles is astonishingly fast and, as in most models considered, actually precedes the increase in VO₂.

**Rodents**

Compared with the horse and dog, very little is known about pulmonary VO₂ kinetics in rodents (e.g. mice and rats). Although VO₂ steady states can be measured with high fidelity in both rats⁴⁸,⁶⁵ and mice⁶⁴, it is much more difficult to measure the rate of change or the dynamics of VO₂ in these animals. Specifically, VO₂ is usually measured in small animals by placing them in a relatively large chamber, and subsequently sampling the gases (CO₂ and O₂) during steady states. Therefore, because of the gross mismatch of tidal volume (extremely low in small rodents) to chamber volume size (thereby increasing the time required for proper mixing of the gases), the fidelity of VO₂ measurements during non-steady states is greatly reduced. Nevertheless, Chappell has managed,
through the elegant design of a suitable open-circuit flow system, to collect VO₂ kinetic data in the mouse. Thus, across the rest-to-running transition, the deer mouse (Peromyscus maniculatus) can increase its VO₂ with $\tau \approx 20-25$ s (Fig. 9). In addition to these rapid kinetics, an impressive VO₂max ($\sim 175$ ml O₂ min⁻¹ kg⁻¹) was measured. Apparently, in these creatures, the same very high VO₂max can be achieved by either exercise or cold exposure. This observation raises the intriguing possibility that the rapid VO₂ kinetics in the deer mouse may have resulted from environmental temperature challenges rather than exercise per se.

As in the case of the mouse, very few studies have measured VO₂ kinetics in the laboratory rat. It has been assumed, based on demonstrated high VO₂max values (70–80 ml min⁻¹ kg⁻¹)⁴⁸,⁶³, that the rat would display rapid VO₂ kinetics (as discussed in the Introduction; in many instances $\tau$ of VO₂ kinetics is proportional to VO₂max). However, it was only recently that VO₂ kinetics in the rat, or more specifically rat muscle, was described. Behnke et al.⁶⁵ demonstrated that, across the rest-to-electrically induced contractions, rat skeletal muscle (i.e. spinotrapezius) VO₂ follows a mono-exponential time course to the steady state with $\tau < 20$ s (Fig. 10). This was the first study within muscle to demonstrate that VO₂ increases almost immediately (i.e. no apparent time delay) at the onset of contractions, which is consistent with current concepts of a phosphate-linked metabolic control system (see, e.g., Whipp and Mahler²²). In addition, the muscle studied in that investigation (i.e. spinotrapezius) has only a relatively modest oxidative capacity (measured by citrate synthase activity; $\sim 14$ μmol min⁻¹ g⁻¹ in spinotrapezius)⁶⁶. Therefore, during treadmill exercise, where muscles with high oxidative capacities are recruited (e.g. red gastrocnemius; citrate synthase activity $\sim 36$ μmol min⁻¹ g⁻¹), VO₂ kinetics would be expected to be even more rapid than that demonstrated in the spinotrapezius, although this has not yet to be documented. In the future, it would be important to be able to measure and understand the control of VO₂ dynamics in the laboratory rat (and mouse) because many of the major chronic diseases that affect humans (e.g. diabetes and chronic heart failure) can be surgically, pharmacologically or even genetically induced in these animals.

### Invertebrates and reptiles

As noted throughout this text, the majority of VO₂ dynamics studies have been performed upon mammals. However, arthropods (e.g. insects and crustaceans) comprise the largest and most diverse group of animals on earth. Surprisingly, given their numerical superiority and capacity for harming mankind (locusts, mosquitoes, fruit flies) or helping mankind (bees, leeches, crabs), little is known about the aerobic responses to any form of locomotion within this phylum (i.e. Arthropoda). Nevertheless, novel and inventive experimental techniques have been developed to study the metabolic responses of a few select species such as the crab and cockroach. Specifically, the ghost crab (Ocypode guadichaudii; Fig. 11a), has a single-chambered heart, and relies upon gill chambers for O₂ extraction after inspiration (via openings on legs) of either water or air. Both of these structural adaptations could pose serious limitations to O₂ uptake and delivery. In humans, O₂ is drawn into the lungs where it diffuses across an extremely thin blood-gas barrier into the circulation. However, in the crab, O₂ must diffuse through a chitin layer of the gills that has a diffusive conductance for O₂ that is much less (i.e. greater resistance to diffusion) than that of the human blood-gas interface. Indeed, McMa-
hon67 proposed that it is this chitin layer which poses the major limitation to the rate of O₂ diffusion into the blood. Combined with the sluggish increase in heart rate at the onset of exercise68, it is not surprising that V˙O₂ kinetics at exercise onset is slow in this species. Nevertheless, ghost crabs do exhibit a V˙O₂ response to treadmill exercise that is qualitatively similar to that of mammals, i.e. a mono-exponential increase to a steady state (Fig. 11b)69. However, the half time (t ᵃ/₂) of this response averages around 100 s, corresponding to t = 144 s (i.e. t = t₁/₂ ÷ 0.693 for a first-order reaction) at a velocity of 0.28 km h⁻¹, running sideways. It should be mentioned that this particular species appears to be an exception amongst crabs, as the majority of these creatures that have been studied exhibit even slower V˙O₂ dynamics68,70.

Amongst those species in which V˙O₂ dynamics and V˙O₂max have been studied, the lungless salamander (Platodon jordani) possibly represents the lower extreme of aerobic function. These animals must rely on their skin for the exchange of respiratory gases. Indeed, the lungless salamander has been studied extensively as a model of diffusion limitation71,72. With respect to O₂ uptake, this reptile, which normally performs rapid, sprint-type exercise that is anaerobic in nature, demonstrates a disappointingly low V˙O₂max of ~7–8 ml min⁻¹ kg⁻¹. Given this low aerobic capacity, it should not be surprising that the V˙O₂ on-kinetics for this animal is extremely slow, i.e. τ ≈ 180 s. From one perspective, the lungless salamander may be likened to the patient with severe lung disease who exhibits a substantial diffusion limitation to O₂ uptake.

**Amphibians**

Within the amphibian class, it has typically been the anuran order (frogs and toads that lack a tail) in which problems related to metabolic control have been studied. One particular challenge for measuring V˙O₂ kinetics during locomotory activity in frogs and toads is that they move on land by means of saltatory movement, which means that they hop rather than walk or run. Notwithstanding this impediment, Walton and Anderson73 measured V˙O₂ at the onset of hopping activity in Fowler's toad (Bufo woodhousei fowleri) (Fig. 12). Fowler's toad has a V˙O₂max of ~20 ml min⁻¹ kg⁻¹ and, according to the relationship shown in Fig. 3, very slow V˙O₂ kinetics is to be expected. From the responses in Fig. 12 we have calculated τ of 4.24 and 6.72 min for transitions to hopping at 0.09 and 0.45 km h⁻¹, respectively.

The amphibian cardiorespiratory system does not appear to have been designed to support either rapid or substantial increases in oxidative phosphorylation (V˙O₂). However, key features within amphibian skeletal muscle make it excellent for the study of metabolic control. First, individual muscle fibres are relatively large compared with human or rodent muscle cells, individual myocytes can easily be separated into distinct fibre types and amphibian muscle can possess quite high mitochondrial volume densities. Second, anuran muscle lacks myoglobin and thus, in accordance with Fick's law of diffusion,
Some of the first skeletal muscle \(\dot{V}O_2\) kinetics data for many early as well as current studies of muscle fibres, have made these animals the model of choice for measuring PO2 essentially instantaneously and keeping the rise in \(\dot{V}O_2\) following the contraction as 'immedi-
tations'. Using phosphorescence quenching to a series of repetitive isometric tetanic contrac-
tions in isolated X. laevis muscles, Nagesser measured the rise and fall in \(\dot{V}O_2\) following 5–10 s tetanic con-
trations with mono-exponential kinetics (\(t^\infty\)). These advantages, plus the overall robustness of anuran muscle and single muscle fibres, have made these animals the model of choice for many early as well as current studies of muscle function and metabolic control.

**Whole muscle**

Some of the first skeletal muscle \(\dot{V}O_2\) kinetics data were collected over 75 years ago. Fenn measured the rise and fall in \(\dot{V}O_2\) following 5–10 s tetanic contrac-
tions in isolated semitendinosus of the English frog (Rana pipiens). \(\dot{V}O_2\) was calculated by measuring the fall in \(O_2\) in a stirred and sealed chamber. Given that the chamber volume was large and the response time of the \(O_2\)-measuring device long, Fenn described the rise in \(\dot{V}O_2\) following the contraction as 'immedi-
te'. More recently, Mahler has utilized isolated frog muscles to demonstrate that the muscle \(\dot{V}O_2\) control is a linear, first-order process. Specifically, he demonstrated that \(\tau\) for \(\dot{V}O_2\) kinetics during recovery from differ-
ning periods of tetanic contraction was invariant with the metabolic demand.

**Single myocytes**

The large, easily fibre-typed, robust frog myocytes can be isolated with tendons intact allowing for concomi-
tant measurement of metabolic variables and force. Furthermore, studying the single myocyte removes many confounding factors associated with fibre (type) recruitment and \(O_2\) delivery that are present when studying intact muscles. To our knowledge, Nagesser et al. performed the first measurements of \(\dot{V}O_2\) in single frog (African clawed frog, Xenopus laevis) myocytes at the onset of contractions. While the kinetics per se were not formally characterized, their measurements revealed that the \(\dot{V}O_2\) response at the onset and offset of contractions was quite rapid in the highly oxidative type III and markedly slower in the least oxidative type I myocyte. Most recently, \(\dot{V}O_2\) kinetics have been measured in single isolated X. laevis lumbrical muscle myocytes during a series of repetitive isometric tetanic contrac-
tions. Using phosphorescence quenching to measure \(\dot{V}O_2\) essentially instantaneously and keeping the chamber dead space to a minimum, these studies revealed that \(\dot{V}O_2\) increased at the onset of contrac-
tions with mono-exponential kinetics (\(\tau \approx 12\, s\)).

Whilst it is obviously challenging to measure \(\dot{V}O_2\) kinetics in single myocytes, this technique is proving valuable in the study of the key issues associated with metabolic control at exercise onset. Specifically, the heated contention regarding whether \(\dot{V}O_2\) kinetics is limited by \(O_2\) delivery to the muscle or metabolic inertia within the myocytes themselves can be addressed in single myocytes. For example:

1. Kindig et al. demonstrated that progressively increasing the extracellular \(\dot{V}O_2\) from 20 to 60 mmHg did not alter the initial speed of the fall in \(\dot{V}O_2\) starting with the same second of contraction onset, suggesting that an extra-
cellular \(\dot{V}O_2\) of 20 mmHg provides a sufficient driving force that does not compromise \(\dot{V}O_2\) kinetics.

2. The creatine kinase-catalysed breakdown of PCr is believed to play an important role in maintaining sufficient energy for contraction at the onset of work and the hypothesis that this reaction contributes to the metabolic inertia evidenced at exercise onset was tested. When creatine kinase was acutely inhibited pharmacologically, the fall in \(\dot{V}O_2\) at contractions onset was markedly speeded compared with matched control trials. This finding demonstrates that the creatine kinase reaction contributes to the ‘metabolic inertia’ seen at exercise onset.

3. \(\dot{V}O_2\) kinetics is faster in highly oxidative myocytes than in their low oxidative counterparts at equivalent extracellular \(\dot{V}O_2\) values.

What clearly remains to be resolved in amphibian muscle is the anomaly between findings at the single isolated myocyte versus those of the whole exercising animal. Specifically, single myocytes may evidence fast \(\dot{V}O_2\) kinetics whereas those for the whole animal is exorbitantly slow (Fig. 12). These findings are certainly not consistent with amphibian \(\dot{V}O_2\) kinetics being limited by oxidative enzyme inertia within the exercising muscles. It is possible, however, that akin to disease conditions that limit muscle \(\dot{O}_2\) delivery in humans and other mammals, the amphibian pulmonary and cardiovascular systems operate so sluggishly that their whole-body \(\dot{V}O_2\) kinetics is limited by an inability to deliver \(\dot{O}_2\) in sufficient quantity to utilize the inher-
ently rapid potential of myocyte \(\dot{V}O_2\) kinetics in some myocytes.

**Conclusions**

Within the animal kingdom, the broad relationship between \(\dot{V}O_2\) kinetics and \(\dot{V}O_{max}\) demonstrated in humans is found across a range of \(\dot{V}O_{max}\) values approaching two orders of magnitude, from the aerobi-
cally pedestrian lungless salamander to the fleet Thor-
oughbred racehorse. Judicious selection of animal models within this range has provided compelling evi-
dence that, within healthy mammals, muscle and pul-
monary \(\dot{V}O_2\) kinetics are limited by processes within
Oxygen uptake kinetics in different species

the myocyte. Thus, removal of NO-mediated inhibition of mitochondrial function and creatine kinase inhibition both speed VO$_2$ kinetics. The amphibian may constitute an exception in that isolated frog myocytes exhibit markedly faster VO$_2$ kinetics than found in the intact, hopping animal. This finding suggests the presence, in the frog, of an upstream (i.e. O$_2$ delivery) limitation to VO$_2$ kinetics akin possibly to humans with cardiac or pulmonary dysfunction.

There is a marked paucity of applicable data on VO$_2$ kinetics in fish, diving mammals, birds and also different insect species. However, their specialized adaptations in response to unique environmental and energetic challenges will probably provide additional key insights into metabolic control and are worthy of future consideration. In addition, the present review may be justly criticized for lack of consideration of animal behaviours and also locomotory patterns that may impact on muscle energetics and thus VO$_2$ control. For example, it is by no means certain that the slow component of VO$_2$ kinetics is manifested frequently or even at all within the native habitat. Dogs hunting in packs and relying on persistence rather than sustained speed may either increase VO$_2$ as a function of speed during bipedal locomotion as do quadrupeds, may achieve great speeds and fast VO$_2$ kinetics without the necessity for engaging the slow component$^{1,2}$.

As with other lines of inquiry, it is evident that comparative physiological approaches can yield important original information regarding the control of VO$_2$ kinetics. This philosophy was espoused by the incomparable Knut Schmidt-Nielsen, who opined that, ‘For every physiological question, there is an animal model designed specifically to answer it.’

Acknowledgements

This review was adapted from Oxygen Uptake Kinetics in Sport, Exercise and Medicine by Jones and Poole$^5$, with kind permission from Routledge, London and New York. The authors acknowledge the substantial grant support from the National Institutes of Health, Heart, Lung and Blood Institute and also the American Quarter Horse Association. The excellent suggestions of the reviewers led to substantial improvements in this manuscript and are gratefully noted.

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