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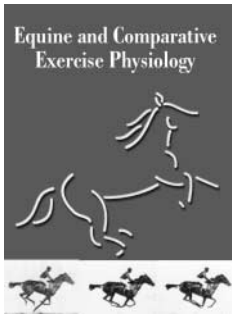

Oxygen uptake ($\dot{V}O_2$) kinetics in different species: a brief review

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Abstract

When a human begins to move or locomote, the energetic demands of its skeletal muscles increase abruptly and the oxygen (O_2) transport system responds to deliver increased amounts of O_2 to the respiring mitochondria. It is intuitively reasonable that the rapidity with which O_2 transport can be increased to and utilized by ($\dot{V}O_2$) the contracting muscles would be greater in those species with a higher maximal $\dot{V}O_2$ capacity (i.e., $\dot{V}O_{2max}$). This review explores the relationship between $\dot{V}O_{2max}$ and $\dot{V}O_2$ dynamics or kinetics at across a range of species selected, in part, for their disparate $\dot{V}O_{2max}$ capacities. In healthy humans there is compelling evidence that the speed of the $\dot{V}O_2$ kinetics at the onset of exercise is limited by an oxidative enzyme inertia within the exercising muscles rather than by O_2 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 $\dot{V}O_{2max}$ and the speed of $\dot{V}O_2$ kinetics among different species, it is possible to identify species or individuals within a species that exhibit widely disparate mass-specific $\dot{V}O_{2max}$ capacities but similar $\dot{V}O_2$ kinetics (i.e., superlative human athlete and horse).

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

Glossary of terms

A	amplitude of $\dot{V}O_2$ response
CP	critical power
DO_2	diffusive O_2 conductance
LT	lactate threshold
MRT	mean response time (time delay + time constant; denotes time to 63% of final response)
L-NAME	L-nitro-arginine methyl ester (inhibits NOS)
NO	nitric oxide
NOS	nitric oxide synthesis
PCr	phosphocreatine
Phase I	initial increase in $\dot{V}O_2$ at exercise onset caused by elevated pulmonary blood flow (also called the cardiodynamic phase)
Phase II	exponential increase in $\dot{V}O_2$ that is initiated when venous blood from the exercising muscles arrives at the lungs. Corresponds closely with muscle $\dot{V}O_2$ dynamics
Phase III	steady-state $\dot{V}O_2$ response present for moderate and heavy, but not severe, exercise
PO_2	partial pressure of O_2
RBC	red blood cell
TD	time delay
t	time
τ	time constant; time to 63% of final response
$t_{1/2}$	half time; time to 50% of final response. 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
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_{2max}$	maximal oxygen uptake (achieved under conditions of large muscle mass exercise unless otherwise specified)

Subscripts

e	extracellular
i	intracellular
p	primary component
s	slow component

Introduction

This brief review adopts a comparative physiological approach to explore oxygen uptake ($\dot{V}O_2$) kinetics across extremely diverse species. The rate at which $\dot{V}O_2$ adjusts to meet the new energy demand at the transition from one metabolic rate to another (i.e. $\dot{V}O_2$ 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. $\dot{V}O_2$ kinetics are generally faster in fitter humans and animal species than in their sedentary or less fit counterparts as judged by their maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$). In humans, after exercise training, the speeding of $\dot{V}O_2$ kinetics is usually associated with an increased $\dot{V}O_{2max}$. In contrast, decrements in $\dot{V}O_{2max}$ that accompany chronic disease are typically associated with slowed $\dot{V}O_2$ kinetics. Judicious selection of the poorly aerobic lungless salamander[1] ($\dot{V}O_{2max} < 10\,ml\,min^{-1}\,kg^{-1}$) and the Thoroughbred horse[2] or deer mouse[3] ($\dot{V}O_{2max} = 160–220\,ml\,min^{-1}\,kg^{-1}$) permits analysis of the relationship between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ and the investigation of metabolic control over a much broader range of absolute and mass-specific $\dot{V}O_{2max}$ 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 $\dot{V}O_2$.

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 $\dot{V}O_2$ ($\dot{V}O_{2max}$), 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

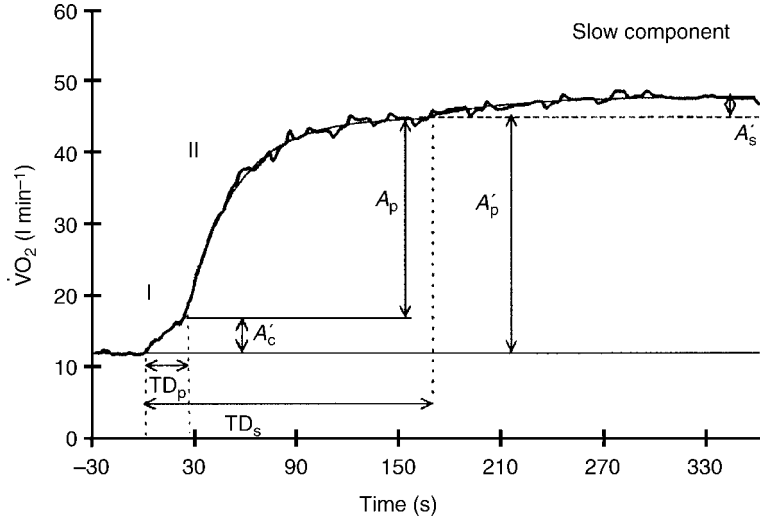

Fig. 1 The dynamic profile of O_2 uptake ($\dot{V}O_2$) in the Thoroughbred horse at the onset of heavy-intensity exercise. Time zero is exercise onset. The profile is very similar, albeit more rapid, than that of the human. Specifically, at exercise onset there is an initial cardiodynamic phase (Phase 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_p 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]

FIG. 2 The Thoroughbred horse (*Equus caballus*) running on a high-speed equine treadmill. Through thousands of years of selective breeding, this animal is one of the top athletes in the world, achieving maximal $\dot{V}O_2$ values[2] exceeding 200 ml min^{-1} kg^{-1}. The bias-flow system seen here enables collection of respired gases and high-fidelity resolution of $\dot{V}O_2$ kinetics

pulmonary $\dot{V}O_2$ does not follow a 'stepwise' response profile[4]. 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ response following the onset of exercise has been well characterized[6–8]. 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 $\dot{V}O_2$ within Phase I) that is followed by a rapid exponential increase in $\dot{V}O_2$ (Phase II) with a time constant (τ) of some 20–45 s (in healthy humans) that drives $\dot{V}O_2$ to the actual, or towards the initially anticipated, steady-state value (Phase III) within approximately 3 min. Phase I represents the O_2 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 $\dot{V}O_2$ response is variously described as the 'fast component', the 'primary component' or the 'fundamental component' in the $\dot{V}O_2$ kinetics literature). The pulmonary $\dot{V}O_2$ kinetics in Phase II therefore largely reflects the kinetics of O_2 consumption in the exercising muscles, although there is a temporal lag between events at the muscle and those recorded at the lung[9]. 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 O_2 content reaches its nadir. At

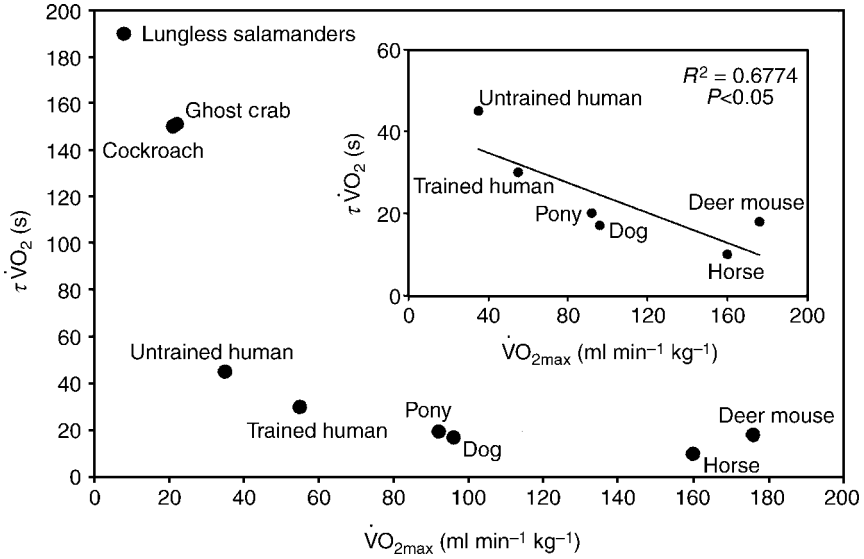

FIG. 3 Relationship between the time taken to achieve 63% of the total increase (τ) of O_2 uptake and the mass-specific $\dot{V}O_{2max}$ in some of the different species featured in this review. These animals evidence a range of $\dot{V}O_{2max}$ values from <10 to $\sim$180 ml min^{-1} kg^{-1}. Inset demonstrates the correlation between τ of $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ in mammalian species. Please note that, although the correlation is significant, using a linear model to describe the relationship between $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$) and $\dot{V}O_{2max}$ may not be strictly appropriate and should not be considered as unequivocal evidence for cause and effect

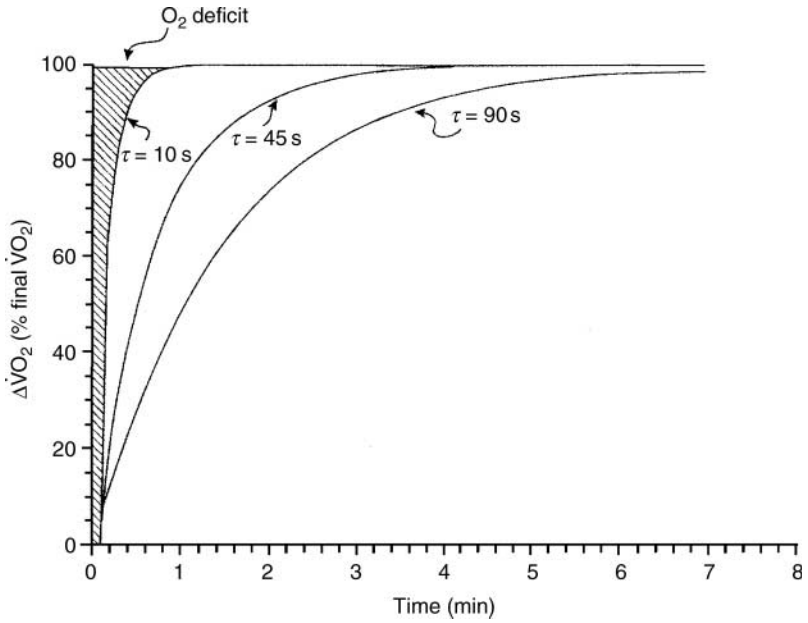

FIG. 4 Schematic demonstration of the effect of altering the speed of $\dot{V}O_2$ kinetics (τ) on the O_2 deficit. Time zero is exercise onset. The range of τ values given represents those measures in a racehorse (10 s), sedentary human (45 s) and a cardiac patient (90 s). The shaded area represents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

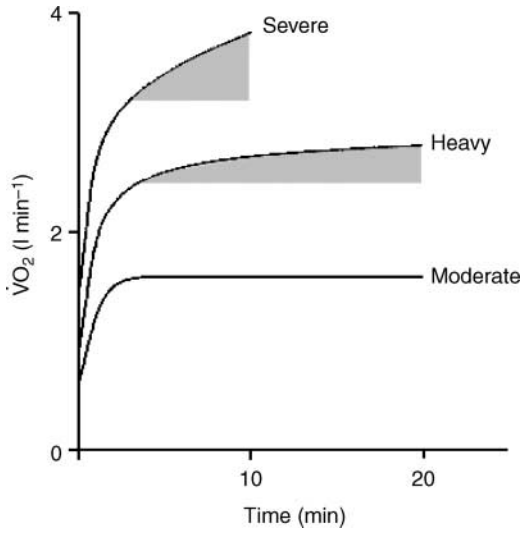

FIG. 5 Schematic representation of the $\dot{V}O_2$ response to constant work-rate exercise in the moderate (below the lactate threshold), heavy (above the lactate threshold) and severe (above the asymptote of the power–time relationship for high-intensity exercise or critical power) exercise domains. 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 ($\dot{V}O_{2max}$) at or before fatigue

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 $\dot{V}O_2$ ($\Delta\dot{V}O_2$) across the transient and the speed of the $\dot{V}O_2$ response denoted by the time constant (τ) of the $\dot{V}O_2$ response from the onset of exercise (τ represents the time taken to achieve 63% of $\Delta\dot{V}O_2$): O_2 deficit $= \Delta\dot{V}O_2 \times \tau$, where $\Delta\dot{V}O_2$ is given in 1 min^{-1} and τ in fractions of a minute. Thus, for a given $\Delta\dot{V}O_2$, the faster the $\dot{V}O_2$ response (smaller τ), 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 τ) 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

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) $\dot{V}O_2$ increases in close proportion to the running speed or work rate. Within the moderate intensity domain, the speed of the Phase II $\dot{V}O_2$ 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)[10,11]. 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 $\dot{V}O_2$ at which blood lactate (and $\dot{V}O_2$) can be stabilized and typically occurs mid-way between the speed or work rate that elicits LT and $\dot{V}O_{2max}$ on a standard incremental test[12,13]. There is some evidence that the Phase II $\dot{V}O_2$ 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 $\dot{V}O_2$ kinetics that becomes apparent after approximately 2 min following exercise onset and is superimposed upon the primary $\dot{V}O_2$ response (Figs 1 and 5). This slow component elevates the $\dot{V}O_2$ *above* rather than *towards* the $\dot{V}O_2$ that would be calculated for a particular running speed or work rate by extrapolation of the $\dot{V}O_2$ response to moderate exercise. Depending on the characteristics of the slow component, achievement of the steady-state $\dot{V}O_2$ may be delayed by 10–15 min or more.

Severe exercise comprises those work rates lying between CP and $\dot{V}O_{2max}$ as assessed during an incremental exercise test in which fatigue is reached in $\sim$10 min. In the severe domain, the slow component causes $\dot{V}O_2$ 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 $\dot{V}O_2$ may rise with a close to mono-exponential profile that is truncated at $\dot{V}O_{2max}$. However, for all work rates in the severe domain, when exercise is continued to the point of exhaustion, $\dot{V}O_{2max}$ is attained. Consequently, the severe intensity domain presents a broad range of running speed or work rate at which it is possible to attain $\dot{V}O_{2max}$.

Given the finite kinetics of $\dot{V}O_2$, it is inevitable that some work rates are so high that fatigue intervenes before $\dot{V}O_{2max}$ can be achieved. This domain has recently been termed '*extreme exercise*'[14]. Fitter individuals will exhibit faster $\dot{V}O_2$ kinetics and it would therefore be expected that such individuals would require less time at these extreme work rates to reach $\dot{V}O_2$s approaching their $\dot{V}O_{2max}$.

Model characterization of $\dot{V}O_2$ kinetics

It has been established that the $\dot{V}O_2$ response in Phase II is essentially exponential in character[15–17]. 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 $\dot{V}O_2$) and feedback control of the response until the error signal is eliminated[18]. An exponential function has an amplitude and a time constant (τ; the equivalent of the reciprocal of the rate constant, 1/k)[19] that reflects the time required for the attainment of 63% of the total amplitude. The exponential nature of the $\dot{V}O_2$ response in Phase II can therefore be described with the following equation:

$$\dot{V}O_2(t) = \dot{V}O_2(b) + A(1 - e^{-(t-TD)/\tau}),$$

where $\dot{V}O_2(t)$ is the $\dot{V}O_2$ at any point in time, $\dot{V}O_2(b)$ is the baseline $\dot{V}O_2$ before the commencement of the square-wave transition to a higher work rate, A is the steady-state amplitude of the $\dot{V}O_2$ response, and $(1 - e^{-(t - TD)/\tau})$ is the exponential function describing the rate at which $\dot{V}O_2$ 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 τ is the time constant. Therefore, for a τ 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 (4τ) have elapsed.

The exponential increase of pulmonary $\dot{V}O_2$ 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[20,21]. This strongly suggests that muscle $\dot{V}O_2$ kinetics is principally

under feedback control from one or more of the products of high-energy phosphate splitting[22].

For heavy- and severe-intensity exercise, an additional exponential term is required for satisfactory fitting of the $\dot{V}O_2$ on-response following the completion of Phase I:

$$\dot{V}O_2(t) = \dot{V}O_2(b) + A_P(1 - e^{-(t_p - TD_p)/\tau_p}) + A_s(1 - e^{-(t_s - TD_s)/\tau_s}),$$

where A_p and A_s are the amplitudes of the $\dot{V}O_2$ 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 ($\sim 10\,000$ l min^{-1}) flow-by or bias-flow systems has facilitated resolution of $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ response to moderate-intensity exercise in the horse is preservation of the mono-exponential kinetics. This response occurs despite the presence of a massive (~ 14 kg) spleen that contracts at exercise onset, resulting in an almost doubling of arterial haemoglobin concentration and therefore arterial O_2-carrying capacity within 20–60 s[23].

It is beyond the scope of this review to detail the specific anatomy and physiology of O_2 transport among all species presented herein. However, where pertinent to the central issue of understanding the possible control mechanisms for $\dot{V}O_2$ 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 $\dot{V}O_{2max}$ and the speed of the $\dot{V}O_2$ kinetics at exercise onset demonstrated in humans, the Thoroughbred horse is capable of achieving maximal $\dot{V}O_2$ values near 200 ml min^{-1} kg^{-1} and the speed of the $\dot{V}O_2$ kinetic response is correspondingly rapid (Figs 1 and 3). $\dot{V}O_2$ kinetics were first measured in the pony in 1984[24] and subsequent investigations have studied $\dot{V}O_2$ kinetics in Standardbred, Thoroughbred and Quarter horses. However, it was not until recently that a rigorous investigation was undertaken to formally characterize equine $\dot{V}O_2$ kinetics[4].

$\dot{V}O_2$ kinetics in the horse

While previous investigations had studied $\dot{V}O_2$ kinetics in equids[25,26], prior to the work of Langsetmo *et al.*[4] $\dot{V}O_2$ was not measured rapidly enough to accurately assess $\dot{V}O_2$ kinetics. By obtaining gas-exchange data on a second-by-second basis and studying $\dot{V}O_2$ 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, $\dot{V}O_2$ kinetics were well fit by a two-phase exponential model (cardiodynamic + primary phases), the primary phase of which was very rapid ($\tau \approx 10$ 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. ~ 21 s) but markedly slowed compared with that during moderate running. Additionally, heavy exercise was attended (with one exception in that investigation) by a $\dot{V}O_2$ slow component which occurred ~ 135 s after the onset of exercise.

The $\dot{V}O_2$ kinetics reported by Langsetmo *et al.*[4] have subsequently been replicated by Geor *et al.*[27]. In that investigation, in which Standardbred horses were transitioned almost instantaneously from a walk to

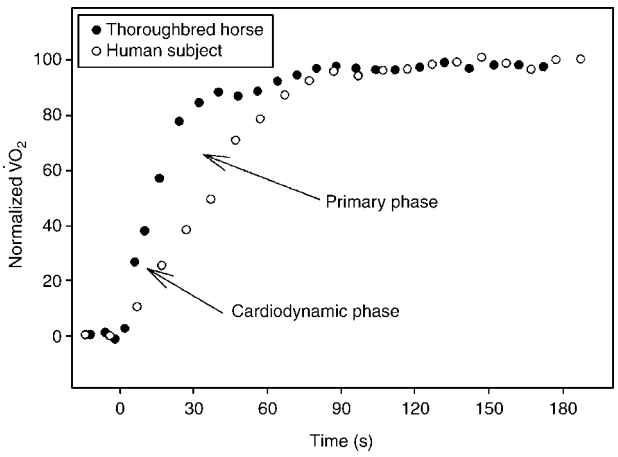

Fig. 6 Comparison of $\dot{V}O_2$ kinetics (normalized, i.e., %Delta $\dot{V}O_2$ from baseline) between the horse and human for moderate-intensity exercise. Time zero is exercise onset. Note that the horse demonstrates much more rapid dynamics than the human; however, the horse still demonstrates three distinct phases (i.e. Phase I – cardiodynamic phase, Phase II – primary phase and Phase III – steady state)

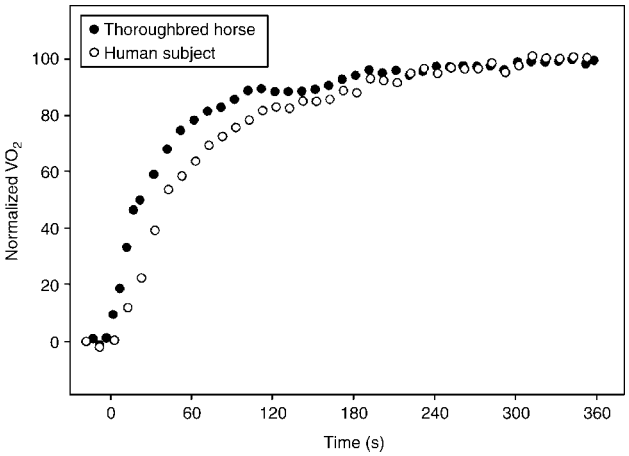

FIG. 7 Comparison of $\dot{V}O_2$ kinetics (normalized, i.e., %Delta $\dot{V}O_2$ from baseline) between the horse and human for heavy-intensity exercise. Time zero is exercise onset. Note that, as in Fig. 6 (moderate exercise), the horse demonstrates more rapid dynamics than the human and both horse and human demonstrate a slow component at roughly the same point of exercise (~120–150 s after exercise onset)

supramaximal treadmill speeds (i.e. speeds 15% greater than those attained during $\dot{V}O_{2max}$ elicited via ramp protocol), the $\dot{V}O_2$ primary τ (Phase II) was ~23 s. This τ was shortened significantly to ~16 s when the exercise trial was preceded by a warm-up. For the horses in that investigation, the absolute $\dot{V}O_2$ approached 60 l min^{-1} (150 ml min^{-1} kg^{-1})!

Comparison of the horse and human

Despite the capacity to reach maximal relative $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ kinetics that may resemble those seen in Figs 6 and 7 for the horse[5].

Figure 6 demonstrates $\dot{V}O_2$ 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 $\dot{V}O_2$ is in the horse compared with the human. Again, in the heavy domain (Fig. 7), key features of the $\dot{V}O_2$ on-kinetic response (i.e. three distinct phases) are similar between the horse and human. As depicted in Fig. 7, $\dot{V}O_2$ onset kinetics in the Thoroughbred horse are significantly faster than those reported in man. However, Langsetmo *et al.*[4] demonstrated a clear slowing of the equine $\dot{V}O_2$ on-kinetic response when running at speeds in the heavy *versus* moderate domain. Whether this slowing of the $\dot{V}O_2$ kinetics from moderate to heavy exercise occurs in humans is controversial. Specifically, many studies have demonstrated that the speed of the primary $\dot{V}O_2$ amplitude rise is unchanged as work intensity increases from moderate to heavy in humans[28–31]. In contrast, several investigations also studying human subjects have reported slowed $\dot{V}O_2$ on-transient kinetics in response to heavy compared with moderate exercise[30–38]. 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 O_2 delivery via an augmented influx of red blood cells (RBCs) during periods of increased metabolic demand may place a constraint on the speed of $\dot{V}O_2$ kinetics in the heavy domain that is unique to this species. There may also be fibre-type recruitment profiles that may slow the $\dot{V}O_2$ 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[4]. It is also true that some humans do not evidence a discernible slow component during heavy exercise.

Why are $\dot{V}O_2$ 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 O_2 culminates, ultimately, in prodigious maximal $\dot{V}O_2$ 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[39] 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 O_2 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})[40]. However, despite these ventilatory rates, severe arterial hypoxaemia nearing 60 mmHg

is incurred during intense running[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 (~1 μm) than that of other mammals (~0.3 μm 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_2-carrying capacity[23,41]. Finally, in the Thoroughbred racehorse muscle comprises ~50% of the body mass and that muscle contains a dense capillary network and a correspondingly high mitochondrial volume density[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^{-1}, the horse represents an excellent model to study control of $\dot{V}O_2$ 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 L-NAME). Whilst nitric oxide (NO) is necessary to attain peak cardiac outputs and systemic O_2 delivery in the horse[39], it also inhibits mitochondrial oxygen consumption by binding to cytochrome c oxidase. Kindig *et al.*[44] demonstrated, in the face of a reduced cardiac output and presumably muscle blood flow, that $\dot{V}O_2$ 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_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 $\dot{V}O_2$ kinetics to values close to those observed during moderate-intensity running. Subsequent research, shown in Fig. 8, demonstrated that NOS inhibition sped $\dot{V}O_2$ kinetics ~30% at the onset of moderate running (NOS inhibition $\tau = 12$ s *versus* control $\tau = 18$ s)[45]. These findings have been confirmed in humans[46,47] and collectively demonstrate that the rapidity of $\dot{V}O_2$ kinetics at exercise onset can be enhanced by removing the NO brake on mitochondrial function.

Dog

The domestic dog (*Canidae*), like the horse, represents another extreme athlete, with $\dot{V}O_{2max}$ values almost double that of humans (i.e. ~100 ml O_2 min^{-1} kg^{-1})[48]. In addition, the dog as an experimental modality has

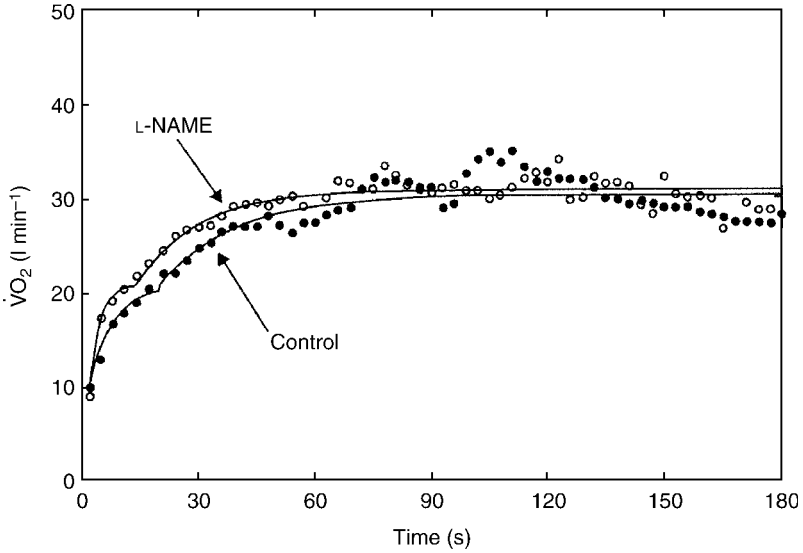

Fig. 8 Effect of L-nitro-arginine methyl ester (L-NAME; an inhibitor of nitric oxide synthase) administration on $\dot{V}O_2$ kinetics. Time zero is exercise onset. L-NAME alleviates the NO inhibition of mitochondrial O_2 consumption, thereby reducing the metabolic inertia at exercise onset and speeding $\dot{V}O_2$ kinetics. Adapted from Kindig *et al.*[45]

played a pivotal role in filling the void between isolated single-fibre (usually amphibian) and whole-organism (e.g. human) preparations. Specifically, canine $\dot{V}O_2$ kinetics has been studied both within the whole body and in surgically isolated but otherwise intact isolated muscle groups. Whereas pulmonary and muscle $\dot{V}O_2$ can be measured simultaneously in the human[9,49,50], the experimental conditions (e.g. blood O_2 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 $\dot{V}O_2$ kinetics has stemmed from research using the dog.

Whole-body versus isolated muscle preparations

$\dot{V}O_2$ kinetics has been studied extensively in dog locomotory muscle groups[51–54]. However, few studies have focused on quantifying pulmonary $\dot{V}O_2$ kinetics in conscious, exercising dogs. One such study was performed by Marconi *et al.*[55] and was the first to quantify the $\dot{V}O_2$ 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-load treadmill exercise) and measured the ensuing whole-body $\dot{V}O_2$ on-kinetics. These investigators demonstrated that the dog has extremely rapid $\dot{V}O_2$ on-kinetics with $\tau \approx 20$ 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 investigation[55] was the similarity between whole-body pulmonary $\dot{V}O_2$ on-kinetics and those found in the dog isolated *gastrocnemius* complex (pulmonary $\dot{V}O_2$, $\tau \approx 20$ s[55]; isolated *gastrocnemius* $\dot{V}O_2$, $\tau = 15 - 17$ s[51]), thereby substantiating that pulmonary $\dot{V}O_2$ 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 $\dot{V}O_2$ in anaesthetized dogs, demonstrated no difference in $\dot{V}O_2$ on-kinetics between pulmonary and muscle (both ~17 s) during electrical stimulation.

Dog isolated muscle $\dot{V}O_2$ 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 physiochemical properties (e.g. gas contents) of that blood. Specifically, the investigator can manipulate O_2 delivery independently of O_2 uptake[53,54] or vice versa (see Grassi *et al.*[57]) to elucidate the mechanisms governing the rate of $\dot{V}O_2$ increase. For example, using the dog isolated *gastrocnemius* complex (comprised of *gastrocnemius–plantaris* muscles) first described by Stainsby and Welch[58], Grassi *et al.* have demonstrated that muscle $\dot{V}O_2$ on-kinetics for moderate-intensity contractions (yielding $<60\%$ $\dot{V}O_{2max}$) are not affected by:

1. An increase in peripheral O_2 diffusion evoked via hyperoxia or hyperoxia concomitantly with a rightward shift of the haemoglobin–O_2 dissociation curve (via the drug RSR-13). Both of these paradigms act to increase the driving force for O_2 from the capillary to the myocyte, thus facilitating enhanced transcapillary O_2 flux. The $\dot{V}O_2$ kinetics was not altered by these manipulations, with τ being 24–26 s under all conditions[54].
2. A faster adjustment of O_2 delivery at exercise onset evoked by setting the pre-contracting blood flow to the same values attained during steady-state contractions. $\dot{V}O_2$ kinetics was unchanged at $\tau = 17 - 19$ s for both a spontaneous and pre-adjusted increase in blood flow to the muscle[53].

As can be seen from these two latter series of experiments, dog muscle demonstrates rapid $\dot{V}O_2$ on-kinetics that is not limited by O_2 delivery at least in the moderate intensity domain.

Mechanisms responsible for rapid $\dot{V}O_2$ on-kinetics in the dog

There are many adaptations in the dog that contribute to rapid $\dot{V}O_2$ kinetics. However, it is evident that the dog enjoys an extremely high mitochondrial volume density in most locomotory muscles[59]. Moreover, the kinetics of blood (and therefore O_2) delivery to these muscles is astonishingly fast and, as in most models considered, actually precedes the increase in $\dot{V}O_2$[60–62].

Rodents

Compared with the horse and dog, very little is known about pulmonary $\dot{V}O_2$ kinetics in rodents (e.g. mice and rats). Although $\dot{V}O_2$ steady states can be measured with high fidelity in both rats[48,63] and mice[64], it is much more difficult to measure the rate of change or the dynamics of $\dot{V}O_2$ in these animals. Specifically, $\dot{V}O_2$ is usually measured in small animals by placing them in a relatively large chamber, and subsequently sampling the gases (CO_2 and O_2) 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ kinetic data in the mouse[3]. Thus, across the rest-to-running transition, the deer mouse (*Peromyscus maniculatus*) can increase its $\dot{V}O_2$ with $\tau \approx 20$–25 s (Fig. 9)[3]. In addition to these rapid kinetics, an impressive $\dot{V}O_{2max}$ (~ 175 ml O_2 min^{-1} kg^{-1}) was measured. Apparently, in these creatures, the same very high $\dot{V}O_{2max}$ can be achieved by either exercise or cold exposure. This observation raises the intriguing possibility that the rapid $\dot{V}O_2$ 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 $\dot{V}O_2$ kinetics in the laboratory rat. It has been assumed, based on demonstrated high $\dot{V}O_{2max}$ values (70–80 ml min^{-1} kg^{-1})[48,63], that the rat would display rapid $\dot{V}O_2$ kinetics (as discussed in the Introduction; in many instances τ of $\dot{V}O_2$ kinetics is proportional to $\dot{V}O_{2max}$). However, it was only recently that $\dot{V}O_2$ 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*) $\dot{V}O_2$ follows a mono-exponential time course to the steady state with $\tau \approx 20$ s (Fig. 10). This was the first study within muscle to demonstrate that $\dot{V}O_2$ 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 Mahler[22]). In addition, the muscle studied in that investigation (i.e. *spinotrapezius*) has only a relatively modest oxidative capacity (measured by citrate synthase activity, an enzyme of the tricarboxylic acid cycle indicative of oxidative capacity; ~ 14 μmol min^{-1} g^{-1} in *spinotrapezius*)[66]. Therefore,

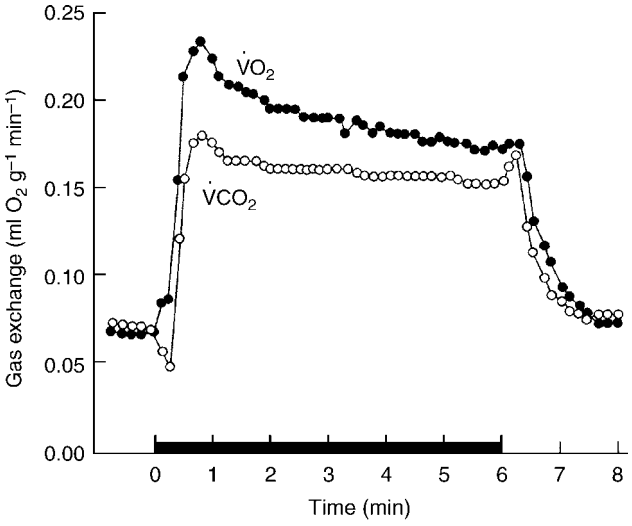

FIG. 9 $\dot{V}O_2$ on-kinetics for the deer mouse (*Peromyscus maniculatus*). Time zero is the onset of exercise. Note the rapid increase in $\dot{V}O_2$ which overshoots the steady state[3]

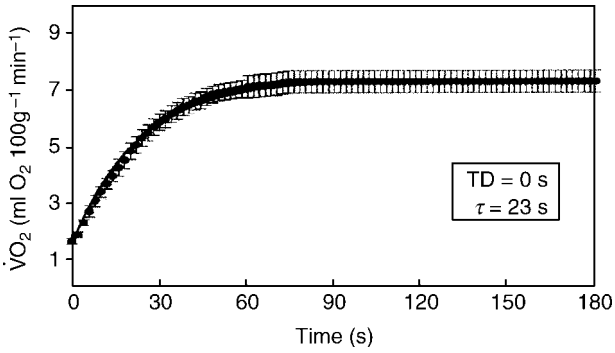

FIG. 10 Oxygen uptake ($\dot{V}O_2$) profile across the rest-to-electrically induced muscular contractions in rat *spinotrapezius*. Note that at stimulation onset (time zero) $\dot{V}O_2$ increases without discernible delay in a mono-exponential fashion to the steady state. Adapted from Behnke *et al.*[65]

during treadmill exercise, where muscles with high oxidative capacities are recruited (e.g. red *gastrocnemius*; citrate synthase activity ~ 36 μmol min^{-1} g^{-1})[66], $\dot{V}O_2$ kinetics would be expected to be even more rapid than that demonstrated in the *spinotrapezius*, although this has yet to be documented. In the future, it would be important to be able to measure and understand the control of $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 O_2 extraction after inspiration (via openings on legs) of either water or air. Both of these structural adaptations could pose serious limitations to O_2 uptake and delivery. In humans, O_2 is drawn into the lungs where it diffuses across an extremely thin blood–gas barrier into the circulation. However, in the crab, O_2 must diffuse through a chitin layer of the gills that has a diffusive conductance for O_2 that is much less (i.e. greater resistance to diffusion) than that of the human blood–gas interface. Indeed, McMa-

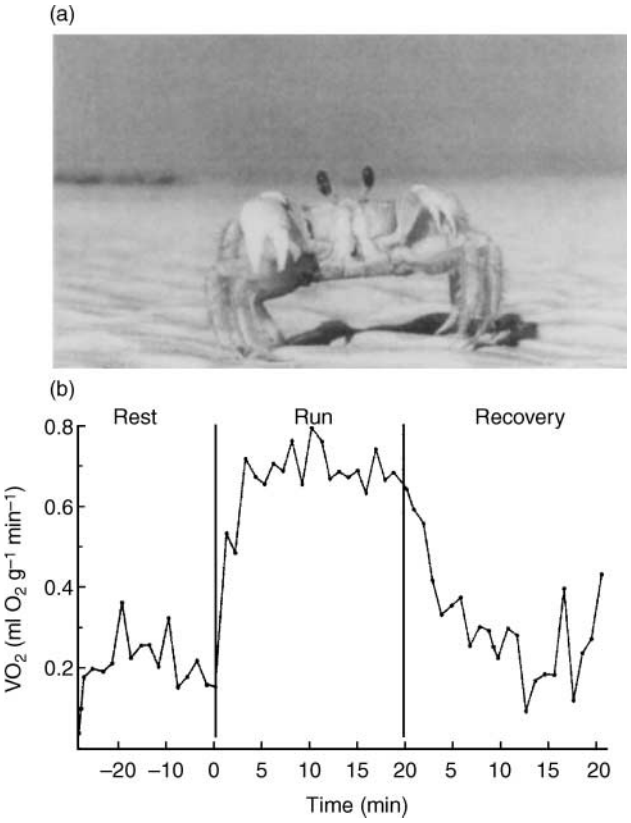

FIG. 11 The ghost crab (*Ocypode guadichaudii*) (a), believed to be the fastest land crab, exhibits $\dot{V}O_2$ kinetics with $\tau \approx 144$ s during sideways treadmill running (b) (adapted from Full and Herreid[69,70], with permission). Time zero is the onset of exercise

hon[67] proposed that it is this chitin layer which poses the major limitation to the rate of O_2 diffusion into the blood. Combined with the sluggish increase in heart rate at the onset of exercise[68], it is not surprising that $\dot{V}O_2$ kinetics at exercise onset is slow in this species. Nevertheless, ghost crabs do exhibit a $\dot{V}O_2$ 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 ($t_{1/2}$) of this response averages around 100 s, corresponding to $\tau = 144$ s (i.e. $\tau = t_{1/2} \div 0.693$ 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 $\dot{V}O_2$ dynamics[68,70].

Amongst those species in which $\dot{V}O_2$ dynamics and $\dot{V}O_{2max}$ have been studied, the lungless salamander (*Plethodin 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 limitation[71,72]. With respect to O_2 uptake, this reptile, which normally performs rapid, sprint-type exercise that is anaerobic in nature, demonstrates[1] a disappearingly low $\dot{V}O_{2max}$ of ~7–8 ml min^{-1} kg^{-1}. Given this low aerobic capacity, it should not be surprising that the VO_2 on-kinetics for this animal is extremely slow, i.e. $\tau \approx 180$ s^1. From one perspective, the lungless salamander may be likened to the patient with severe lung disease who exhibits a substantial diffusion limitation to O_2 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 $\dot{V}O_2$ 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 Anderson[73] measured $\dot{V}O_2$ at the onset of hopping activity in Fowler's toad (*Bufo woodhousei fowleri*) (Fig. 12). Fowler's toad has a $\dot{V}O_{2max}$ of ~20 ml min^{-1} kg^{-1} and, according to the relationship shown in Fig. 3, very slow $\dot{V}O_2$ 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 ($\dot{V}O_2$). 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,

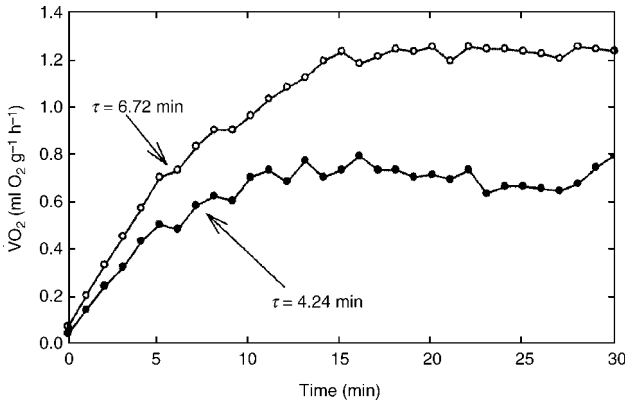

FIG. 12 Pulmonary $\dot{V}O_2$ of Fowler's toad (*Bufo woodhousei fowleri*) during 30 min of treadmill hopping at 0.09 km h^{-1} (closed symbols) and at 0.45 km h^{-1} (open symbols). Time zero is exercise onset. Note that mean response times (broadly analogous to τ for the overall response) are extremely slow (see text for details)[73]

the fall in muscle intracellular PO_2 is a direct measure of $\dot{V}O_2$. (Fick's law of diffusion applied to the single myocyte preparation: $\dot{V}O_2 = DO_2(P_eO_2 - P_iO_2)$, where DO_2 is the muscle O_2 diffusion constant and P_iO_2 and P_eO_2 represent intracellular and extracellular PO_2, respectively.) 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[74] measured the rise and fall in $\dot{V}O_2$ following 5–10 s tetanic contractions 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 'immediate'. More recently, Mahler[75] 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 τ for $\dot{V}O_2$ kinetics during recovery from differing 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 concomitant 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.*[76] 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 contractions[77,78]. Using phosphorescence quenching to measure PO_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 contractions 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[60–62] can be addressed in single myocytes. For example:

1. Kindig *et al.*[79] demonstrated that progressively increasing the extracellular PO_2 from 20 to 60 mmHg did not alter the initial speed of the fall in P_iO_2 at contractions onset, suggesting that an extracellular PO_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 pharmaceutically, the fall in P_iO_2 at contractions onset was markedly speeded compared with matched control trials[80]. 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 PO_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 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 O_2 in sufficient quantity to utilize the inherently 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 $\dot{V}O_{2max}$ demonstrated in humans is found across a range of $\dot{V}O_{2max}$ values approaching two orders of magnitude, from the aerobically pedestrian lungless salamander to the fleet Thoroughbred racehorse. Judicious selection of animal models within this range has provided compelling evidence that, within healthy mammals, muscle and pulmonary $\dot{V}O_2$ kinetics are limited by processes within

the myocyte. Thus, removal of NO-mediated inhibition of mitochondrial function and creatine kinase inhibition both speed $\dot{V}O_2$ kinetics. The amphibian may constitute an exception in that isolated frog myocytes exhibit markedly faster $\dot{V}O_2$ 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 $\dot{V}O_2$ kinetics akin possibly to humans with cardiac or pulmonary dysfunction.

There is a marked paucity of applicable data on $\dot{V}O_2$ 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 $\dot{V}O_2$ control. For example, it is by no means certain that the slow component of $\dot{V}O_2$ 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 not run fast enough to operate within the classic heavy exercise intensity domain (sustained elevation of blood lactate) or, alternatively, be sufficiently endowed with highly oxidative fibres not to incur a $\dot{V}O_2$ slow component. Horses, on the other hand, bolt from danger at speeds exceeding those that generate a slow component, i.e. speeds for which the $\dot{V}O_2$ requirement exceeds $\dot{V}O_{2max}$. Other creatures, for example the wallaby and kangaroo, which do not increase $\dot{V}O_2$ as a function of speed during bipedal locomotion as do quadrupeds, may achieve great speeds and fast $\dot{V}O_2$ kinetics without the necessity for engaging the slow component[81,82].

As with other lines of inquiry, it is evident that comparative physiological approaches can yield important original information regarding the control of $\dot{V}O_2$ 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

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