Highly Athletic Terrestrial Mammals: Horses and Dogs

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ABSTRACT

Evolutionary forces drive beneficial adaptations in response to a complex array of environmental conditions. In contrast, over several millennia, humans have been so enamored by the running/athletic prowess of horses and dogs that they have sculpted their anatomy and physiology based solely upon running speed. Thus, through hundreds of generations, those structural and functional traits crucial for running fast have been optimized. Central among these traits is the capacity to uptake, transport and utilize oxygen at spectacular rates. Moreover, the coupling of the key systems—pulmonary-cardiovascular-muscular is so exquisitely tuned in horses and dogs that oxygen uptake response kinetics evidence little inertia as the animal transitions from rest to exercise. These fast oxygen uptake kinetics minimize Intramyocyte perturbations that can limit exercise tolerance. For the physiologist, study of horses and dogs allows investigation not only of a broader range of oxidative function than available in humans, but explores the very limits of mammalian biological adaptability. Specifically, the unparalleled equine cardiovascular and muscular systems can transport and utilize more oxygen than the lungs can supply. Two consequences of this situation, particularly in the horse, are profound exercise-induced arterial hypoxemia and hypercapnia as well as structural failure of the delicate blood-gas barrier causing pulmonary hemorrhage and, in the extreme, overt epistaxis. This chapter compares and contrasts horses and dogs with humans with respect to the structural and functional features that enable these extraordinary mammals to support their prodigious oxidative and therefore athletic capabilities. © 2011 American Physiological Society. *Compr Physiol* 1:1-37, 2011.

Introduction

Maximal O_2 Uptake

Muscular exercise presents the supreme challenge to the O_2 transport pathway demanding highly coordinated function of pulmonary, cardiovascular, and muscular systems. In healthy adult humans, the maximal capacity for O_2 transport and utilization is the maximal O_2 uptake ($\dot{V}O_2max$) that is measured during large muscle mass exercise, typically running or cycling, and ranges from 1 to 7 liters/min or 15-90 ml/kg/min. $\dot{V}O_2max$ relates principally to body mass, athletic/cardiovascular fitness, and age. Thus, diminutive, unfit, and older individuals might occupy the low end of this range, whereas superb, endurance-type athletes, for example, cross-country skiers (12) and contemporary cyclists—specifically Miguel Indurain—push the upper limits of human oxidative potential (256).

Impressive though the apogee of human athletic performance is, it pales in comparison with the 180 mph (290 km/h) swoops of the peregrine falcon (*Falco peregrinus anatum*) or 46,000-mile yearly (average 126 miles (203 km) per day) odyssey of the sooty shearwater (*Puffinus griseus*). With respect to speed, among terrestrial mammals the cheetah (*Acinonyx jubatus*) reigns supreme achieving, albeit fleetingly, top speeds in excess of 70 mph (113 km/h), which makes the fastest humans (<30 mph or 48 km/h) seem rather pedestrian, as does the pronghorn antelope, which can sustain speeds of over 50 mph (80 km/h) for several miles (Fig. 1). However, of all athletic species, none have enchanted humankind as have the horse (*Equus caballus*) and the dog (*Canis familiaris*). Although the Thoroughbred horse has only been developed within the last 300 years (403), for over 6 millennia, horses have been bred selectively for speed (and to carry a rider) at speeds approaching 55 mph (88 km/h 246, 341) (Fig. 2). The highly physiologically specialized Greyhound, sled dog, and Foxhound are similarly capable of extraordinary bursts of speed (Greyhound >45 mph (72 km/h), 406; Fig. 1) and endurance (Alaskan sled dog, 1000+-mile (1,600+ km) Iditarod). These animals certainly cannot lay claim to the highest mass-specific O_2 fluxes in the mammalian world—that distinction likely goes to the diminutive masked (*Sorex cinereus*; ref. 280) or Etruscan (*Suncus etruscus*; ref. 437) shrews (body mass 2-4 g, $\dot{V}O_2max$ 400-500 ml/kg/min). However, for their body masses, athletic breeds of horses and dogs have far higher mass-specific $\dot{V}O_2max$'s than expected (Fig. 3). This capacity is the consequence of the strong dependence of athletic potential on oxidative function, and has resulted in the elite race

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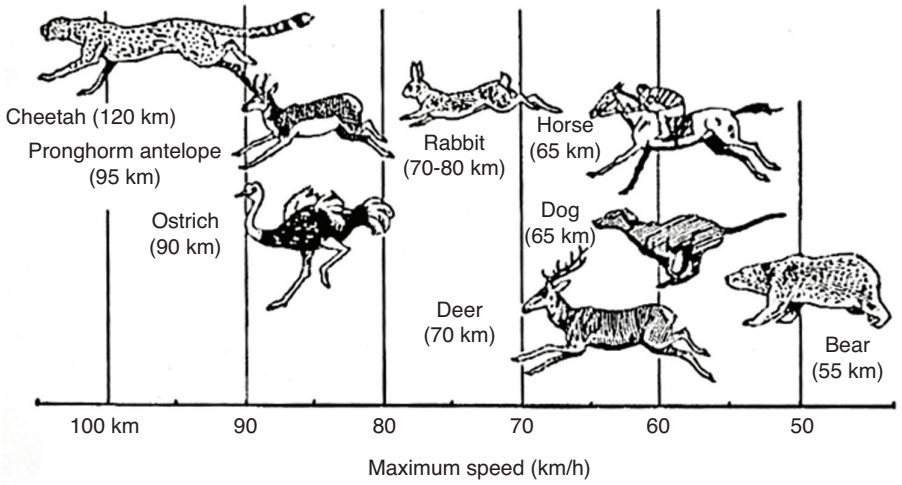


Figure 1 Estimated maximum speeds for a selection of terrestrial mammals and the ostrich. Note that the horse is the only animal depicted here for whom the speed recorded is measured carrying a rider and also that the fastest horses clocked are Quarter Horses (~55 mph, 88 km/h; ref. 341) rather than Thoroughbreds (as shown).

horse having a $\dot{V}O_2$max of 110 liters/min (≥220 ml/kg/min) (321, 322, 465). These prodigious O_2 fluxes are the highest ever measured and bear testament to the extreme integration and development of the O_2 transport pathway in the horse. Whereas it is conceivable that a 10-ton African elephant (*Loxodonta africana*) in full amble (they cannot run) or a 110-ton blue whale (*Balaenoptera musculus*) fleeing a pod of killer whales (*Orcinus orca*) may exceed these absolute (i.e., liter/min) rates of O_2 utilization, these have never been measured.

This article focuses on those structural and functional attributes of the pulmonary, cardiovascular, and muscular pathways (Fig. 4) that facilitate these extraordinary O_2 fluxes within the horse and the dog. The basic principles controlling convective and diffusive O_2 transport are dealt with elsewhere within this volume and hence receive only cursory attention for comparison purposes among horses, dogs, and humans. This article draws extensively from the formative series of papers investigating the mechanistic bases for the adaptive variations in oxidative potential among species authored by Weibel, Taylor, Hoppeler and colleagues (49, 172, 192, 193, 196, 416-418, 424, 438-442) to compare and contrast the attributes of athletic and nonathletic species. In addition, the excellent works of Fedde (94, 95, 222, 273, 314, 333, 429), Gollnick (22,23,374), Marlin (205,256-258,394,395), Hinchcliff (51, 161, 199, 226, 410), McKeever (28, 152, 160, 199, 270, 271), Persson (306-309), Gillespie (111, 112), Mitchell, Musch and colleagues (241,282-286,292,299,412), Johnson, Hsia and colleagues (175-177), Jones (5, 52, 190-193, 448), Lindstedt (190, 192, 238, 239), Staaden (406, 407), Harris, Snow, Butler, and Woakes (8, 38, 39, 66, 149, 463), Rivero and Piercy (351), and Wagner (62, 84, 138, 388, 389, 426-430) have been invaluable. These pioneering scientists have faced the daunting challenges of making physiologic measurements in animals running at high speed and, in so doing, have built on the remarkable achievements of scientific legends such as Zuntz (468-471), who, in the late 19th century, made sentinel $\dot{V}O_2$ measurements in running horses and dogs.

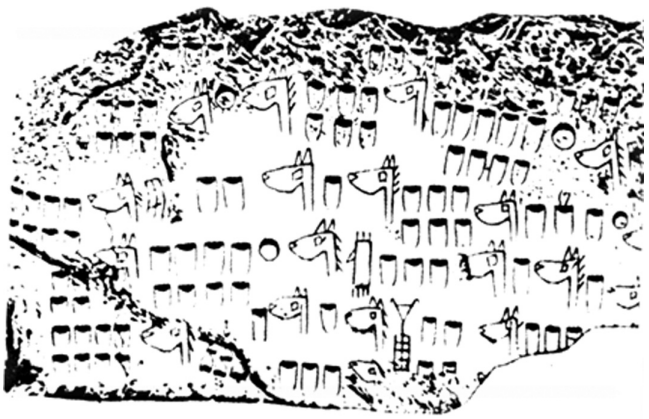


Figure 2 Chaldean horse pedigree chart (circa 4000 BCE) thought to present evidence for selective breeding of horses at least 6 millennia ago. Reproduced with permission from Lyons and Petrucelli (246) and the World Health Organization, Geneva.

This article draws preferentially upon measurements made in horses, dogs, and humans (for comparison purposes) during physiological exercise conditions (i.e., running) and resorts to consideration of anesthetized preparations or other species only where absolutely necessary. Special attention is afforded to the pathological consequences of extreme upregulation of the O_2 transport pathway that include exercise-induced arterial hypoxemia (EIAH) and pulmonary hemorrhage (EIPH), particularly in the horse. Some obvious gaps in our knowledge exist. These include the paucity of ventilatory measurements in the galloping Greyhound due, in part, to their unwillingness to run on treadmills and the encumbrance with breathing and thermoregulation that a mask obligates.

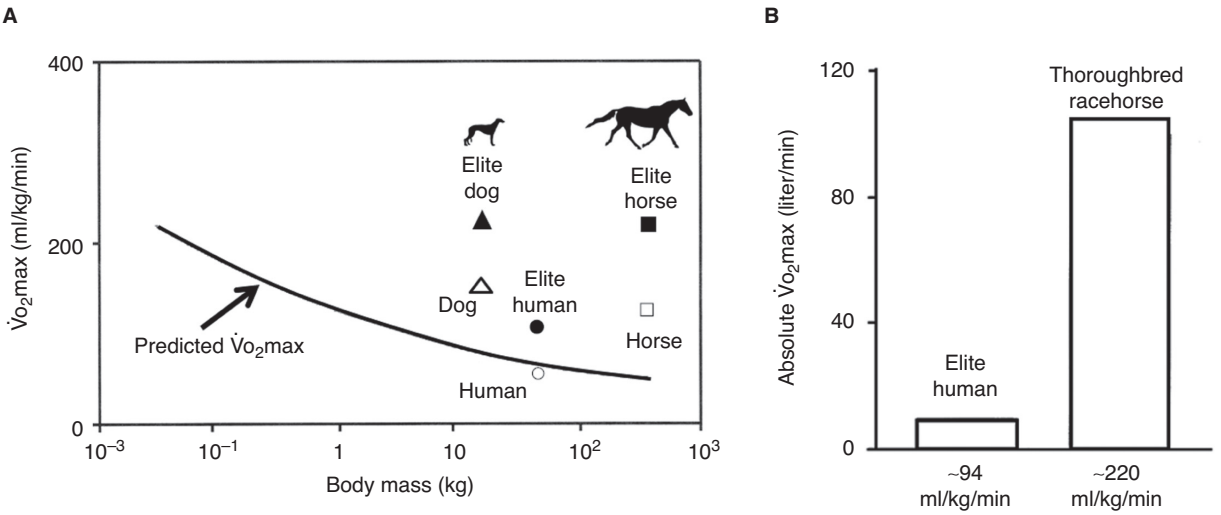


Figure 3 (A) Body mass-specific maximal O_2 uptake ($\dot{V}o_2$max) plotted as a logarithmic function of body mass for a selection of mammals with body masses differing over 5 orders of magnitude (solid line from Linstedt et al. ref. 239). Notice the extraordinary values plotted for the horse (non-elite, 222, 239, 318, 322, 326; elite, 465) and dog (Foxhound, 286; elite dog (Greyhound), 406). Human values from Astrand and Rodahl (12). (B) Comparison of absolute $\dot{V}o_2$max in an elite human athlete (12) and the Thoroughbred race horse (465).

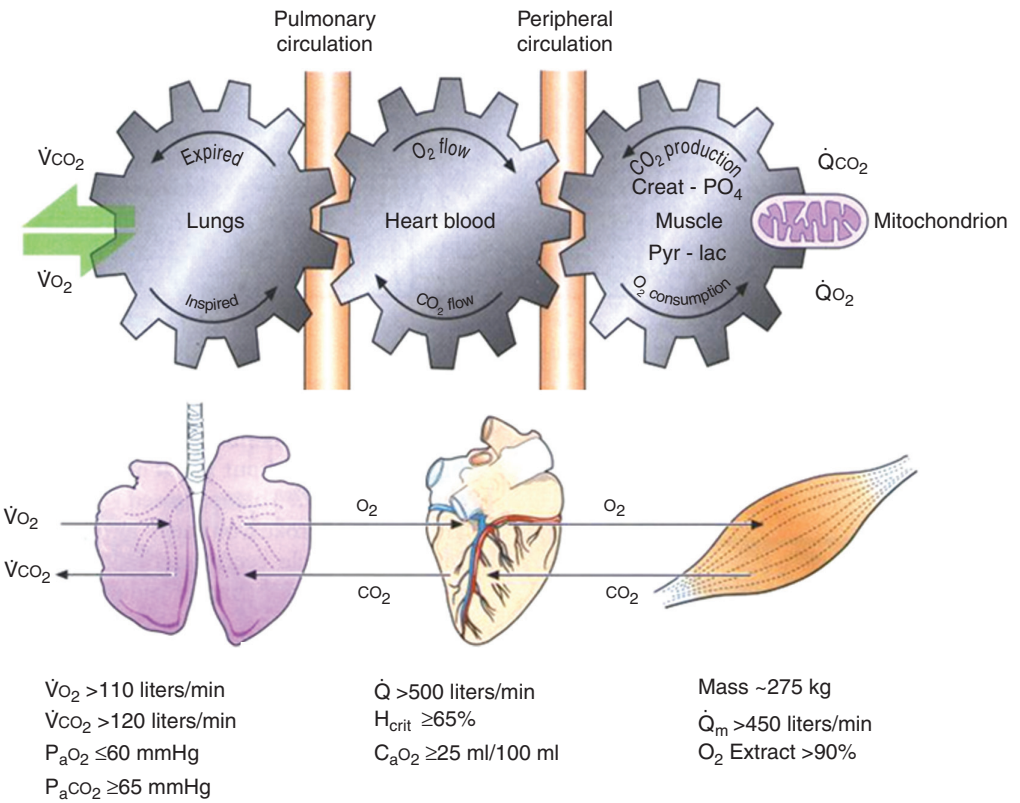


Figure 4 Illustration of the pathway for O_2 from atmosphere to its site of utilization within the muscle mitochondria. The enmeshed cogs illustrate the tightly coordinated function of the respiratory (lungs), cardiovascular (heart, blood and vessels), and muscle systems requisite for effective transport of O_2 and support of locomotory muscle energetics. $\dot{Q}O_2$, mitochondrial O_2 delivery; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; Creat-PO_4, creatine phosphate; Pyr, pyruvate; Lac, lactate; $\dot{Q}CO_2$, mitochondrial CO_2 production; $\dot{Q}O_2$, mitochondrial O_2 consumption. Upper panel redrawn from Wasserman et al. (433). Values given are for elite Thoroughbred horse.

We have therefore elected to place the horse center stage and, where possible, compare and contrast the available information for the dog at the very end of the article. In addition, observing the processes of diffusive gas exchange across the blood-gas barrier in the lung and at the blood–myocyte interface in the exercising muscle(s) during maximal exercise has so far presented intractable technical challenges. In these instances, we have resorted to extrapolations from other breeds, lower exercise levels, alternative models, and, where appropriate, emergent theoretical constructs.

Finally, whereas skeletal muscle, rather than the cardiovascular system or lungs, is responsible for setting the exercising O_2 demands and, with respect to the limitations on maximal O_2 flux, the cardiovascular system functions most strongly as a gatekeeper, and thus either may justifiably be ordered first, we have elected to follow the O_2 pathway from the atmosphere across the lungs and around the cardiovascular system to its site of utilization within the exercising muscle(s). However, the sections are constructed so that the readers can dip into them or reorder them as best serves their needs.

$\dot{V}O_2$ kinetics

How fast can $\dot{V}O_2$ increase at exercise onset?

Unless asleep or in contrived laboratory conditions, humans and animals are rarely in a prolonged steady state. When a human or animal transitions between different metabolic rates such as rest to running, the ATP requirement increases immediately whereas $\dot{V}O_2$ increases with finite speed or kinetics (Fig. 5; also see $\dot{V}O_2$ Kinetics chapter in this volume for a comprehensive coverage of this topic). The speed of these kinetics is of crucial importance because ATP not replenished by oxidative metabolism must be restored by substrate-level phosphorylation (anaerobic glycolysis and reduction of creatine phosphate, CP, stores) that incurs what has been termed an O_2 deficit (158). Three phases of the $\dot{V}O_2$ response to moderate exercise are discernible, each of which corresponds to a discrete physiological event (450,453,455,457-459). Thus, at the onset of moderate-intensity running (below the lactate threshold, T_{lac}), $\dot{V}O_2$ increases in a biphasic fashion, with an immediate phase (Phase I) thought to be driven by the elevated cardiac output ($\dot{Q}$) that accelerates the flow of venous blood through the lungs (Fig. 6). This is followed, some 15- to 20-s later, by the primary response (Phase II), which is initiated by the arrival, at the lung, of venous blood from the exercising muscles with a lower O_2 content. In Phase II, $\dot{V}O_2$ rises exponentially to the steady state (Phase III), which is reached when both $\dot{Q}$ and O_2 extraction by the working muscles reach their steady-state values. This response is typically modeled as a time delay (TD) and exponential with time constant, τ (which is the time taken to reach 63% of the final $\dot{V}O_2$). For heavy ($>T_{lac}$) or severe exercise (above the asymptote of the velocity-time-to-

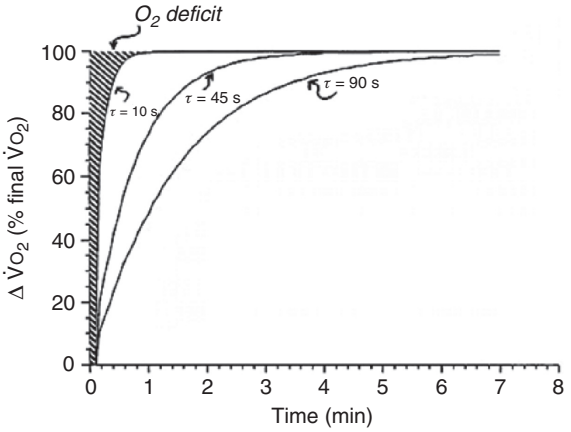


Figure 5 Effect of O_2 uptake ($\dot{V}O_2$) kinetics on the magnitude of the O_2 deficit (shaded area) as a function of relative $\dot{V}O_2$. The time constant, τ, denotes the time taken to reach 63% of the final response (steady-state $\dot{V}O_2$). Values for τ given, 10, 45, and 90 s, correspond to the Thoroughbred horse/elite human cyclist/marathon runner (185, 217,222), healthy young human and heart failure patient, respectively (301). Notice that the longer τ values (i.e., slower $\dot{V}O_2$ kinetics) mandate incurrence of a proportionally larger O_2 deficit. Redrawn from Poole (318).

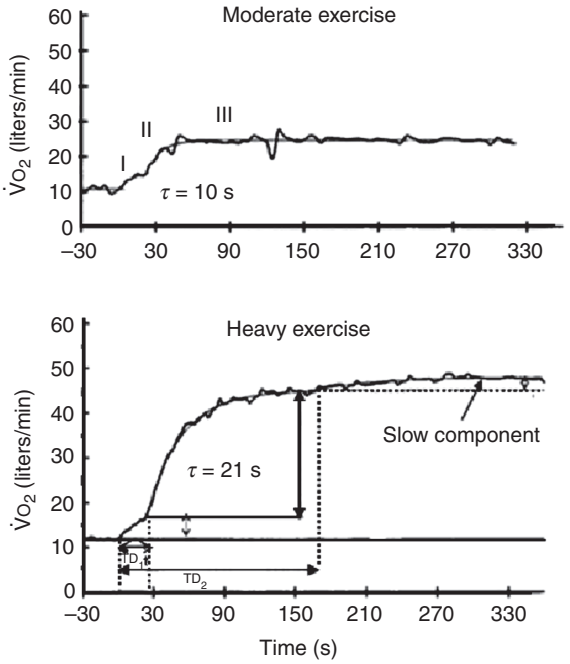


Figure 6 O_2 uptake ($\dot{V}O_2$) response kinetics at the onset of moderate (top panel, i.e., sublactate threshold, 7 m/s) and heavy (bottom panel, i.e., supralactate threshold, 10 m/s) intensity running in the Thoroughbred horse (redrawn from Langsetmo et al. 222). I, II, and III correspond to the respective phases of the $\dot{V}O_2$ kinetics (omitted from bottom panel for clarity). τ is the time constant of the phase II response. In the bottom panel, TD_1 and TD_2 denote the time delays prior to onset of phase II (primary fast exponential response) and slow component $\dot{V}O_2$ response, respectively. Note the slowing of the fast exponential $\dot{V}O_2$ (phase II) kinetics from moderate to heavy exercise and the emergence of the $\dot{V}O_2$ slow component for heavy- but not moderate-intensity running.

fatigue relation, critical velocity, CV, leading to $\dot{V}O_2$max and rapid exhaustion, see the *Adaptations to Training* section), the kinetics become more complex as about 80 to 120 s following the transition a second, slowly developing $\dot{V}O_2$ component (termed the slow component) becomes superimposed on the more rapid "primary" response (16,17,222,302,369,451,459; Fig. 6). In the severe exercise intensity domain, the slow component of $\dot{V}O_2$ drives it to its maximum ($\dot{V}O_2$max) (316, 319, 334, 336, 337, 453). These characteristic $\dot{V}O_2$ responses within the moderate, heavy, and severe exercise intensity domains bear a striking qualitative similarity between horses and humans (202, 203, 222, 318, 454).

For two individuals who transition to a given $\dot{V}O_2$, the one with the fastest kinetics (shortest τ), will have the least increase in intracellular lactate concentration ([lactate]) and fall in CP and therefore the lowest O_2 deficit (which can be approximated as $\Delta\dot{V}O_2 \times \tau$, where $\Delta\dot{V}O_2$ is the rise in $\dot{V}O_2$ from rest to steady state (186, 453, 459). Large O_2 deficits thus reflect a greater degree of intracellular perturbation, more rapid glycolysis leading to glycogen depletion, and poor exercise tolerance. Very fit individuals are characterized by high values for $\dot{V}O_2$max and fast kinetics (low τ) (134, 185, 217, 312, 339, 445). Compared with normal healthy humans for whom τ ranges typically from 30 to 45 s (and may be 90 s or longer in aged or patient [cardiac, pulmonary, diabetic] populations; refs. 18, 25, 43, 45, 122, 271, 288, 296, 384; rev. 325), the lowest τ's (fastest kinetics) ever measured in humans (8-10 s) were recorded for elite Belgian cyclists (217, see also 17) and also for Paula Radcliffe, who holds the world record in the women's marathon (185). In 1997, Langsetmo and colleagues (222) reported the first high-resolution $\dot{V}O_2$ kinetics data in Thoroughbred/Quarter Horses. In this group of subelite animals, $\dot{V}O_2$max ranged from 95 to ~150 ml/min/kg and τ for moderate exercise averaged 10 s (Figs. 6 and 7). As a direct consequence of these astonishingly fast $\dot{V}O_2$ kinetics, elite human athletes and horses can undertake substantial transitions between metabolic rates while minimizing their O_2 deficit and conserving muscle glycogen stores (201-203, 222, 338).

The crucial question as to whether the speed of $\dot{V}O_2$ kinetics is limited by O_2 delivery or metabolic inertia within the exercising muscles has fostered considerable polemic among respiratory physiologists. This issue is presented in depth in the $\dot{V}O_2$ Kinetics chapter in this volume. However, germane to the focus of the present article, some of the clearest evidence that the speed of the $\dot{V}O_2$ kinetics is not limited by muscle O_2 delivery *per se* has emerged from experiments on running horses and dog muscles and therefore will be considered here. Specifically, Kindig and colleagues (201, 202) measured $\dot{V}O_2$ kinetics following the onset of moderate- and heavy-intensity running in horses under control and L-NAME conditions. L-Nitro arginine methyl ester (L-NAME) induces a broad-spectrum blockade of nitric oxide synthase, thereby reducing the bioavailability of nitric oxide (NO). Two properties of NO are pertinent here: (i) It is a potent vasodilator acting within the skeletal muscle vasculature (162) and (ii)

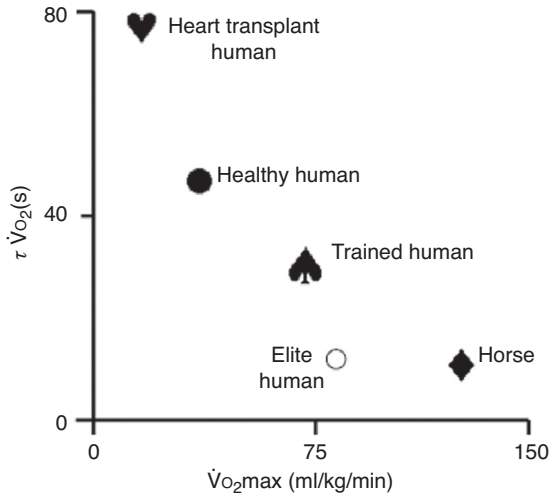


Figure 7 Time constant, τ, of the O_2 uptake ($\dot{V}O_2$) kinetics plotted as a function of maximal O_2 uptake ($\dot{V}O_2$max) for human heart transplant patients and their healthy controls (301), trained humans (339), elite humans (185), and the Thoroughbred horse (nonelite, 222).

NO inhibits mitochondrial oxidative function, particularly at the level of cytochrome oxidase (36). As seen in Figure 8, L-NAME acts to speed $\dot{V}O_2$ kinetics at the onset of moderate exercise in the horse. This is also true for heavy exercise in the horse (202) and for all intensities of exercise in the human (188, 189, 460) but not for surgically isolated, electrically stimulated canine muscle (121, see possible explanation for these disparate results in ref. 264). Thus, for the horse as for the human, relieving the NO inhibition of mitochondrial function speeds up $\dot{V}O_2$ kinetics despite the concomitant lowering of $\dot{Q}$ (207) and likely skeletal muscle blood flow ($\dot{Q}_m$) (162)—and thus muscle O_2 delivery—that occurs with NO blockade. These experiments support the contention that there is an abundance of O_2 available to the exercising muscle

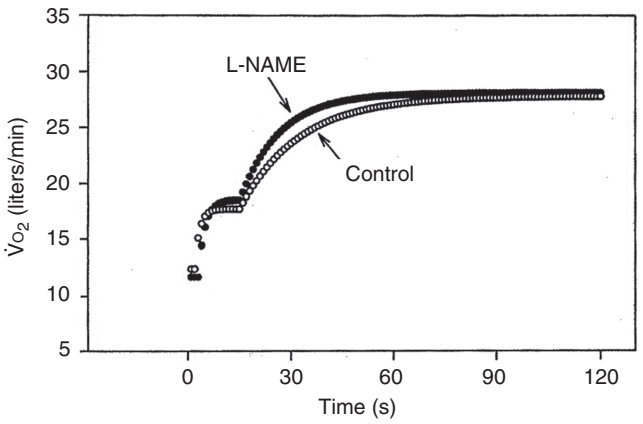


Figure 8 Nitric oxide synthase inhibition by L-NAME (N^G-L-nitro-arginine methyl ester) significantly speeds O_2 uptake ($\dot{V}O_2$) kinetics at the onset of moderate-intensity running (7 m/s) in the Thoroughbred horse. Redrawn from Kindig et al. (201).

mitochondrial oxidative machinery across the rest–exercise transition. The finding that increasing skeletal muscle O_2 delivery to the canine gastrocnemius-plantaris complex prior to submaximal or maximal intensity contractions either does not speed $\dot{V}O_2$ kinetics (submaximal, 119) or does so very minimally (maximal, 120) is also consistent with the site of limitation for $\dot{V}O_2$ kinetics residing within the contracting muscle(s).

Constant Speed and Incremental Exercise Responses

Like humans, horses can achieve steady-state $\dot{V}O_2$'s during moderate ($<T_{lac}$) and heavy ($>T_{lac}$) exercise (Fig. 6), whereas for higher running speeds in the severe domain that yield $\dot{V}O_2max$, $\dot{V}O_2$ does not evidence a steady state but rises to a $\dot{V}O_2max$ that can be sustained only fleetingly (e.g., Fig. 9, upper panel; 222). Those techniques that require gas exchange steady states such as the multiple inert gas infusion methods for resolving ventilation–perfusion relationships are thus forced to accept a quasi-steady state during severe-intensity exercise (429).

As for humans, the incremental exercise test, where work rate or running speed is increased fractionally each minute or so until the individual becomes exhausted, typically within 10 to 15 minutes, has become a popular technique for measuring the cardiorespiratory responses to exercise. This test is useful for measuring aerobic parameters ($\dot{V}O_2$ at the T_{lac} and $\dot{V}O_2max$) as well as the cardiovascular/hemodynamic, ventilatory, blood gas, and acid–base responses throughout the range of submaximal to maximal running speeds achievable.

Common features of the response to incremental exercise in the horse and human

Despite the far greater capacity for ventilation and gas exchange of the horse than for the human, there are several common features of the exercise response to a rapidly incremented exercise test deserving of mention. (i) $\dot{V}O_2$ (and heart rate [HR]) may increase as a close-to-linear function of running speed regardless of the trot–canter–gallop transitions (Fig. 9, panel A; 222, 266). $\dot{V}O_2$ may exhibit a defined plateau at $\dot{V}O_2max$: Often, however, the highest $\dot{V}O_2$ is achieved within the last minute of the test at the fastest speed attained (Fig. 9, panel A; 222). (ii) There is a clearly defined breakpoint in the $\dot{V}CO_2$ vs $\dot{V}O_2$ relationship. However, in the horse, this occurs at consistently higher $\dot{V}O_2$'s (~63% $\dot{V}O_2max$) than T_{lac} (~50% $\dot{V}O_2max$, 222, 266, Fig. 9, panel B). (iii) Toward $\dot{V}O_2max$, the respiratory exchange ratio (RER, $\dot{V}CO_2/\dot{V}O_2$) rises above 1.0 to achieve final maximal exercising values of 1.1 to 1.2 (222). Unlike humans, in horses, this elevation of RER to more than 1.0 results exclusively from the buffering of H^+ by bicarbonate, as arterial PCO_2 does not fall (see the *Disparate responses to incremental exercise in the horse and the human* section). (iv) Cardiac output increases as an approximately linear function of $\dot{V}O_2$, but due, in part, to the hemoconcentration from splenic discharge that elevates systemic hematocrit (H_{crit}) from ~30% to over 60% (Table 1) and arterial O_2 content (CaO_2) to more than 25 ml/100 ml (Table 1; 322), the slope of this relationship is somewhat lower than the 5 to -6 liters $\dot{Q}$/liter $\dot{V}O_2$ observed in the human (rev. 317). (v). Both horses and humans have a muscle oxidative capacity that exceeds that of the pulmonary-cardiovascular systems to supply O_2. Thus, the elevated $\dot{Q}$ present when horses run up an incline elevates muscle O_2 delivery and $\dot{V}O_2max$ (208, 265, 267). (vi). In the opposite direction,

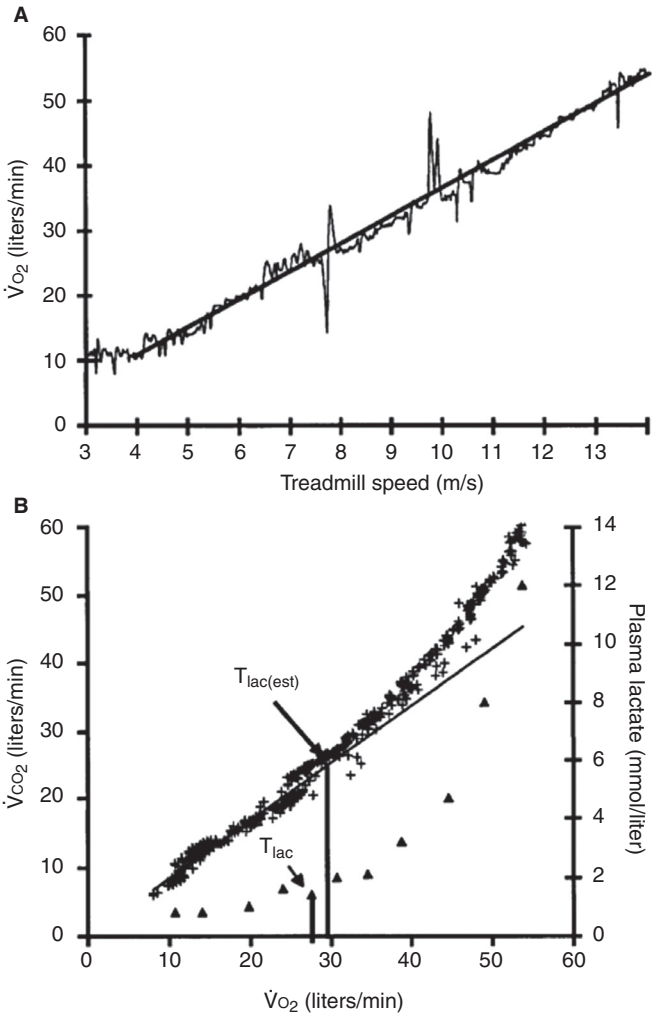


Figure 9 (A) O_2 uptake ($\dot{V}O_2$) response to an incremental exercise test where treadmill speed was increased 1 m/s each minute (from a 3 m/s baseline) until volitional fatigue in a nonelite Thoroughbred horse (222). Note highly linear (solid line) increase of $\dot{V}O_2$ as a function of speed despite trot–canter–gallop transitions. Note only fleeting attainment of $\dot{V}O_2max$ at highest speed. (B) Determination of lactate, T_{lac} and gas exchange, $T_{lac(est)}$ thresholds in the Thoroughbred horse during same test as in (A). $T_{lac(est)}$ was discriminated by the nonlinearity of $\dot{V}CO_2$ with respect to $\dot{V}O_2$ which detects the additional CO_2 produced consequent to HCO_3^- buffering of H^+ emanating from the exercising muscles (222, 266).

Table 1 Cardiovascular Responses to Maximal Exercise in a 500-kg Horse*

Variable	Rest	Exercise	Exercise/ rest ratio
Heart rate, beats/min	30	210-250	7-8
Cardiac output			
liters/min	30	240 to >450	8-13
SV, ml	1000	1700	1.7
Systemic systolic/diastolic arterial blood pressure, mmHg	130/80	230/110	1.6
Pulse pressure, mmHg	50	120+	3-4
Pulmonary artery pressure, mmHg	20-30	90-140	3-4
Hemoglobin concentration, g/dl	13	17-24	1.3-1.6
Hematocrit, %	30-40	60-70	1.5-2.3
O_2 uptake ($\dot{V}O_2$), ml/min/kg	2-4	160-220	40-110
liters/min	1.5-2.0	80-110	40-75
a-$\bar{v}O_2$ difference, ml/100 ml	5	20-25	4-5

*Data from 74 and 80, in part.

perturbations that reduce muscle O_2 delivery (e.g., splenectomy, 307, 426) reduce $\dot{V}O_2$max in the horse.

Disparate responses to incremental exercise in the horse and the human

Notwithstanding the similarities documented above, there are also distinct differences between the horse and the human. These include the following: (i) During the gallop, horses couple their breathing 1:1 with stride frequency (so called locomotory-respiratory coupling or LRC, 1, 13, 34, 38, 39, 93, 173, 463; c.f. humans, 31). This results in maximal breathing frequencies of 140 to 180/min compared with ~ 50 to 60/min in humans (173, 256, 266, 294, 304). (ii) The horse is an obligate nasal breather, and, because of the massive peak ventilatory flow rates demanded (>60 liters/s through each naris), the nasal passages tend to collapse on inhalation (166, 326). At any given airflow rate, this partial narrowing forces generation of even greater negative alveolar pressures which exacerbates rupture of the blood-gas barrier (81, 109, 166, 326). (iii) The astronomical values of $\dot{Q}$ achieved by the elite horse (>450 liters/min) necessitate far higher mean arterial pressure (MAP, >200 mmHg), pulmonary arterial pressure (PaP, >120 mmHg, 80, 322), and pulmonary capillary luminal pressure than those present in humans. (iv) The high intraluminal (positive) and alveolar (negative) pressures summate across the fragile blood-gas barrier, causing rupture, exercise-induced pulmonary hemorrhage (EIPH), and, on occasion, overt epistaxis (71, 81, 322). (v) Blood gases are not regulated as tightly in the horse as in the human (84, 94, 321, 322, 429, 455; rev. 449). Indeed, temperature-corrected arterial P_{CO_2} (Pa_{CO_2}) can rise to more than 60 mmHg and arterial P_{O_2} (Pa_{O_2}) fall to less than 60 mmHg exercise-induced arterial hypoxemia (EIAH) toward maximal running speeds (8, 9, 22, 84, 94, 294, 429). This occurrence is almost universally reported in the horse where it is more extreme than that found even in women and/or extremely aerobically fit humans (62, 145, 340). It is remarkable that despite the prodigious levels of gas exchange achieved in the horse during maximal exercise, the arterial blood gases resemble those of a severely emphysematous human patient with grossly dysfunctional lungs and a maximal gas exchange capacity some 1% to 2% that of the elite horse (c.f., 398, 425). In this regard, it is pertinent that the ventilatory system of the Thoroughbred horse is unresponsive to inspired CO_2 during high-intensity exercise (220). (vi) The ventilation threshold seen in humans that may be broadly temporally associated with T_{lac} (24, 40, 323, 433-435) is absent in horses (266). Indeed, from 7 m/s to the maximal speed (15 m/s) attained on an incremental treadmill test (increments 1 m/s/min) $\dot{V}O_2$ rises linearly with running speed but $\dot{V}E$ rises to less than 30% of that seen from rest to 7 m/s: Thus, the ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$ plummet (266, 294) helping to drive Pa_{O_2} downward and Pa_{CO_2} upward (294). This behavior presents as a very severe version of the mechanical limitations to $\dot{V}E$ seen particularly in healthy, very fit humans and especially women (61, 62, 142, 144, 146, 147, 184, 263). (vii) Blood [lactate] may rise to more than 30 mmol in the horse compared with 8 to 15 mmol in humans, but, owing to superior muscle and blood buffering of hydrogen ions, the pH does not fall as low as observed in humans during and following maximal exercise (12, 35, 149, 266, 294, 413). (viii) The lower surface area to body (and muscle) mass in the horse proves a greater challenge for heat dissipation than in humans. Consequently, body core temperature can rise extremely quickly in the horse and routinely achieves values of more than 42°C without discernible adverse effects (72, 94, 164, 256, 266, 294, 443).

These distinctions between species are afforded greater attention in their appropriate sections later.

Pulmonary System

Structure

Lung and airways

That the horse during maximal exercise becomes hypoxemic and hypercapnic has been considered, by some, as lung failure. In contrast, the position defended here is that the horse lung has evolved masterfully to facilitate the enormous $\dot{V}E$'s required to exchange over 110 liters/min each of O_2 and CO_2. Whereas the long history of athletic selection has successfully increased the heart size to 1%-2% of body mass, there simply has not been room in the thorax to undergo a proportional expansion of the lung.

Consideration of Fick's law of diffusion is instructive to compare and contrast the human and the horse to gain insights into how the horse lung subserves the apogee of mammalian

gas exchange:

$$\dot{V}_{gas} = \frac{A}{T} \times D_L(P_{alveoli} - P_{blood})$$

where $\dot{V}_{gas}$ corresponds either to O_2 moving from the alveolar space across the blood-gas barrier of area A and thickness T or CO_2 moving in the opposite direction. D_L for simplicity represents the functional diffusing capacity for the whole lung, which will be far higher for CO_2 than for O_2, in part, because it is largely dependent upon the solubility of the gas in the blood-gas barrier (~18 times higher for CO_2 than for O_2). $P_{alveoli} - P_{blood}$ denotes the driving pressures for O_2 or CO_2 across the blood-gas barrier.

The total lung capacity of a 500-kg horse may exceed 80 liters, and this supports a truly prodigious alveolar surface area estimated at almost 2500 m^2 (compared with 80-100 m^2 in humans), which equates to almost 10 doubles tennis courts (107, 256). Microscopically, the horse and human lungs appear similar. However, to reach the alveolar sac, there are almost twice as many airway generations in the horse (i.e., 38-43) versus the human (i.e., 23). In the horse, the alveoli themselves are somewhat smaller than found in humans (horse 70-180 μm, human 200-300 μm), giving a surface area of some 15,000 to 100,000 μm^2 each. Of course, not all the alveolar surface area brings blood into the intimate proximity of the alveolar gas and hence pulmonary capillary surface area (horse, 1700 m^2) may be the fairest estimate of A in Fick's law at least while running at $\dot{V}O_2max$. To accomplish this remarkable transposition of blood and alveolar gas, the pulmonary capillaries form a dense, catenated network that envelops each alveolus. In the horse at rest, the pulmonary capillary volume is some 1.8 times greater than in a steer of similar mass (52). Because the pulmonary capillaries are not supported (as are their counterparts in skeletal and cardiac muscles, 32, 33), they are subject to collapse when intraluminal pressure is low (i.e., at the apex of the human lung or dorsal aspect of the quadruped lung) or alveolar pressure becomes positive on exhalation. When $\dot{Q}$ and pulmonary arterial pressure (PaP), and hence capillary intraluminal pressure, rise during exercise, pulmonary capillary surface area will be increased by the processes of recruitment (of previously nonflowing capillaries) and distension (114, 135, 342, 467). Compared with humans (~0.3 μm thickness), the 6- to 7-μm diameter horse pulmonary capillaries have a thicker blood-gas barrier; (i.e., T in Fick's law equation (see the *Pulmonary Function* section) such that the total wall thickness—capillary endothelium, basement membrane, and alveolar epithelium—is ~1.0 μm; refs. 30, 107).

Several particular aspects of the horse's pulmonary anatomy are of interest here (Fig. 10). First, the horse's relatively long neck mandates an extended trachea and

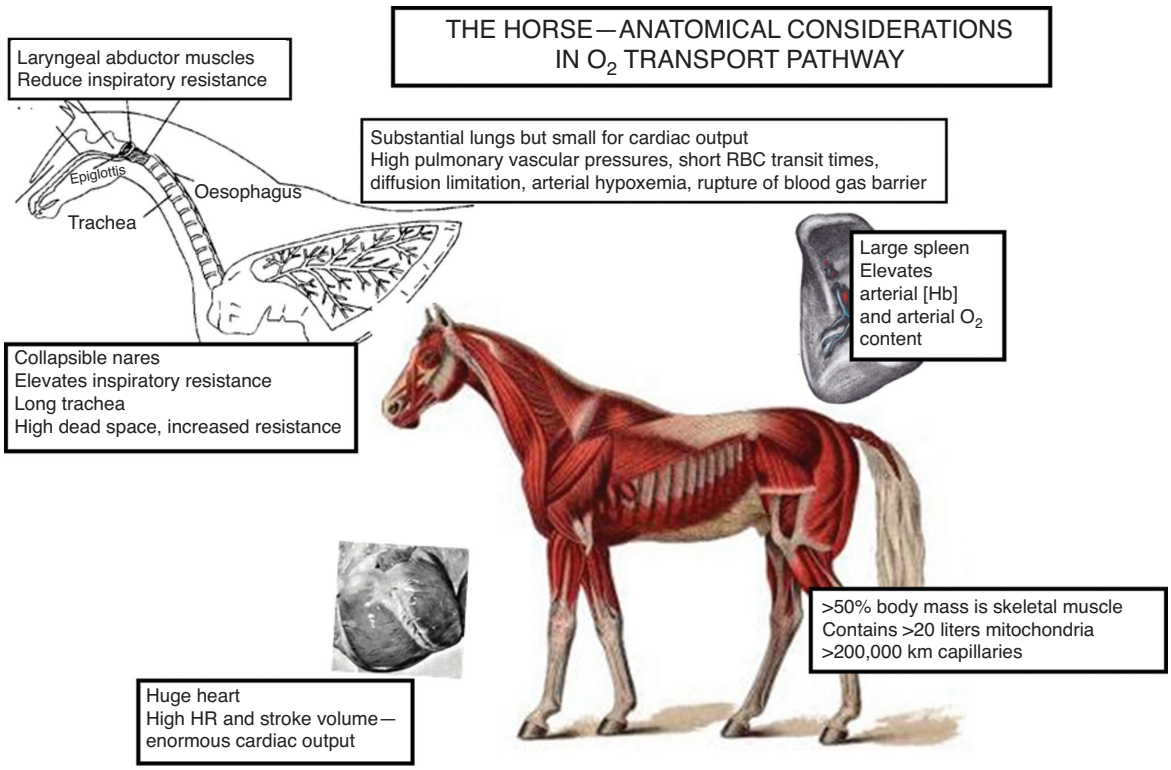


Figure 10 The unique anatomy of the horse illustrating the following key features in the O_2 transport pathway: (1) Unsupported nasal passages. (2) Laryngeal abductor muscles. (3) Long trachea. (4) Large lung capacity (but modest for cardiovascular system). (5) Dorsocaudal lobes where EIPH is most pronounced. (6) Large heart. (7) Large muscular spleen. (8) Great muscle mass with enormous absolute mitochondrial mass. See text for more details.

increases the volume of anatomic dead space, V_D, that must be overcome on each breath. Compared with the approximation of 1 ml V_D per pound body mass in humans, it may reach 3000 ml (i.e., 3 ml/lb or 6.6 ml/kg) in the resting horse. Thus, for a resting tidal volume, V_T, of 5 liters, V_D/V_T is 0.6, which is calculated to fall below 0.3 during maximal exercise (e.g., 304). Second, just rostral to the nasoincisive notch, the nasal passageway is unsupported. This constitutes the site of nasal passage narrowing during forceful inhalations when alveolar and hence airway intraluminal pressures become very negative. Prevention of this partial collapse has been achieved by means of the Flair equine nasal strip (see the *Exercise-induced pulmonary hemorrhage* section), which becomes a crucial issue as the horse is an obligate nasal breather during exercise and the upper airways present the major site of airflow resistance in the horse (≥70%, 10,81,166,326). Third, with respect to minimizing inspiratory resistance, it is pertinent that the exercising horse employs laryngeal abductor muscles during inspiration to increase tracheal cross-sectional area to about fourfold that present during resting expiration (219). Finally, compared with cattle and pigs, horses have relatively little pulmonary vascular smooth muscle (rev. 361). Thus, the horse evidences only a weak response to, for example, pulmonary hypoxic vasoconstriction, which induces a prolonged and substantial pulmonary hypertension when cattle and pigs are at moderate-to-high altitude. As discussed below (see the *Exercise-induced pulmonary hemorrhage* section), a weak, non–endothelin-mediated (293) vasoconstrictive tone does persist within the horse pulmonary vasculature even at maximal exercise and this can be reduced or abolished with inspired nitric oxide as evidenced by the fall in mean PaP at $\dot{V}O_2$max (205).

Respiratory muscles

In ponies, the respiratory muscles comprise ~5.5% of body mass and, during maximal exercise, can receive close to 15% of the cardiac output (253). As discussed below (see the *Pulmonary Function* and *Locomotory-respiratory coupling* sections), Marlin and colleagues (256, 257) determined that there is little or no chest wall expansion with inspiration in the galloping horse, which would seem to marginalize the inspiratory function *per se* of the external and internal intercostals and associated muscles from driving ventilatory flow directly. Rather, although these muscles may contract vigorously during galloping, and their blood flow response to exercise suggests that they do, their functional role may be to stabilize the chest wall for locomotory and possibly respiratory biomechanical advantage. This supports the notion that the diaphragm, which is often considered to be the principal inspiratory muscle in humans, may also serve a key role, along with thoracoabdominal segment extension/compression (257), in generating the ventilatory response to high-intensity exercise in the horse.

It has been a common misconception that the diaphragm consists simply of a thin musculotendinous sheath that serves to separate thoracic and abdominal compartments (333). In contrast to this opinion, the horse diaphragm comprises nearly 1% of body mass and is beautifully architectured to provide an extensive and powerful caudal displacement of the lungs and abdominal contents. Morphometrically, the muscular diaphragm averages 2 to 3 cm in thickness and contains a rich capillary and mitochondrial network (49, 171, 333). Horse diaphragmatic citrate synthase activity (a marker for mitochondrial oxidative capacity) is up to 55 μm/g/min, which is three- to fourfold that of the untrained human quadriceps (c.f., 235, 333). Moreover, in ponies and horses, costal diaphragm blood flow approaches 3.5 liters/kg/min exceeding by far that of all other respiratory and locomotory muscles (248-254).

Function

The highest $\dot{V}O_2$max published to date in the racehorse is 217 ml/kg/min (465). For a body mass of 500 kg, this corresponds to 108.5 liters O_2/min. Assuming an RER of 1.1, $\dot{V}CO_2$ will be close to 120 liters/min (321, 322, 465). At an arterial P_{CO_2} of 60 mmHg, this mandates an effective alveolar ventilation of ~1410 liters/min, which at a dead space:tidal volume (V_D/V_T) ratio of 0.3 (304) corresponds to a total minute ventilation over 2100 liters. At a stride and respiratory frequency of 130/min, V_T would be ~16 liters. This is slightly lower per kg body mass (~0.030) than that found in humans at maximal exercise (0.035) (304) and represents less than 40% (and maybe even <20%) of total lung capacity in the horse (it should be noted that the estimates of horse lung volumes of 40 to 49 liters were made on partially collapsed lungs and total lung capacities in the 80 to 100 liters range are more likely; see 52, 256).

The same calculations for Secretariat, arguably the greatest contemporary horse, whose $\dot{V}O_2$max has been estimated on the basis of heart mass (see the *Cardiovascular System* section) to exceed 120 liters/min would produce 132 liters/min $\dot{V}CO_2$ and require a total ventilation over 2300 liters/min to regulate his arterial P_{CO_2} at 60 mmHg.

These calculations provide a basis for understanding why the horse hypoventilates during high-intensity exercise, which both exacerbates the EIAH and negates the possibility of respiratory compensation for the metabolic acidosis that is a characteristic of humans. Figure 11 portrays graphically the alveolar ventilation equation:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{PaCO_2} \times k$$

where k is a constant that converts pressure to volume. Notice that in order for Secretariat to hyperventilate at maximal exercise and reduce arterial P_{CO_2} to 30 mmHg, $\dot{V}_A$ and $\dot{V}_E$ would have to exceed 3100 and 4600 liters/min, respectively, which, even if mechanically possible, would mandate an extraordinary respiratory energetic cost (8). The respiratory muscle blood flow and $\dot{V}O_2$ associated with that ventilatory work would presumably be diverted from the locomotory muscles and, if so, detract substantially from the horse's athletic performance. That the respiratory muscles can "steal" $\dot{Q}$ (and hence

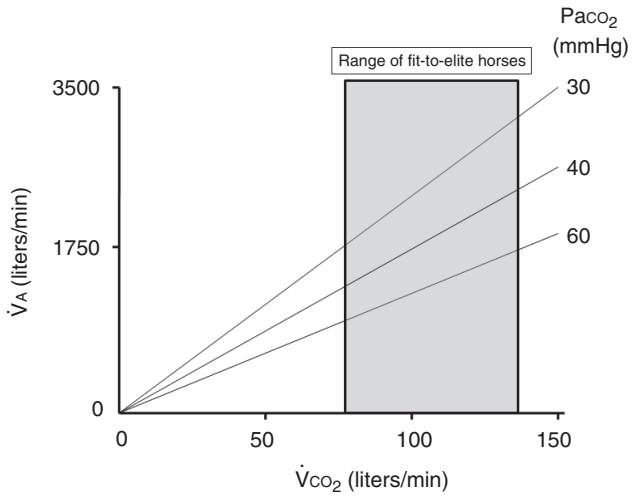


Figure 11 Required alveolar ventilation ($\dot{V}_A$, BTPS) plotted as a function of $\dot{V}_{CO_2}$. Note the phenomenally high $\dot{V}_A$'s and therefore $\dot{V}_E$'s (20%-30% higher than $\dot{V}_A$; ref. 304) that would be required if the horse chose to regulate its arterial P_{CO_2} (Pa_{CO_2}) at 40 mmHg or hyperventilated (Pa_{CO_2} 30 mmHg) as do humans.

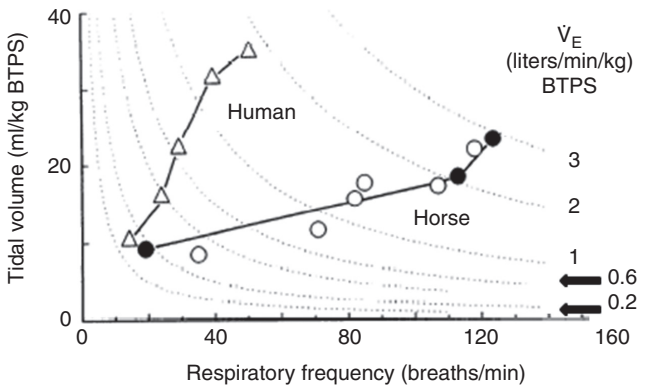


Figure 12 Breathing patterns at rest and up to near-maximal exercise in Thoroughbred horses and humans. Human data are from Clark et al. (47), horse data are from Hornicke et al. (173) and Pelletier and Leith (304). Note that, at the higher exercise intensities, horses achieve high mass-specific $\dot{V}_E$'s (dotted isopleths) by means of increased respiratory frequency in contrast to humans in whom mass-specific V_T increases preferentially. From Pelletier and Leith (304) with permission.

$\dot{Q}_{O_2}$) from the locomotory muscles during high-intensity exercise has been demonstrated in man (143, 148).

Locomotory-respiratory coupling

Breathing pattern control differs markedly between the horse and the human during submaximal and maximal exercise. Specifically, humans are not constrained to a particular stride to respiratory coupling ratio (31) and only 1% to 2% of V_T is generated by LRC (14). In contrast, at the canter and the gallop, the horse couples breathing 1:1 with stride frequency, and it has been proposed that LRC mechanically powers $\dot{V}_E$ to a substantial degree (34). As discussed below, it is doubtful whether this is true. However, this ventilation–locomotion synchrony (LRC) does mean that the prodigious $\dot{V}_E$'s of the exercising horse are achieved by the modulation of V_T at a breathing frequency that is dictated by the stride frequency (Fig. 12).

The provocative suggestion that LRC in quadrupeds is an obligatory mechanical constraint that powers inspiration and expiration, and in so doing acts to substantially reduce the energetic costs of ventilation (34), runs counter to several observations: (i) The diaphragm (4-5 kg; ref. 333) and other respiratory muscles have a substantial mass, great oxidative capacity, and an extremely high blood flow and metabolic rate during high-intensity exercise (248-250). (ii) Electromyographic studies indicate that the diaphragm is highly active in running horses (1). (iii) Breathing and stride frequency can be uncoupled in the galloping horse, for example, by breathing high CO_2 mixtures (111). (iv) Substantial transdiaphragmatic pressures are generated during exercise (402), which would contraindicate a passive sloshing backward of the abdominal contents or partial piston-like effect from this movement as the sole or even principal mechanism for the caudal motion of the diaphragm on inhalation.

Interestingly, Marlin and colleagues (257), using Respitrace bands, observed that during galloping, increases in both chest and abdominal circumference were 180° out of phase with inspiration and expiration. This was interpreted as evidence for elongation of the thoracoabdominal segment being the principal determinant of V_T during the canter and the gallop. In contrast, during lobeline-induced hyperpnea at rest, the four- to sixfold increase in V_T could be accounted for, in part, by chest wall expansion, which, as distinct from that seen at the gallop, occurred in-phase with inhalation. This observation demonstrates that the equine rib cage is not so stiff that it precludes chest wall participation in the exercise-induced hyperpnea. Rather, it appears that during fast locomotion (canter and gallop), it may be advantageous for the horse to lock the chest wall in place, possibly to increase thoracic stability and aid locomotory biomechanics.

Padilla and colleagues (294) tested the hypothesis that, if LRC is requisite for generating the high V_Ts, and hence $\dot{V}_E$'s of maximal exercise, $\dot{V}_E$ should drop substantially and immediately at the gallop–trot transition. As seen in Figure 13 at the gallop-trot transition, $\dot{V}_E$ did not decrease below that seen at the gallop for at least 15 s (i.e., ~30 breaths) and in three of five horses actually increased transiently above galloping levels. Subsequently, $\dot{V}_E$ was sustained over 1200 liters/min for in excess of 3 min. During this latter period, the breathing pattern changed dramatically, with frequency falling and V_T increasing reciprocally. These data are not consistent, with LRC being obligatory for achieving the high V_Ts and $\dot{V}_E$'s found in the exercising horse. Although not examined in this latter study, it is quite possible that the contribution of thoracoabdominal elongation crucial for increasing V_T at the canter and the gallop (257) was replaced by chest wall expansion at the trot and this facilitated attainment of tidal volumes close to 20 liters (Fig. 13; ref. 294).

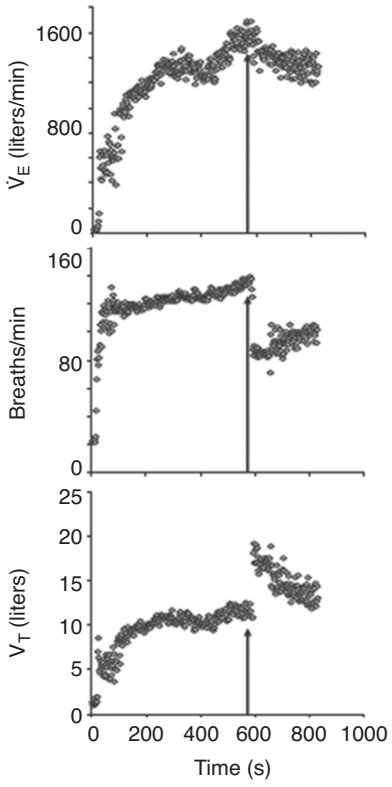


Figure 13 Breath-by-breath ventilation ($\dot{V}_E$), breathing frequency (*f*), and tidal volume (V_T) for a Thoroughbred horse at rest, during, and following (trotting recovery) a maximal incremental treadmill exercise test. Arrows denote the beginning of trotting recovery period. Note that $\dot{V}_E$ does not decrease upon cessation of galloping but is retained at or above maximal exercise levels for ~15 to 30 s by reciprocal changes in *f* (decrease) and V_T (increase). Indeed $\dot{V}_E$'s were maintained at more than 1200 liters/min for over 3 min following the transition to the trotting recovery. With kind permission from Padilla et al. (294).

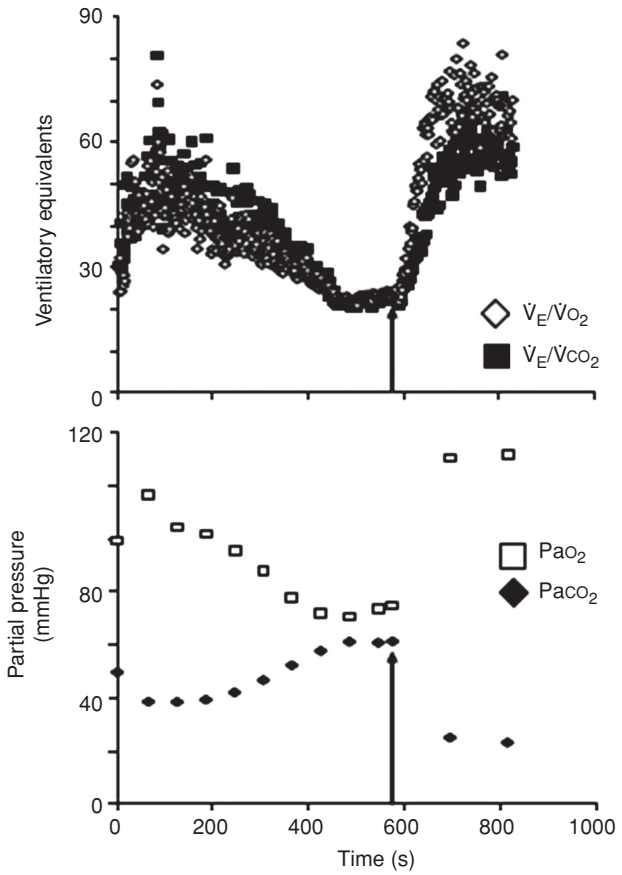


Figure 14 Ventilatory equivalents for O_2 uptake ($\dot{V}_E/\dot{V}O_2$) and CO_2 output ($\dot{V}_E/\dot{V}CO_2$) (top) and arterial partial pressure of O_2 (PaO_2) and CO_2 ($PaCO_2$) for the same Thoroughbred horse performing rest–incremental test to gallop–trot transition shown in Figure 13. Arterial blood gases are temperature corrected (94). Arrows denote the gallop–trot transition. Note the pronounced hypoventilation evidenced by the inexorable decrease of $\dot{V}_E/\dot{V}O_2$ and particularly $\dot{V}_E/\dot{V}CO_2$ that elevates $PaCO_2$ and contributes to the exercise-induced arterial hypoxemia (EIAH) neither of which is characteristic of, or prevalent in, healthy humans. See text for additional information. With kind permission from Padilla et al. (294).

Exercise-induced arterial hypoxemia and hypercapnia

As running speed increases toward the maximum, blood leaving the horses' lungs becomes progressively more hypoxemic and hypercapnic such that, in the extreme, temperature-corrected values for PaO_2 (94) fall below 60 mmHg and $PaCO_2$ rises above 60 mmHg (Figs. 14 and 15; refs. 23, 294, 429). Unlike humans where EIAH can occur in certain populations, especially in very fit athletes and women (60, 144-147), in the horse, EIAH is an almost universal occurrence (22, 84, 160, 207, 304, 420, 427). This EIAH can be partially relieved by unloading the respiratory system using a helium–O_2 (heliox) mixture (84) and wholly reversed by raising the inspired O_2 fraction from 0.21 to 0.35 (427). Whereas EIAH lowers hemoglobin (Hb)–O_2 saturation, it is important to realize that because of the influx of red blood cells (RBCs) from the spleen, exercising arterial O_2 content remains far above resting levels (Fig. 15, right panel). Exercise training in horses may exacerbate EIAH, although Christley et al. (46) found that the ~6 mmHg lowering of PaO_2 was wholly offset by an elevated arterial [Hb] such that CaO_2 during maximal exercise increased significantly from 23.9 to 25.8 ml/100 ml.

The mechanisms responsible for EIAH (and hypercapnia) have evoked considerable scientific interest and are discussed below in order of decreasing quantitative importance.

Alveolar-capillary O_2 diffusion limitation

In both humans (11, 60, 138, 144-147) and equids (23, 298, 368), the alveolar-arterial PO_2 difference (ΔA-aPO_2) increases as a function of exercise intensity. However, in the horse, it is consistently associated with a fall in alveolar PO_2 and thus the increasing ΔA-aPO_2 is driven by decreased arterial PO_2. Applying the multiple inert gas infusion technique, Wagner and colleagues (429) resolved that more than 70% of the ΔA-aPO_2 in horses during high-intensity treadmill running

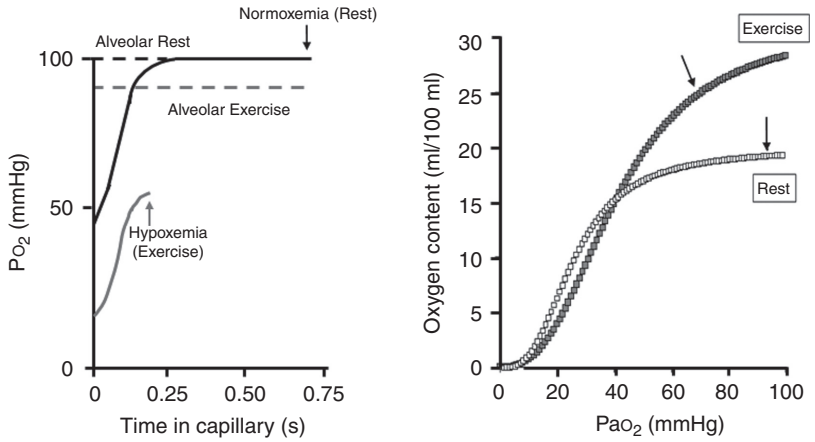


Figure 15 Schematics representing (left) Partial pressure of O_2 (P_{O_2}) in the red blood cell (RBC) as a function of pulmonary capillary transit time at rest and during maximal exercise. Note the reduction in alveolar P_{O_2} during exercise (due, in part, to alveolar hypoventilation, see Figs. 13 and 14) and the extreme decrease in RBC P_{O_2} as it enters (0 s) and leaves (<0.25 s later) the capillary during maximal exercise compared with rest. (right) O_2 dissociation curves in the Thoroughbred horse at rest (open symbols) and during maximal exercise (closed symbols). Pa_{O_2} denotes the arteriolar partial pressure of O_2. The arrows denote the arterial points under each condition. Note that the exercise-induced hemoconcentration elevates the O_2-carrying capacity almost twofold above rest, but during maximal exercise, the alveolar hypoventilation and short RBC transit times in the pulmonary capillary (diffusion limitation) conspire to reduce the arterial O_2 content far below the potential limit. See text for further details. Redrawn from Poole (318).

resulted from alveolar end-capillary diffusion disequilibrium (Fig. 15, left panel).

Alveolar-capillary O_2 diffusion limitation is driven primarily by very short pulmonary capillary RBC transit times that result from the inability of the pulmonary capillary bed to expand volumetrically more than two- to threefold from rest to exercise. In comparison, $\dot{Q}$ increases by a factor of from 8 to 13 (Table 1). This means that capillary RBC transit times fall precipitously according to the relation:

$$\text{RBC transit time (s)} = \frac{V_c}{\dot{Q}}$$

where V_c is the pulmonary capillary blood volume. Thus, using the disproportional increases of V_c and $\dot{Q}$ given above, from rest to exercise, RBC transit time will fall between 3/8 and 2/13 ($\dot{Q}$'s well over 400 liters/min, see the *Cardiovascular System* section) of that found at rest. If mean capillary RBC transit time is ~0.8 s at rest, then values as short as 0.3 to 0.12 s are calculated for maximal exercise. Karas and colleagues (193) calculated a value for mean capillary RBC transit time of 0.35 s in ponies, but these animals certainly did not have the immense $\dot{Q}$'s of the Thoroughbred horse. In humans, V_c has been calculated to be ~213 ml (106). For healthy individuals with $\dot{V}_{O_2}$max's between 3 and 4 liters/min, maximal $\dot{Q}$ is estimated at 20 to 30 liters/min, which would give a mean capillary RBC transit time of ~0.6 to 0.4 s. This quantitative comparison of the human versus horse certainly seems to provide an explanation for the increased incidence and severity of EIAH in the horse, particularly when considering that these are mean transit times and there is likely considerable dispersion about this mean. As such, in the exercising horse even if the mean transit time approaches 0.3 s, which might be adequate for more than 90% Hb–O_2 saturation, there must be a population of RBC transit times that are disappearingly short. Moreover, because of the sigmoidal shape of the Hb–O_2 dissociation curve, RBCs at the upper end of the transit time distribution, and therefore greater O_2 saturation, cannot compensate fully for their desaturated counterparts. The net effect of mixing hypoxemic with normoxemic blood in the pulmonary veins will be arterial hypoxemia. This hypoxemia will also be exacerbated by any fluid exudation across the blood-gas barrier into the alveolar space (see the *Exercise-induced pulmonary hemorrhage* section) and the rightward shift of the Hb–O_2 dissociation curve (reduced Hb–O_2 affinity, i.e., Bohr effect) caused by elevated blood temperatures, arterial hypercapnia, and acidosis (metabolic and respiratory).

As discussed by Wagner and colleagues (429), the dog presents an interesting contrast to the horse. Although morphometric estimates of 0.29 s for canine mean pulmonary capillary RBC transit time are somewhat shorter than those for the pony (0.35 s) (193), Schumaker et al. (388) found no evidence for significant $\Delta A\text{-}aP_{O_2}$ in normal dogs during high-intensity exercise. Given the high maximal $\dot{Q}$'s combined with the relatively modest V_c's in canines, this is puzzling: Whether this is also true for the Greyhound and other athletic breeds remains to be determined. The explanation

may be that horses and humans have greater heterogeneity of transit times or diffusion–perfusion matching than present in dogs.

Alveolar hypoventilation

As discussed above and presented in Figures 11 and 14, despite generating prodigious airflows the ventilatory equivalents for O_2 and CO_2 fall progressively during exercise as the rise in $\dot{V}_E$ and $\dot{V}_A$ per unit of gas exchange is truncated. The consequence of this is that the alveolar P_{CO_2} (P_{ACO_2}) rises and alveolar P_{O_2} (P_{AO_2}) falls. As calculated from the alveolar gas equation:

$$P_{AO_2} = P_{IO_2} - \left(\frac{P_{ACO_2}}{RER}\right) + \left[P_{ACO_2} \times F_{IO_2} \times \left(\frac{1 - \text{RER}}{\text{RER}}\right)\right]$$

where P_{IO_2} is the partial pressure of moistered air entering the alveolar space and F_{IO_2} is the fraction of inspired O_2. When P_{ACO_2} rises to 65 mmHg and RER is 1.1 (207, 266, 294, 427) P_{AO_2} will fall to 90 mmHg. Note that this situation is further accentuated by the retention of CO_2 in the arterial blood that would, if exhaled, have elevated RER further and in so doing have helped elevate P_{AO_2}. The interference of elevated P_{aCO_2} with Hb–O_2 binding (Bohr effect, right shift of the Hb–O_2 dissociation curve) will also impair O_2 loading in the pulmonary capillary.

For the human who hyperventilates to an arterial (and therefore P_{ACO_2}) of 30 mmHg and an RER of 1.3 (449) in response to the metabolic acidosis and other factors associated with high-intensity exercise, P_{AO_2} rises from ~100 mmHg at rest to 126 mmHg. Consequently, under these circumstances estimated P_{AO_2} is ~36 mmHg lower in the horse than human during maximal exercise and therefore contributes significantly to EIAH in the horse.

Mild ventilation-to-perfusion ($\dot{V}_A/\dot{Q}$) mismatch

Wagner and colleagues (429) hypothesized that the very high pulmonary arterial pressures (PaP, >120 mmHg, see the *Exercise-induced pulmonary hemorrhage* section) present in the galloping horse would increase $\dot{V}_A/\dot{Q}$ mismatch above that found in exercising humans who achieve mean PaP's between 35 and 40 mmHg (428). However, this was not the case. Whereas humans have a substantial increase in $\dot{V}_A/\dot{Q}$ mismatch during high-intensity exercise, it is unchanged in horses. This is particularly surprising given the propensity of the horse for EIPH.

Shunt

High-intensity exercise does not elevate intrapulmonary shunting in horses, which remains at or below 1% of $\dot{Q}$ from rest to near-maximal running speeds (389, 429). Whereas the multiple inert gas technique used by Wagner and colleagues (429) cannot assess directly blood shunted via the bronchial or thebesian vasculature, to produce the degree of hypoxemia (and ΔA-aP_{O_2}) found in that study, a postpulmonary shunt of 8% $\dot{Q}$ or ~24 liters/min would have been required. This magnitude of postpulmonary shunt is almost impossible to conceive.

One final note regarding EIAH in elite Thoroughbred racehorses: On the basis of heart size and the calculated $\dot{Q}$'s and metabolic rates for these horses, it is likely that both alveolar-capillary O_2 diffusion limitation and hypoventilation leading to low alveolar P_{O_2}'s are more severe in these animals. Consequently, it is expected that EIAH would be even more pronounced in the elite horse at $\dot{V}_{O_2}$max.

Exercise-induced pulmonary hemorrhage

EIPH denotes the rupture of the blood-gas barrier and escape of RBCs into the alveolar space and subsequently the airways. It is a serious health concern for horses that are exercised intensely or for prolonged periods and is a cause of poor performance (72, 75, 81, 300, 360). Traditionally thought to be a rare occurrence in humans, there is some evidence that, under certain circumstances, exercise may promote fluid leakage into the alveolar space (380) and also that frank EIPH may occur (110, 446). In comparison, in horses, examination of the lungs by endoscopy or bronchoalveolar lavage has revealed that EIPH is prevalent in Thoroughbreds, Standardbreds, and Quarter Horses during high-intensity running and is also associated with nonracing equine athletes including cross country, reigning, cutting, hunter-jumper, steeplechase, barrel, and draught horses (rev. 81). There is also recent evidence that prolonged submaximal running that generates lower but more sustained pulmonary capillary transmural pressures also causes EIPH (72). Thus, although overt epistaxis is uncommon in ~95% of horses, they do experience EIPH of varying severity after high-intensity running, and understanding the mechanistic bases of EIPH and its prevention constitutes a major focus of equine research (37, 81, 159, 223, 259, 343). To this end, it is pertinent that the use of bronchoalveolar lavage, which detects EIPH preferentially in the dorsocaudal region, has improved the ability to detect and importantly quantify the degree of hemorrhage (72, 81, 221, 273).

Elegant experimental approaches including the injection of 10- to 15-μm microspheres into the jugular vein have demonstrated that the blood detected in the lungs originates from the pulmonary rather than systemic (bronchial) circulation as originally thought (191). Subsequent electron microscopic studies by Erickson and colleagues (Fig. 16; ref. 79, see also 101) actually captured RBCs emerging from tears in the fragile blood-gas barrier (rev. 447).

Whereas EIPH has a complex etiology (81), rupture of the exquisitely thin blood-gas barrier (0.3-1 μm thick, depending upon species, 30) arises ultimately from very high, positive intraluminal pressure coupled with extremely negative alveolar

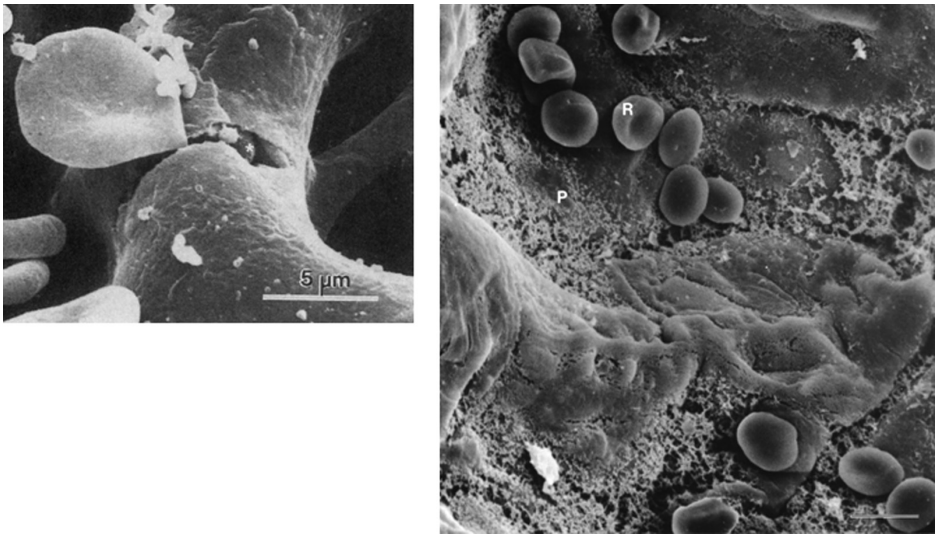


Figure 16 Rupture of the fragile blood-gas barrier. *Left*: Red blood cell (RBC) escaping from a fracture in the alveolar epithelium into the alveolar space. Reproduced with kind permission from Fu et al. (101). *Right*: Exercise-induced pulmonary hemorrhage (EIPH) in the alveolus of the equine lung. Reproduced with kind permission from Erickson et al. (79). Abbreviations: R, RBC; P, proteinaceous material. Scale bar = 5 μm.

pressure that summate across the blood-gas barrier resulting in mechanical failure (79, 81, 447, 448).

Key mechanisms implicated in EIPH in the horse include the following:

1. Pulmonary hypertension (mean PaP > 120 mmHg, 74, 82, 191, 291) resulting from extraordinarily high $\dot{Q}$'s, small cross-sectional area of the atrioventricular (AV) valves (321, M. Roger Fedde and Howard H. Erickson, unpublished findings), exercise-induced hyperviscosity (95, 96), regurgitation through AV valves caused by high ventricular pressures (466), ventricular relaxation rates that are too slow to permit sufficiently rapid filling of the ventricle at lower left atrial pressures (75, 81, 255), and putative arteriolar vasoconstriction (200, 205, 208)—although this latter mechanism may also serve a protective role as NO-induced reduction of PaP actually increases the severity of EIPH (200, 205).

2. Extremely negative intrapleural and alveolar pressures that are increased by factors that raise airway resistance. In particular, laryngeal hemiplegia (53) and inspiratory nasal collapse (78, 81, 109, 326).

3. Small airways inflammation secondary to previous incidences of EIPH (70, 290).

4. Mechanical stresses of respiration and locomotion that summate in the dorsal-caudal lobes (387).

5. $\dot{Q}$ distribution within the lung that results in very high flows to the dorsocaudal region (27, 81).

6. Altered mechanical characteristics of lung parenchyma such that the severity of EIPH within a given horse increases progressively with cumulative damage over weeks, months, or years (75, 78, 81, 256).

In vivo and *in vitro* approaches have been used to demonstrate that threshold PaP's exist above which the integrity of the blood-gas barrier is compromised (221, 273, 447). Initial successful investigative and therapeutic approaches aimed at reducing EIPH targeted reducing PaP, whereas more recently, attention has been focused on improving lung function and reducing the magnitude of the inspiratory negative pressures. Collectively, these approaches include the following:

1. Reducing PaP by decreasing systemic and pulmonary blood volumes with the high-loop diuretic furosemide reduces EIPH by ~50% (78, 81, 109, 204, 291).

2. Applying Flair nasal strips to constrain collapse of the nasal passages effectively reduces inspiratory resistance and the capillary transmural pressure gradient as well as whole-body $\dot{V}O_2$ and decreases EIPH by ~50% (109, 166, 204, 326).

3. Reducing the inflammatory response to EIPH episodes by immunomodulatory approaches (70) has also proven successful at reducing but not eliminating EIPH.

Unsuccessful approaches that have been tested in carefully controlled laboratory trials include NO inhalation (205) and Chinese herbal remedies (71). Inhaled NO treatment

that reduces PaP actually exacerbates EIPH (200, 205). This dissociation between EIPH severity and PaP has also been demonstrated during inclined running which lowers PaP but increases EIPH (208). These findings suggest that, under normal circumstances, pulmonary vascular conductance may be carefully regulated to protect more susceptible regions of the lung (i.e., the dorsocaudal lobes) from hypertensive damage. However, whilst removal of this control may lower overall PaP, it may open up more fragile vascular pathways and, within the dorsocaudal lobes, elevate capillary pressures to levels that subsequently rupture the blood-gas barrier. In this regard, it is pertinent that there is a differential sensitivity to vasodilators across lung regions (305) that may be responsible for negating the effects of gravity on $\dot{Q}$ distribution in the horse lung and ensuring preferential $\dot{Q}$ distribution to the dorsal versus ventral regions of the lung (27, 76, 163, 399).

Cardiovascular System

Structure

Heart

Heart mass is the principal determinant of maximal stroke volume (SVmax), cardiac output ($\dot{Q}$), and consequently aerobic capacity ($\dot{V}O_2max$) and athletic performance. In humans, this relationship has emerged from electrocardiographic (ECG), ultrasonographic, radiographic, and postmortem analyses of heart size. For example, seven-time Boston marathon winner Clarence DeMar's healthy heart was huge for his body size, with coronary arteries threefold larger than typical for his nonathletic peers (151). The multiple Olympic champion distance runner Paavo Nurmi's heart was reportedly three times larger than predicted for his body mass (151).

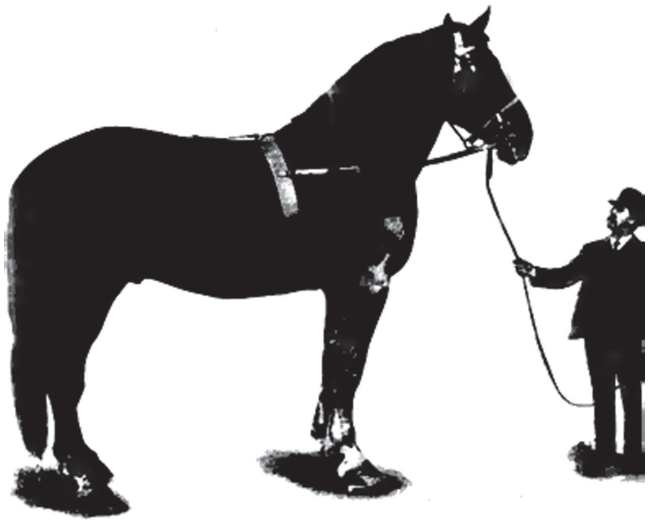
Heart mass in horses averages ~1% of body mass, which exceeds that for other nonathletic species, including humans (Fig. 17), and, in exceptional animals, may be as high as 2% (151, 321, 322, 436). Compared with nonracing breeds, the hearts of racing horses are proportionally larger (see Table 2 for some famous horses and their respective heart mass). Sham's heart at 18 lb (8.2 kg) was the heaviest healthy heart ever weighed (151). Unfortunately, his superb athleticism was overshadowed because he had the misfortune to overlap careers with Secretariat to whom he was consistently runner-up. To many, Secretariat was the greatest horse ever: he won the Olympics of horse racing, the Triple Crown, and several decades later still holds the track record at Belmont Park (2 min 24.4 s for 1.5 miles on turf) (321, 322). Although Secretariat's heart was never weighed, the same pathologist, Dr. Thomas Swerczek, who weighed Sham's heart has estimated that Secretariat's heart, which appeared in perfect condition, weighed 22 lb (10 kg, ~2% body mass). Assuming this estimate to be correct, Figure 18 predicts that Secretariat could have attained $\dot{Q}$'s over 500 liters/min and a $\dot{V}O_2max$ exceeding 120 liters/min! Figure 17 allows direct visual comparison between the heart size of an exceptional racehorse (Key to the Mint, heart mass 15.8 lb, 7.2 kg) and that of an unexceptional stallion of similar body mass.

Accepting that heart mass in and of itself is no guarantor of athletic supremacy, the common finding of exceptionally large hearts in superb racehorses has stimulated interest in developing accurate, noninvasive techniques to estimate heart mass. With respect to the QRS complex, the mean/average duration in milliseconds of the QRS complex—for ECG leads I, II, and III—is termed the "heart score" and correlates with racing performance and also heart mass determined at autopsy (151, 210). Thus, larger hearts exhibit a wider QRS complex and their higher heart score would, in theory, be predictive of a higher SV and therefore maximal value for $\dot{Q}$. Unfortunately, not all studies have supported the relationship between heart score and heart mass (125, 140, 232, 233, 376) or performance (313). Irrespective of the latter disagreement, heart scores may be genetically determined (408), with the gene responsible for coding for heart mass located on the X chromosome (151).

A compelling perspective on the horse heart as a mechanical pump is that it achieves such high $\dot{Q}$'s and that it does so through valves that are of very modest diameters. Specifically, the cross-sectional area of the right AV valve has been measured at ~61 cm^2, whereas the left AV valve is only ~60% of this (38.1 cm^2; ref. 321, and M. Roger Fedde and Howard H. Erickson, unpublished observations). The resistance to flow mandated by this small AV valve may be an important factor in raising left atrial, pulmonary venous, pulmonary capillary, and thus PaP's and, in so doing, contribute to EIPH.

Spleen and circulation

The Thoroughbred race horse has a blood volume of ~10% of body mass (i.e., ~50 liters, 306, 307, 426), of which ~75% resides in the systemic circulation. Thus, of the total blood volume, 45% is in the venous and 11% in the arterial system. The ability to deliver O_2 to the periphery is a function of both $\dot{Q}$ and arterial O_2 content (CaO_2). We have already appreciated the very high $\dot{Q}_{max}$'s achieved by the horse and have considered that during high-intensity exercise the PaO_2 in the blood leaving the lung may fall to 60 mmHg or lower at which pressure the Hb is far from fully saturated with O_2. However, as seen in Table 1, the horse's systemic hematocrit increases from 30% to 60%, or more, as the huge muscular spleen contracts and dumps more than 12 liters of comparatively small ~5.5-μm diameter (2) RBCs into the circulation, thereby approximately doubling the circulating RBC mass (278,306-308,426). Splenic mass is significantly greater in racing horse breeds than in their nonracing counterparts (i.e., stock, draught, and Arabian) (210). As might be intuited, overall splenic reserve is correlated with splenic mass and total blood volume rather than body mass *per se* (140, 306, 307).



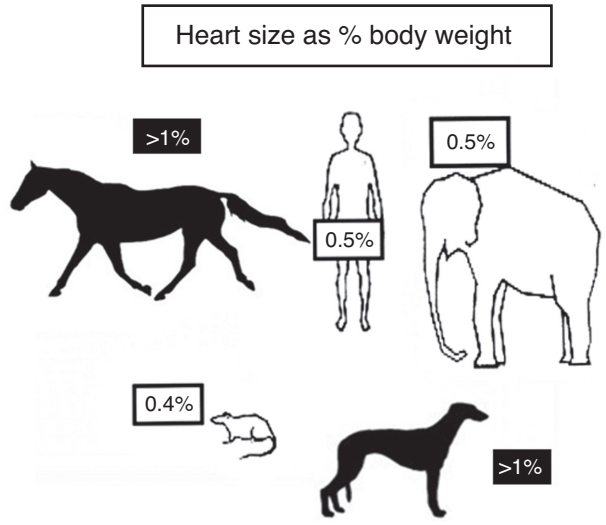


Table 2 Heart Weights of Famous Race Horses (151)

Name of horse (color, sex, year of birth)	Heart, lb	Weight, kg
Secretariat (ch.s. 1970)	22	10
Sham[a] (ch.s. 1970)	18	8.2
Mill Reef[a] (b.s. 1968)	16.9	7.7
Key to the Mint (b.s. 1969)	15.8	7.2
Easy Goer (ch.s. 1986)	15	6.8
Althea (ch.m. 1981)	15	6.8
Eclipse (ch.s. 1764)	14	6.4
Phar Lap (ch.g. 1926)	14	6.4
Star Kingdom (ch.s. 1946)	14	6.4
Tulloch (b.s. 1954)	13.5	6.2
Killaloe (b.m. 1970)	12.9	5.9

[a]Some pathologic enlargement (may add 2-3 lb to heart weight).
Abbreviations: b, bay; ch, chestnut; g, gelding; m, mare; s, stallion

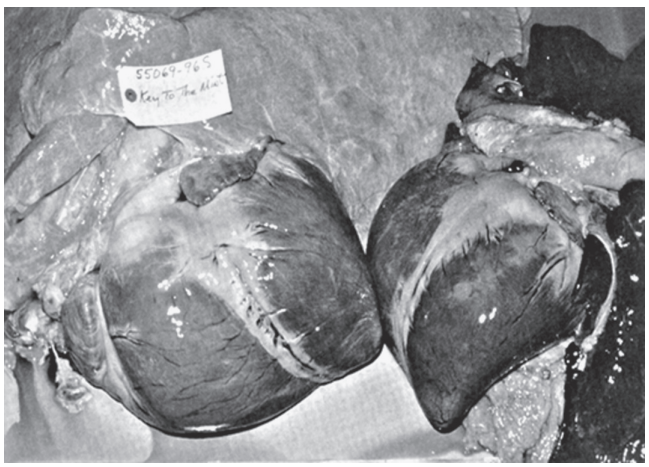


Figure 17 It is not simply heart mass (and therefore pumping capacity and muscle O_2 delivery) that facilitates superb O_2 transport potential and athletic ability in the Thoroughbred horse but the ratio of heart mass to body mass. Dr. Le Gear, one of the world's largest horses (body mass 3940 lb or 1791 kg), must surely have possessed an enormous heart (*top panel*). Photograph courtesy of Mr. Weldon Dudley. However, among species differing in body mass (*center panel)* from the 250 g rat to the 4,000 to 12,000 kg (8,800-26,400 lb) elephant, the horse's heart, and in particular the Thoroughbred's heart, is outstandingly large and averages more than 1% body mass, reaching an estimated 2% in the extreme (318, 321, 322). Note also that the mixed-breed dog's heart averages close to 1% body mass (and up to 1.7% for Greyhound, see *The Athletic Dog* section). Both are proportionally larger than that of the human, rat, or elephant. *Lower panel*: Comparison of heart size in a champion Thoroughbred (Key to the Mint, 7.2 kg, 15.8 lb, left-hand side) with that of an average stallion of similar body mass (5.5 kg, 12 lb, right-hand side). Photograph courtesy of Dr. Thomas Swerzek.

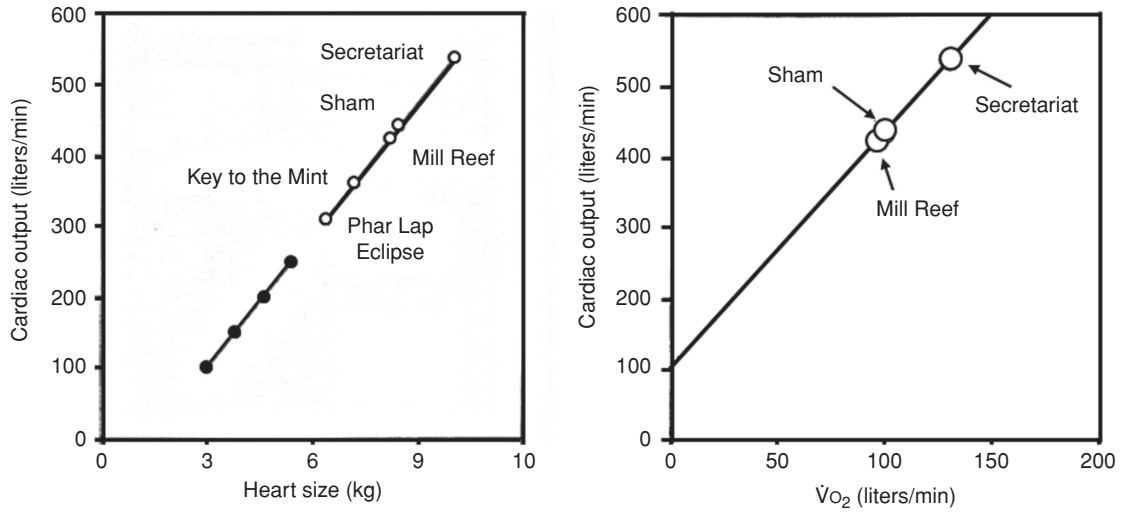


Figure 18 Relationship between cardiac output ($\dot{Q}$) and either heart mass (*left panel*) or O_2 uptake ($\dot{V}o_2$) (*right panel*) during maximal exercise. The solid symbols at the left are from the data of Evans and Rose (91, 92) , whereas the hollow symbols are extrapolated from that relationship using either the measured or estimated (Secretariat) heart weights published for each named horse (151). For the $\dot{Q}$ to $\dot{V}o_2$ relationship at the right, an arterial-venous O_2 difference ($\Delta CaO_2 - C\bar{v}O_2$) of 22.8 ml/100 ml blood is assumed to estimate maximal O_2 uptake ($\dot{V}o_2max$) values for Secretariat, Sham, and Mill Reef. Note Secretariat's $\dot{Q}$ (~540 liters/min) and $\dot{V}o_2max$ (>120 liters/min or ~240 ml/kg/min at 500 kg of body mass). Redrawn from Poole and Erickson (321, 322) and Poole (318).

Function

In horses, as in humans, the high energetic capability of skeletal muscle outstrips the ability of the cardiovascular system to deliver all the O_2 that it can utilize. This means that during large muscle mass exercise such as running (or cycling, swimming in humans), $\dot{V}o_2max$ may be increased by any perturbation that raises skeletal muscle O_2 delivery. This O_2 delivery limitation has been repeatedly demonstrated within humans and/or select mammalian species by a range of paradigms, all of which raise $\dot{V}o_2max$, either of the whole body or isolated muscle groups, significantly (317, 321, 322, 430):

1. Elevating $\dot{Q}$ via increased SV by means of either running horses on an incline (6°) (265, 267) or removing the constriction of the pericardial sac (dogs, 412; pigs, 137).

2. Raising Cao_2 by either increasing circulating blood volume and systemic hematocrit by reinfusion of autologous RBCs (humans, 113) or breathing high O_2 mixtures (humans, 214; horses, 427).

3. Knee extensor exercise reduces the mass of exercising muscle(s) to ~15% to 20% of that during conventional cycling and elevates mass-specific $\dot{Q}$ and $\dot{V}o_2$ of recruited muscles several-fold above that seen during whole-body exercise (humans, 4, 345).

Conductive O_2 transport (lungs to muscle)

From the above, it is evident that high rates of O_2 delivery ($\dot{Q}o_2$) are requisite for achieving high $\dot{V}o_2max$'s, and it is therefore instructive to break down $\dot{Q}o_2$ into its components:

$$\dot{Q}o_2 = \dot{Q} \times Cao_2$$
$$\dot{Q} = HR \times SV$$

Therefore,

$$Cao_2 = ([Hb] \times 1.34 \times \text{fract. } O_2 \text{ Sat}) + (\sim 0.3 \text{ ml}/100 \text{ ml dissolved } O_2 \text{ [small and therefore neglected below]})$$
$$\dot{Q}o_2 = HR \times SV \times [Hb] \times Hb\text{–}O_2 \text{ binding capacity} \times \text{fract. } O_2 \text{ Sat}$$

Horse blood has a somewhat higher O_2 affinity than human blood with a P_{50} (O_2 pressure that gives 50% Hb–O_2 saturation) of ~25 mmHg (3, 21) as compared with 27 mmHg in humans (3), which is in keeping with the general leftward shift in P_{50} with increased body mass seen across the animal kingdom; for example, elephant P_{50} = 22 (20), dog P_{50} = 29 (19), rat P_{50} = 38 (136), mouse P_{50} = 52 (136). Thus, in the horse at rest as for humans, arterial blood is close to fully saturated with O_2 (i.e., ≥97%).

Table 1 details the rest and maximal exercise values for key cardiovascular variables in the horse. During exercise, SV in the horse is primarily a function of heart mass and may increase ~70% above resting to achieve values of ~ 1700 ml in a fit Thoroughbred and exceed 2000 ml in an exceptional animal (74, 80, 321, 322). Although maximal HR across species generally declines with increasing body mass, horses typically achieve HR's between 210 and 250 at maximal exercise, which is somewhat high for their mass. Together HR and SV conspire to elevate $\dot{Q}$ from 30 liters/min at rest to over 450 liters/min in the elite running race horse

(Fig. 18). As for humans, the horse's highly developed vasomotor system can redistribute this $\dot{Q}$ among the appropriate organs, depending upon whether the demands call for digestive or locomotory activity. Thus, at rest, only about 15% of the 30 liters/min $\dot{Q}$ (i.e., ~4.5 liters) perfuses skeletal muscle, whereas during maximal exercise, skeletal muscle receives more than 80% of 450 liters/min (360 liters/min, i.e., >80-fold resting values) (Fig. 19; refs. 5, 74, 80, 321, 322). To achieve these exercising $\dot{Q}$'s and direct $\dot{Q}$ preferentially to skeletal muscle, systolic/diastolic pressures increase from resting (130/80 mmHg) to well over 230/110 mmHg (MAP > 200 mmHg, 26, 74, 89, 174, 200, 201, 297), with pulse pressure widening from 50 to over 120 mmHg. MAP is determined by the product of $\dot{Q}$ and total peripheral resistance (TPR). In turn, TPR is set primarily by the total cross-sectional area of all flowing arterioles (principal site of resistance to $\dot{Q}$) and also blood viscosity that rises as a function of the elevated exercising systemic hematocrit (95,96,461). Thus, there is a massive exercise-induced arteriolar vasodilation in active skeletal muscle that acts to increase vascular conductance and lower TPR (48,59,65,228,229,275, 321,370,371,391) whereas the increased blood viscosity acts to constrain the full magnitude of this effect.

Cardiovascular control subserves two vital and sometimes opposing demands: while maintaining MAP within an acceptable range, $\dot{Q}_m$ must achieve levels commensurate with O_2 and substrate needs. On the one hand, excessive MAP will impair vascular integrity and promote fluid exudation from the vasculature resulting in tissue damage, whereas, on the other hand, excessive vasodilation will reduce MAP and compromise $\dot{Q}$ to critical organs such as the brain. Within skeletal muscle even at maximal exercise, there is a profound sympathetic vasoconstrictor tone, at least in humans (372), and the elevation of $\dot{Q}$ and lowering of TPR in horses run maximally on the incline (208, 267) suggest that this occurs to some degree in horses. As mentioned in the *Pulmonary System* section, there is also evidence that the pulmonary vasculature sustains some vasoconstrictor tone even during maximal exercise (200, 205).

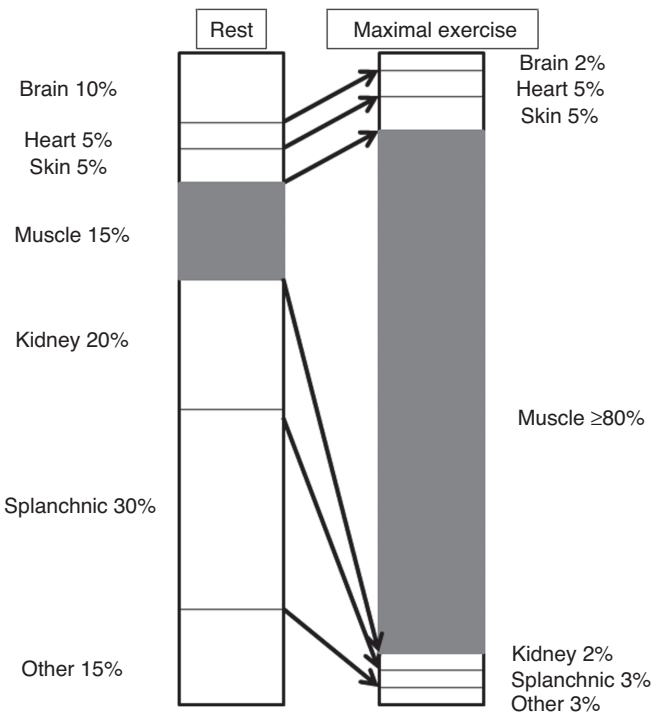


Figure 19 Distribution of cardiac output ($\dot{Q}$) at rest and during maximal exercise in the Thoroughbred horse. It is likely that skeletal muscle blood flow may reach 90% of $\dot{Q}$. Values from Erickson (74), Armstrong et al. (5), and Erickson and Poole (80).

With respect to Ca_{O_2}, sympathetically mediated splenic contractions increase circulating blood volume and elevate systemic hematocrit from 30% at rest to 60+% shortly after the onset of maximal exercise which increases [Hb] up to ~24 ml/100 ml. If the ~97% Hb–O_2 saturation at rest was maintained during maximal exercise, Ca_{O_2} would increase to an impressive 30 ml/100 ml or so. However, depending on the degree of EIAH, values in the 25 to 28 ml/100 ml range are found (74, 80). Thus, EIAH limits the maximal O_2 extraction to ~20 to 26 ml/100 ml (74, 80). Whereas the mechanisms that determine the maximal O_2 extraction and O_2 diffusing capacity (D_{O_2}) are considered below in the *Muscular System* section, it is appropriate to discuss here how $\dot{Q}$ and O_2 extraction or arterial-venous (or mixed venous) O_2 difference ($\Delta Ca_{O_2} - C\bar{v}_{O_2}$) conflate to yield a given $\dot{V}_{O_2}max$.

Thus, according to the Fick principle:

$$\dot{V}_{O_2}max = \dot{Q}(\Delta Ca_{O_2} - C\bar{v}_{O_2})$$

Figure 20 (362, 430) illustrates the interdependence of convective (Fick principle) and diffusive (Fick's law) O_2 delivery in setting $\dot{V}_{O_2}max$. Thus, during maximal exercise, at the presiding $\dot{Q}_{O_2}$, $\dot{V}_{O_2}max$ will be determined by the effective muscle O_2 diffusing capacity ($D_{O_2}m$), which is proportional to the slope of the line from the origin to $\dot{V}_{O_2}max$. Notice that the reason venous P_{O_2} does not, and indeed cannot, fall to zero is because this would, by definition, require an infinitely high muscle D_{O_2} (slope projecting vertically up the ordinate). However, in the horse, spectacularly high fractional extractions of more than 90% and low venous P_{O_2}'s close to 10 mmHg have been measured (427), necessitating an enormous D_{O_2}. Note from Figure 20, any increase in $\dot{Q}_{O_2}$ in the absence of an elevated D_{O_2} will increase Cv_{O_2} and decrease fractional O_2 extraction. This aspect of the adaptations to exercise training in the horse is dealt with in the *Adaptations to Training* section.

Muscular System

As detailed below, horse muscles and fiber types evidence some differences from other mammalian counterparts (e.g., very high H^+ buffering potential, 395) but the capillary architecture and mitochondrial oxidative potential are not markedly different. What appears to distinguish the athletic horse from

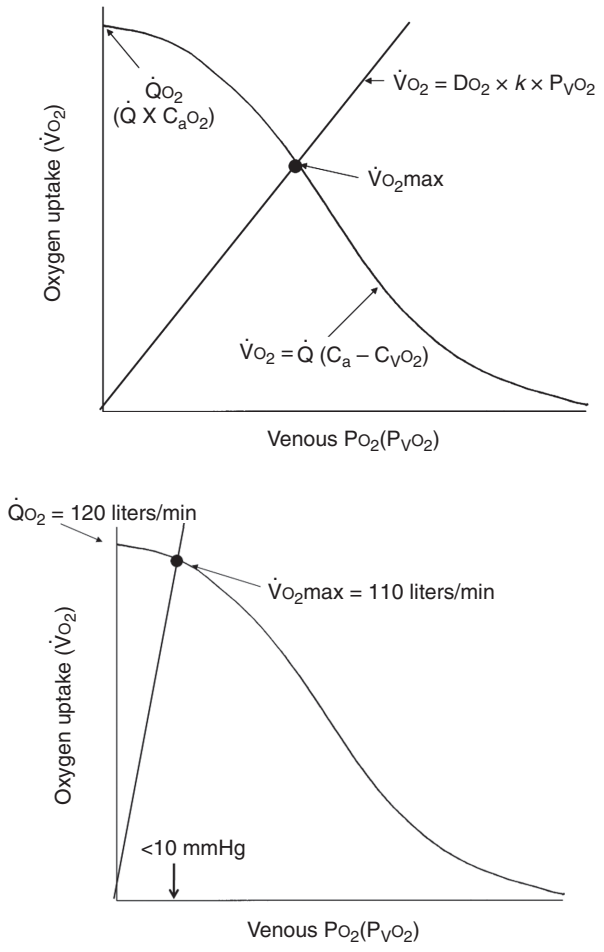


Figure 20 Determination of maximal O_2 uptake ($\dot{V}O_2max$) by conductive ($\dot{Q}O_2$) and diffusive (DO_2) movement of O_2 by the cardiovascular and muscle microcirculatory systems ("Wagner" diagram; 362, 430). The curved line denotes mass balance according to the Fick principle and the straight line from the origin represents Fick's law of diffusion. DO_2 is the effective diffusing capacity and *K* is a constant that relates venous PO_2 to mean capillary PO_2. PvO_2, CaO_2, and $C\bar{v}O_2$ are the partial pressure of venous O_2 and the concentrations of O_2 in arterial and venous blood, respectively. $\dot{V}O_2max$ occurs at the confluence of the two relationships. The *top panel* is a general schematic, whereas the *bottom panel* presents values for an elite Thoroughbred at maximal exercise. Understanding the conductive and diffusive determinants of $\dot{V}O_2max$ is essential for interpreting the structural and functional mechanisms that increase $\dot{V}O_2max$ with exercise training (see the *Adaptations to Training* section). See the text for additional details.

less athletic breeds and other mammalian species is its prodigious muscle mass (absolute and relative to body mass).

Structure

Athletic breeds of horses have a skeletal musculature that exceeds half of their body mass (i.e., ~52%-55% for a mature Thoroughbred) (e.g., 130). This compares with a muscle mass of 30% to 42% for nonathletic horse breeds and most other mammalian species and reflects, in part, the low percentage of body fat in athletic endurance and sprinting horses (198, 351). The structure of equine skeletal muscle has been investigated extensively by percutaneous biopsy sampling most commonly of the gluteus medius muscle (237), the heaviest muscle of the pelvic limb (303) and one which is recruited heavily during running (359). Whereas this provides the possibility of multiple convenient windows into horse muscle structure, there is considerable heterogeneity of fiber types and oxidative capacities within and among muscles (194, 244, 333, 351, 353, 423, 444), as is the case for other species (7, 374). Consequently, generalizations based upon biopsy data should be made with caution. Alternatively, Armstrong and colleagues (5), for example, utilized postmortem analyses that offer the opportunity for a more thorough, though only one-time, sampling of the locomotory muscles of interest.

Skeletal muscle fiber types are differentiated most conveniently on the basis of their myosin heavy-chain isoform (MyHC) (351). Adult horse muscle contains three MyHC isoforms, type I, IIA, and IIX, that have been characterized at the protein, mRNA, and cDNA levels (44, 68, 357). These MyHC define three pure fiber types and two hybrids (1 + IIA and IIA + IIX) (63, 240, 351). As apparent in man and across diverse mammalian species, the type I fiber has a smaller cross-sectional area and greater capillary density than IIA and particularly IIX fibers and lends itself to slower, more economical contractions that do not generate high power or fast rates of shortening that are characteristic of type II fibers (351). It is pertinent that horse muscle does not display as disparate a range of oxidative capacities or capillarities as found within or among muscles of healthy, though not elite, humans (c.f., 351 and 374). Also, important from a regulatory perspective, these horse fiber types contrast markedly with respect to their calcium sensitivity (277), Ca^{2+}-ATPase content (414), high-energy phosphate availability (87), and carnosine content (important for buffering metabolic acidosis during high-intensity exercise, 395) (rev. 351).

The various fiber types form a mosaic pattern within horse muscles, with a preferential distribution of fast-glycolytic IIX toward the superficial proximity (126), as has been described for locomotory muscles in other mammalian species (e.g., rat, 6; human, 374, rev. 351). As might be expected from a functional perspective, horse muscle fiber type composition differs between postural (preferentially type I) and propulsive (type II) muscles (351) and also among muscles belonging to the same synergistic group (5, 373).

As for humans, horse athletic performance is associated with distinct muscle fiber type profiles. Endurance capacity correlates with proportionally more type I and IIA fibers and high muscle oxidative capacity (354, 355, 405). Sprint capacity, in contrast, is associated with a preference for type II fibers (15). However, attempting to assess a horse's performance potential purely based on the fiber composition of particular muscles has lead to equivocal results in Thoroughbreds versus trotters (363, 366, 394). One intriguing finding is that stride length and frequency correlate with the proportion of IIA fibers (309) and fiber size (350, see 351 for review).

Stride length and frequency are of crucial importance not only for running speed but also for ventilation and pulmonary gas exchange (see the *Pulmonary System* section).

Myoglobin concentration is stratified among horse locomotory muscles (from 408 μmol/kg in the superficial rectus femoris up to 832 μmol/kg in the vastus intermedius) and correlates with citrate synthase activity ($r^2 = 0.63$, $n = 7$) across muscles, at least in the Standardbred horse (5). The myoglobin P_{50} for horses is 2.4 mmHg, which is similar to that for human muscles (344,382). The range of myoglobin contents for horse muscles listed above is within the range found for mammalian muscles (50,231), and it is pertinent that within a given muscle (i.e., psoas), the myoglobin concentration across species, ranging in size over several orders of magnitude up to the blue whale (*Balaenoptera musculus*), scales with body mass rather than mass-specific oxidative capacity. This notion is consistent with the role of myoglobin as a facilitator of intracellular, i.e., sarcolemma-to-mitochondrial, O_2 transport. Conversely, recent observations that exercise capacity is supposedly unaffected in mice genetically engineered to lack myoglobin have raised questions regarding whether myoglobin actually serves an essential role in intracellular O_2 movement (105). However, in this regard, it is pertinent that many such mice die *in utero* and the survivors evidence an array of cardiovascular adaptations that includes elevated coronary $\dot{Q}$ and coronary $\dot{Q}$ reserve, capillarity (heart and soleus), and hematocrit (115, 272). In addition, myoglobinless mice have increased expression of hypoxia-inducible factors (HIF-1α and HIF-2), stress proteins (e.g., heat shock protein 27), and vascular endothelial growth factor and increased NO metabolism in select muscles (118). Notwithstanding these adaptations in mice lacking myoglobin and in keeping with Lawrie's (231) finding of increased myoglobin as a function of body mass, and likely fiber size, across species, it may be that myoglobin is more important when intracellular diffusion distances are greater. Thus, the myoglobinless mouse, having very small fibers and diffusion distances, is less affected by the absence of myoglobin than species with much larger muscle fibers such as the horse and the dog would be with respect to intracellular O_2 transport and exercise capacity.

Whereas equine locomotory muscles have a capillarity and mitochondrial volume density (oxidative capacity) that are higher than nonathletic species such as the calf or goat (5, 49, 171), they are by no means extraordinary and certainly do not approach those of more specialized cardiac or diaphragm muscle as seen below. Specifically, equid locomotory muscle capillaries have a smallish luminal diameter of ~4.2 μm and their density ranges from 471 to 737/mm^2 (5, 49, 351, though capillary to fiber ratios may be higher in Thoroughbreds 129), which supports fiber/muscle mitochondrial volumes from ~2% to 9% (197). For comparison, equid diaphragm capillary density is ~1400 capillaries/mm^2 and that in the heart is 2670 capillaries/mm^2 (49). Among other terrestrial mammalian species, substantially higher values are found (>3000 capillaries/mm^2 in rat diaphragm and more than 5000 capillaries/mm^2 in heart 327, 328). However, even these values do not approach the maximum determined so far in the mammalian world. The diaphragm of the 2.6 g lesser shrew (*Sorex minutus*) has a staggering capillary density of 10,400 capillaries/mm^2 (261). Similarly, the mitochondrial volume densities of up to 9% in equine locomotory muscle (171, 197) fall far below the 23% found in humans hearts or those of rats and hamsters (28%) or mice (32%) (381). At the extreme, the diminutive Etruscan shrew has a myocardial mitochondrial volume density of ~45% (437), which may approach the limit for mammalian muscle. Thus, in the horse, unless there are other functional aspects of the microcirculation or mitochondria, which there are not as far as we know, it is the total mass of muscle and therefore capillaries and mitochondrial volumes that are recruited, which is extraordinary and facilitates the horse's impressive $\dot{V}O_2$max. This conclusion is supported by Figure 21 and discussed below in detail.

Function

If neither the mass-specific locomotory muscle microvasculature nor the mitochondrial volume density of the horse is outstanding relative to humans or other species, it would be reasonable to suppose that the mass-specific $\dot{Q}$ would not be especially high at $\dot{V}O_2$max. Locomotory muscle $\dot{Q}$ ($\dot{Q}_m$) during maximal exercise is heterogeneous within and among muscles down to the smallest microcirculatory units and will be determined, in part, by the (A) required recruitment pattern, as it determines the energetic requirements of the muscle fibers, (B) fiber type and oxidative capacity of these muscle fibers, and (C) fiber arrangement, as it affects the distribution of intramuscular pressures (7, 227, 229, 310, 315, 317). In addition, an upper $\dot{Q}_m$ limit is placed on all exercising muscle(s) by the capacity of the heart to generate $\dot{Q}$ and the efficacy of the vasomotor control systems to distribute this $\dot{Q}$ to exercising muscle (i.e., $\dot{Q}_m$) in preference to the skin, digestive system, and other organ systems.

In humans, it has been demonstrated that during cycle ergometer exercise that recruits ~15 kg of muscle, $\dot{Q}_m$ at $\dot{V}O_2$max increases to 1.36 liters/(kg min) (213). However, in subjects of similar fitness who performed knee extensor exercise that recruited only 2.4 kg of active muscle, $\dot{Q}_m$ increased to an impressive 3.85 liters/kg/min that facilitated a mass-specific $\dot{V}O_2$max of ~540 ml/kg/min (345). This provides strong evidence that the achievable $\dot{Q}_m$ is limited to a great degree by cardiac performance, and the finding that higher $\dot{Q}$s and $\dot{V}O_2$max's can be achieved when horses run up an inclined versus level treadmill (208,265) suggests that $\dot{Q}_m$ at maximal exercise may, to some degree, be limited by the heart and its ability to generate $\dot{Q}$ rather than the vasodilatory oxidative capacity of skeletal muscle *per se*. Some of the highest $\dot{Q}_m$'s measured to date [>5 liters/kg/min] were found in select hind limb muscles of the rat (i.e., red portion of the gastrocnemius) during maximal running and the costal diaphragm in response to chemical-induced hyperpnea (7, 227, 317, 335). In the investigation of Poole and colleagues (335), $\dot{Q}_m$ in the white

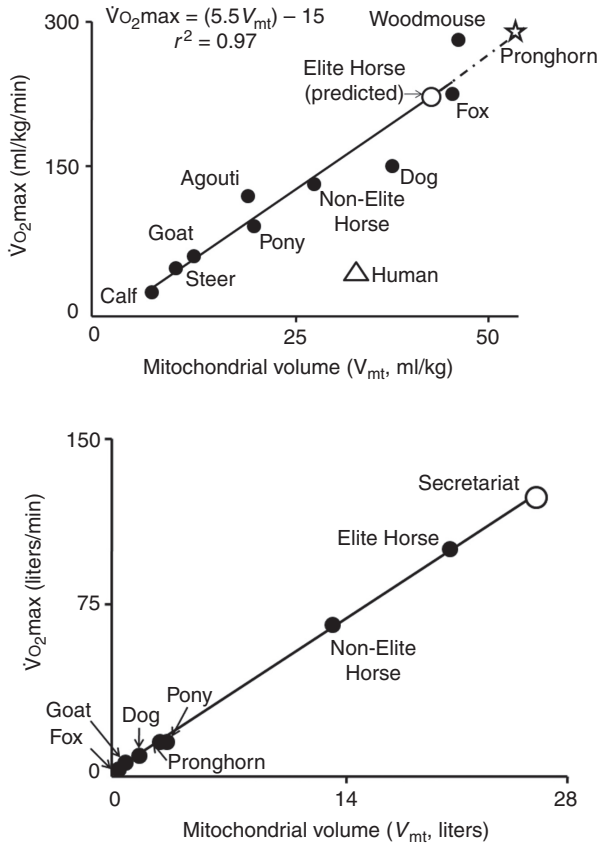


Figure 21 *Top panel*: Relationship between maximum O_2 uptake ($\dot{V}O_2max$) and mass-specific mitochondrial volume for a variety of species varying in body mass over several orders of magnitude. Note that humans fall furthest from this relationship, likely, in part, because of their two-legged anatomy, bipedal gait, and muscle activation patterns as well as their locomotory patterns facilitated by that bipedalism. Based, in part, upon the data summarized in Wagner et al. (430). Point for the elite horse is taken from the data of Young et al. (465) and that for the pronghorn antelope from Lindstedt et al. (239); for both, the mitochondrial volume is estimated from $\dot{V}O_2max$. *Bottom panel*: Select data from top panel expressed in absolute terms with the addition of Secretariat (data from Fig. 18). This relationship supports the notion that the Thoroughbred horse achieves its extraordinary $\dot{V}O_2max$ by means of its very large muscle mass, and therefore total mitochondrial volume, and the ability to supply that mitochondrial volume with O_2. In contrast, the mass-specific muscle blood flow ($\dot{Q}m$) and capillarity as well as the mitochondrial volume density and function appear quite ordinary. See text for additional information.

gastrocnemius averaged only ~1 liter/kg/min compared with ~5.5 liters/kg/min in the red gastrocnemius, which emphasizes the extreme $\dot{Q}_m$ heterogeneity within muscles (as noted previously by Piiper (315), Laughlin and Armstrong (227), and Musch (282). Such heterogeneity offers a cautionary note to the interpretation of mean $\dot{Q}_m$'s within and across horse muscles. However, in the absence of greater spatial fidelity of techniques or the reporting of only mean $\dot{Q}_m$ data in the pertinent publications, these mean data are presented herein.

Respiratory muscle $\dot{Q}_m$'s close to 4 liters/kg/min are present in ponies during high-intensity treadmill running (248-253), which is substantially higher than that present in locomotory muscles in 9-year-old Standardbred horses running at $\dot{V}O_2max$ (134 ml O_2/kg/min [61 liters O_2/min] ref. 5). Cardiac output ($\dot{Q}$) was estimated at 288 liters/min, of which total $\dot{Q}_m$ was ~78% or 226 liters/min. Within the quadriceps muscles, $\dot{Q}_m$ ranged from 0.3 (superficial rectus femoris) up to 1.5 (vastus intermedius) liters/kg/min and this spatial stratification of $\dot{Q}_m$ correlated tightly with oxidative capacity across muscles ($r^2 = 0.90, n = 7$). These values for $\dot{Q}_m$ are certainly not extraordinarily high and, at the presiding capillary volume density present in these muscles, can be calculated to produce a range of mean RBC capillary transit times in the ~1- to 2-s range (5, 196). It is pertinent that, at the highest $\dot{Q}_m$'s measured to date in human quadriceps, estimated mean RBC transit time was between 0.1 and 0.4 s (345, 346), with the shorter values more likely in the subjects in question. Even at these exceptionally short mean transit times, fractional O_2 extraction exceeded 0.8. Putting this into context, unless horse muscle is unlike other muscles in which more than 80% of capillaries support RBC flux at rest and during exercise (206, 209, 332, 347), while running at $\dot{V}O_2max$ horse muscles do not approach capillary RBC transit times that might be considered limiting for O_2 offloading (169). Indeed, that *mixed* venous P_{O_2} falls to ~10 mmHg (83, 266, 429) during maximal exercise indicates that fractional O_2 extraction across the exercising muscles must be extraordinarily high, reflecting a superb matching of $\dot{Q}O_2$ to $\dot{V}O_2$ within and among muscles.

With respect to the above $\dot{Q}_m$'s, which were measured in horses with a far more modest $\dot{V}O_2max$ than the highest on record (i.e., 134 vs. 217 ml/kg/min, 61 vs. ~110 liters/min, c.f., 5 and 465), it would be appropriate to estimate whether the conclusion regarding transit times might be different for elite horses. Accordingly, from Figure 18 where $\dot{Q}$'s of 450 to 540 liters/min are estimated for elite horses, if it is assumed that 90% of this cardiac output can perfuse skeletal muscle (i.e., 405-486 liters/min), total $\dot{Q}_m$ will be 1.8- to 2.2-fold higher than that measured by Armstrong et al. (5). If the highest individual muscle $\dot{Q}_m$'s are scaled upward. Accordingly, mean estimated capillary RBC transit times still would not be expected to fall much below 0.5 s, which is nowhere near as short as those estimated for the subjects of Richardson et al., in whom fractional O_2 extraction across the contracting muscles was preserved at ~0.8 (345). Moreover, as detailed in the *Adaptations to Training* section, it is likely that the elite horse has a far greater skeletal muscle capillarity and larger muscle mass than the Standardbreds examined by Armstrong et al. (5). This increased total capillary volume will act to increase mean capillary RBC transit time above those values that were estimated previously and therefore elevate the opportunity for increasing O_2 extraction and therefore blood–muscle O_2 flux.

Some cautionary notes are indicated here regarding the calculations of mean capillary RBC transit times. (i) In resting muscle capillaries, hematocrit averages 15% to 20%, which is far lower than that measured at systemic levels (211, 212, rev. 209, 332). Hyperemic states such as contractions raise capillary hematocrit toward systemic levels (54, 209, 211, 212), but we have no measurements of muscle capillary hematocrit

in the horse during exercise. The calculations above thus assume that muscle capillary hematocrit at $\dot{V}O_2max$ rises to systemic levels. If it is lower, however, capillary RBC transit times could be far shorter than estimated. (ii) Within resting or contracting muscle, there is an enormous heterogeneity of capillary RBC velocities (209, 317), RBC path lengths, and therefore transit times (378, 379). Thus, the mean values presented here give no appreciation for this distribution or how many capillaries might have disappearingly short transit times even when the mean value might be adequate for effective O_2 extraction. (iii) It is entirely feasible that in the elite Thoroughbred horse racing at over 45 mph, there are locomotory muscles or regions of these muscles that have $\dot{Q}_m$'s far higher than estimated here. However, on the basis of the measurements of high fractional O_2 extractions concomitant with enormously high $\dot{Q}_m$'s, and accordingly very short estimated mean capillary RBC transit times in human quadriceps by Richardson et al. (345), regional $\dot{Q}_m$'s would have to be several fold higher than those measured to date in less athletic horses to occur a transit time limitation. This seems unlikely.

One calculation that puts the scale of muscle O_2 transport in the elite horse at $\dot{V}O_2max$ into perspective is as follows: Within the major locomotory muscles, there are ~19 km of capillaries/ml mitochondria (5,260). Accordingly, for the elite horse with over 21 liters of total muscle mitochondrial volume, there will be an estimated 399,000 km of capillaries through which flows 486 liters/min or (assuming a mean corpuscular volume of 50 μl and 70% packed cell volume) $\sim 7 \times 10^{14}$ RBC/min, each of which, on average, relinquishes close to 90% of its O_2 content.

Adaptations to Training

The cardiovascular and muscular systems demonstrate remarkable plasticity of structure and function in response to a regular program of physical exercise of sufficient intensity and duration. In contrast, whereas the lung itself does perform better in the trained horse in that $\dot{V}O_2max$ and $\dot{V}CO_2max$ both increase, the increased capacity for pulmonary gas exchange in the trained horse is believed to be dictated by the other systems, which will therefore be the focus of this section. Thus, to date, there is not convincing evidence that training the horse elevates alveolar surface area or promotes other structural or functional adaptations in the lung *per se*. Whereas it is true that pulmonary diffusing capacity may increase with training, this improvement is likely the effect of increased venous return from the exercising muscles and consequently higher pulmonary vascular pressures which are expected to increase pulmonary capillary blood volume. There is also likely to be a slightly greater venous blood deoxygenation that will lower inflowing pulmonary venous P_{O_2} (317) and, all else being equal, will elevate the alveolar-capillary O_2 diffusion gradient and enhance O_2 flux. It may also be argued that in the face of greater pulmonary gas exchange demands posttraining, the alveolar P_{O_2} may fall further and consequently the alveolar-arterial P_{O_2} difference will be widened; both effects would act to exacerbate EIAH. It appears, however, that this does not happen and that Ca_{O_2} at $\dot{V}O_2max$ increases after training (46). In other species such as humans and rats, the diaphragm adapts in a similar fashion to locomotory skeletal muscles. Thus, training-induced improvements in respiratory muscles may reduce any respiratory muscle fatigue and elevate $\dot{V}_A$ during maximal exercise posttraining. This would serve to raise P_{AO_2} and may offset the tendency for training to increase EIAH severity.

There exists a substantial literature on training adaptations in other species such as humans, rats, and pigs (42, 58, 98, 167, 168, 170, 181, 224, 225, 262, 317, 374), and this section will avoid an exhaustive review of the topic. In preference, we will focus on understanding the mechanistic bases for the training-induced elevation of $\dot{V}O_2max$ that occurs in horses (Fig. 22).

As mentioned above (see the *Cardiovascular System* section), the ability to generate $\dot{Q}$, and distribute $\dot{Q}O_2m$, has historically been regarded as the primary, if not only, determinant of $\dot{V}O_2max$ and hence its increase with training. However, when Professor Peter D. Wagner conflated the Fick principle (conductive O_2 transport) and Fick's law (diffusive O_2 transport) graphically, it revealed the dependence of $\dot{V}O_2max$ on the coordinated function of each step in the O_2 transport pathway (Fig. 20, upper panel). Hence, the effects of altered O_2 transport within one system, be it pulmonary, cardiovascular, or muscular, on $\dot{V}O_2max$ cannot be independent of the consequences of that altered O_2 transport within other systems.

As depicted in Figure 22, the "Wagner" diagram demonstrates that the training-induced increase of $\dot{V}O_2max$ occurs as

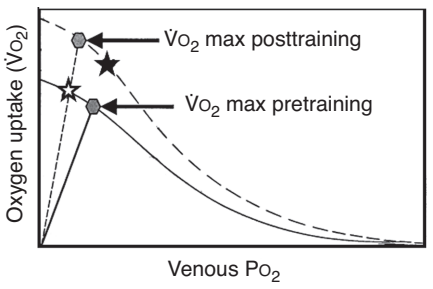


Figure 22 Exercise training improves maximal O_2 uptake ($\dot{V}O_2max$) by elevating both conductive (curved line, due to increased stroke volume and small elevation in Ca_{O_2} see Table 3) and diffusive (straight line, due, in part, to increased capillarity and events within those capillaries) O_2 transport. It is interesting that even a relatively modest decrease (5%-10%) in venous O_2 partial pressure (P_{O_2}) (215, 362) after training (Table 3) requires a far greater percentage elevation (~30%) in muscle O_2 diffusing capacity ($D_{O_2}m$). In addition, from this figure, it is apparent that if training solely acted to increase convective O_2 delivery in the absence of increased $D_{O_2}m$, venous P_{O_2} would have to rise (see posttraining solid star). In contrast, if $D_{O_2}m$ increased in the absence of an elevated cardiac output and muscle O_2 delivery, venous P_{O_2} would fall but the increase in $\dot{V}O_2max$ would be minimal (open star). Figure is redrawn from Poole (318). See the caption to Figure 20 and the text for additional information.

the product of an elevated cardiovascular O_2 delivery ($\dot{Q}O_2$) and an increased fractional O_2 extraction ($\Delta Ca\text{-}C\bar{v}O_2$) such that muscle effluent venous P_{O_2} and mixed-venous P_{O_2} and their respective O_2 contents will fall. In part, because of the hyperbolic relation between $\Delta Ca\text{-}C\bar{v}O_2$ and $\dot{V}O_2$ (317, 456), and that $\dot{V}O_2max$ is so high (and thus $C\bar{v}O_2$ already very low) even in untrained horses, training-induced elevations of $\Delta Ca\text{-}C\bar{v}O_2$ must be quantitatively modest. However, this observation should not be presumed to mean that elevations in effective muscle diffusing capacity ($D_{O_2}m$) are either unimportant or of small magnitude compared with those of $\dot{Q}$. Notice that, from Figure 22, simply increasing $\dot{Q}O_2$ at the same $D_{O_2}m$ will increase venous P_{O_2} (i.e., *decrease* $\Delta Ca\text{-}C\bar{v}O_2$) and thus increasing $\Delta Ca\text{-}C\bar{v}O_2$ by reducing $C\bar{v}O_2$ to ~10% or so as seen in humans after training requires a substantial increase in $D_{O_2}m$ (close to 30% in this example, 362). Consequently, although adaptations of the cardiovascular and muscular systems are considered in separate sections below, their intertwined nature with respect to determining $\dot{V}O_2max$ remains a crucial consideration.

Cardiovascular adaptations

In mammalian systems, exercise training typically increases $\dot{V}O_2max$ up to 25% (Table 3; 12, 35, 167, 317, 322, 370, 374), with the relative improvement depending primarily on the initial level of fitness. The higher $\dot{Q}_{max}$ is driven exclusively by an enlarged SV, as maximal HR does not change (Table 3). In turn, the enlarged SV is the product of an increased ventricular mass and end-diastolic volume (218, 464). Training also elevates blood/plasma volume (215, 270), which elevates cardiac preload by increasing central venous pressure acting to stretch the myocardial fibers, thereby potentially increasing both the force and the velocity at which they contract. This adaptation is not thought to be dependent upon altered myocardial contractility *per se* (370, 383, 385) and is not impacted by cardiac afterload, which is unchanged after training, as MAP remains unaltered despite the higher $\dot{Q}$ and $\dot{Q}_m$. Although this scheme makes physiological sense, it is pertinent that expanding plasma volume in humans does not always increase central venous pressure and SV (370). Another puzzling question relates to the pericardium and its role in restricting ventricular expansion and ventricular end-diastolic volume and hence SV. The experimental removal of the pericardial constraint in dogs (412) and pigs (137) increases SVmax and therefore $\dot{Q}_{max}$ and raises $\dot{V}O_2max$ a similar magnitude to that seen after weeks or months of training. One interpretation of these data is that training chronically stretches the pericardial sac (100) decreasing its stiffness (234) so that after training the rise in cardiac filling pressure required to generate SV is reduced. In this light, the observations of McDonough and colleagues (265, 267) that inclined running in the horse generates a greater SV and $\dot{Q}$ and therefore $\dot{V}O_2max$ than level running suggests that, at least in the horse, the pericardial sac does not represent an intractable obstacle to acute elevations of SV. To date, there is no evidence

Table 3 Principal Cardiovascular Effects of Exercise Training in the Horse at Maximal Exercise*

Variable	% Increase	Reference(s)
$\dot{V}O_2max$	10-25	67, 91, 92, 195, 215, 422
Mean arterial pressure (at max)	NC	
Total peripheral resistance	Decreased	
Conductive O_2 transport, max		
Heart weight	10+	218, 436
Cardiac output, max	Increased	
Stroke volume, max	10+	419
Myocardial hypertrophy		
LV mass	33	218, 464
LV internal diameter	7	464
Plasma volume	19-30	215, 269, 270
Central venous pressure	?	
Pericardial hypertrophy	Yes?	
Systemic [hemoglobin]/hematocrit	NC or decreased	215
Arterial O_2 content (max)	8	46
Red cell mass	15	215
Heart rate, max	NC	28, 92, 99
Muscle diffusing capacity		
Arterial-venous O_2 extraction, max	5	215
Capillarity		
Capillary density	13-36	86, 392, 422
Capillary:fiber ratio	70	354, 422
Myoglobin	?	
Oxidative enzymes	Up to 100	67, 86, 133, 165, 245, 392,
Mitochondrial volume	75-200	411, 422
Capillary hematocrit	Increased?	
Capillary RBC transit time	?	
Velocity—submaximal heart rates/blood lactate concentrations		
V_{200}	NC or increased	55
V_{140}	Increased	396
VLa4	Up to 31	90, 392
La9	(–51)	90
Run time to fatigue (90%-100%$\dot{V}O_2max$)		
Treadmill run time to fatigue	140	422

*$\dot{V}O_2max$, maximal oxygen uptake; V_{200}, V_{140}, running velocity at a heart rate of 200 and 140 beats/min; respectively; VLa4, running velocity that induces a lactic acidosis of 4 mmol/liter; La9, blood lactate concentration at a running velocity of 9 m/s.
Abbreviation: NC, no change; ?, unknown

that pericardectomies have been performed either experimentally in equine exercise studies or as an ergogenic aid in race horses. It is relevant that the training-induced cardiac adaptations are not wholly beneficial to myocardial function. Young and Wood (466) found that training-induced myocardial enlargement promoted the incidence and severity of mitral and tricuspid valvular insufficiency and regurgitation, which reduced the $\dot{Q}$ improvement expected after training.

The lack of alteration of MAP at $\dot{V}O_2max$ after training indicates that the elevated $\dot{Q}$ is matched precisely by a reduction in systemic vascular resistance (370), and the mechanisms for training-induced improvements in muscle vascular function are addressed briefly below (see the *Muscular Adaptations* section).

Muscular adaptations

As discussed in the *Cardiovascular System* section and seen in Figure 22, the training-induced $\dot{Q}$ (and thus $\dot{Q}O_2m$) increases would, if they occurred in the absence of a substantial increase in DO_2m of the exercising muscles, lead to a reduced O_2 extraction (i.e., decreased $\Delta Ca\text{-}C\bar{v}O_2$, solid star in Fig. 22). This section addresses the structural and functional adaptations to training that underlie such increases in DO_2m.

Blood flow redistribution

In contrast to humans, horses evidence modest increases in CaO_2 during submaximal and maximal exercise after training (46, 396) (Table 3). Consequently, training-induced increases in $\Delta Ca\text{-}C\bar{v}O_2$ can be driven by both elevated CaO_2 and reduced $C\bar{v}O_2$. In rats and humans, there is evidence that a decreased $C\bar{v}O_2$ results from a preferential redistribution of training-induced elevations in $\dot{Q}$ to the active muscles where there is a greater fractional and total O_2 extraction, rather than a greater vasoconstriction in other organs (229, 370, 375). In horses after training, a greater proportion of $\dot{Q}$ to the muscle as well as increased capillarity are both expected to reduce $C\bar{v}O_2$. However, as seen from Figure 23, because venous PO_2 (and thus $C\bar{v}O_2$) are so low, normally in the maximally exercising horse any further decrease will be rather small and take a substantial increase in DO_2m to be realized.

Fiber type alterations

In contrast to specific high-resistance training routines that invoke hypertrophy within select fiber populations (152, 393), the effects of endurance-type training on equine muscle fiber size are somewhat equivocal (349, rev. 405). Thus, although there appears to be little hypertrophy with low-resistance training, endurance-trained Arabian horses running at ~80%

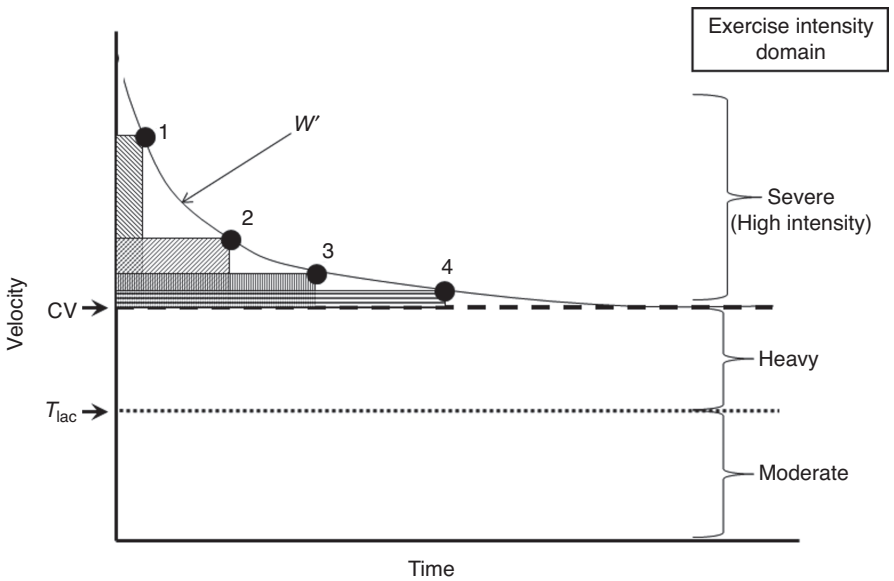


Figure 23 Schematic of velocity vs. time-to-exhaustion for high-intensity exercise. The curve is traditionally constructed by having the individual run to fatigue at four different constant velocities, selected to induce exhaustion in 2 to 20 min, on four or more occasions (points 1-4, separated by at least 1 day). The asymptote parameter is critical velocity, CV, and the curvature constant W′. W′ denotes a finite amount of work (intramuscular energy store, principally composed of creatine phosphate + anaerobic glycolysis) that can be performed above CV and, as shown by the hatched rectangles that denote energy, W′ is the same for all velocities above CV. Exhaustion occurs when W′ is expended. T_{lac} denotes the lactate threshold as determined by a separate ramp exercise test. Each exercise intensity domain evinces a discrete oxygen uptake and blood lactate response. Note that CV demarcates the heavy and severe exercise intensity domains and also that even a modest elevation in CV, which results from endurance training, will facilitate a disproportionate increase in time-to-fatigue at any velocity that was originally more than CV. See the text for more details.

$\dot{V}O_2$max for 50 to 80 min, 4 days per week for 3 months, did evidence a generalized fiber hypertrophy (57). In contrast, Standardbred or Thoroughbred horses display either a minimal fiber hypertrophy (153, 236) or even atrophic responses (85,86,355,365; rev. 351). What is intriguing is that there may be some increase in overall muscle mass, which, if hypertrophy does not occur, can be explained only by hyperplasia as has been claimed, on occasion, in human muscles (401).

Endurance training in horses increases the proportion of type IIA fibers at the expense of IIX fibers (57, 85, 86, 116, 243, 274, 348, 352, 356, 392, 393, 400, 422, 462), as detected by histochemistry and immunohistochemistry as well as other techniques. There have also been reports of endurance training increasing hybrid type I + IIA fibers and pure type I fibers (153, 352, 354, 393), whereas sprint training at exceptionally high intensities may decrease type I fiber numbers (245, 358).

Oxidative enzyme increases

Training induces a rapid and substantial increase in mitochondrial volume density (274, 400, 422), which upregulates Kreb's cycle enzymes as well as those of the electron transport chain and β-oxidation (67, 88, 199, 245, 268, 276, 352, 354, 367, 392, 462). Given that horses appear to have an excess of mitochondrial capacity (as revealed by the increased $\dot{V}O_2$max induced by inclined running, 265, 267), it is conceivable that training-induced increases of oxidative enzyme activity are more important for substrate regulation issues than the achievement of posttraining $\dot{V}O_2$max *per se* (167, 374).

Capillarity

Training-induced capillary neogenesis occurs in horses as evidenced by a 70% elevation of capillary to fiber ratio found in locomotory muscles (352, 422). Other investigations have routinely documented a more modest increase in muscle capillary density (86, 392).

Putative mechanisms for increased total and fractional muscle O_2 extraction after training

In addition to the rapid and profound growth of arterioles and capillaries within skeletal muscle (86, 139, 178, 330, 355, 374, 375, 392, 415, 422), exercise training across species increases the sensitivity of cardiac (123) and skeletal muscle arterioles (216, 224, 225) to vasoactive mediators including NO, prostaglandins, and catecholamines. Exercise training also increases NO bioavailability in myocardium (230) and skeletal muscle neuronal nitric oxide synthase is elevated in highly trained Thoroughbred horses (116). Increased NO bioavailability during exercise may be important not only for increasing total $\dot{Q}_m$ after training but also for refining the distribution of $\dot{Q}_m$ among and within discrete muscle regions to improve $\dot{Q}O_2$ delivery-to-$\dot{V}O_2$ requirements (229, 331). If it is possible for exercise training to increase the mean microvascular P_{O_2} by elevating the $\dot{Q}O_2$-to-$\dot{V}O_2$ ratio as seen in humans with priming exercise (132), this may play an important role in facilitating improved blood–myocyte O_2 flux and also in tightening metabolic control such that better intramyocyte homeostasis is maintained in the trained state.

Thus, after training, capillary length, volume, and surface area per unit muscle fiber volume are all elevated and this occurs in approximate proportion to the elevated muscle oxidative enzyme capacity (317, 329, 330, 374). These changes will act to facilitate blood–muscle O_2 flux from at least two important perspectives: (i) According to the elegant modeling studies of Federspiel and Popel (97) and Groebe and Thews (124) and validated empirically in frog preparations (247), the principal determinant of D_{O_2}m is the number of RBCs resident in the capillary bed adjacent to the contracting muscle fibers. Unless capillary hematocrit at $\dot{V}O_2$max is reduced after training, and it is doubtful that it is, the greater capillary length would increase the RBC content of the capillary bed and thus D_{O_2}m proportionally. (ii) Supposing that $\dot{Q}_m$ increased after training and capillary volume did not, mean capillary RBC transit time would be expected to fall. Thus, the elevated capillary volume after training prevents, or at least constrains, the magnitude of any such fall in mean capillary RBC transit time and, depending on the ratio of Δcapillary volume/$\Delta\dot{Q}_m$ may even increase mean transit time. Although, as argued earlier, transit time may not limit fractional O_2 extraction *per se* for a given blood–muscle O_2 flux, longer transit times act to reduce the required O_2 flux density (per RBC per second) and therefore reduce the fall in intracellular P_{O_2} necessary to generate the required O_2 flux (169). One consequence of this behavior would be a reduced intracellular perturbation of high-energy phosphates, reduced glycolysis, and improved intracellular homeostasis (317).

Linking the O_2 transport system (and training-induced improvements) to locomotory performance

As seen in Figures 5 to 8, $\dot{V}O_2$ kinetics in the horse are strikingly fast at the transition to moderate-intensity exercise but, unlike in humans (rev. 324), are somewhat slowed at higher intensities (Fig. 6, 202, 222). If, as demonstrated extensively in humans (rev. 185), exercise training speeds $\dot{V}O_2$ kinetics at the transition to high-intensity exercise, this would act to reduce the O_2 deficit incurred, which would have important consequences for exercise tolerance. Specifically, for muscular systems high-intensity exercise time-to-fatigue is a hyperbolic function of either running velocity or power generated (Fig. 23; refs. 64,187,281; rev. 155). This is true for a range of species including the horse (226), human (running, 102, 179; cycling, 154-156,287,336,452; rowing, 157; swimming, 431; isometric exercise, 279; knee extensor exercise, 187), mouse (29), and salamander (103). Thus, the time-to-fatigue is a function of two parameters: an asymptote termed critical velocity, CV, which in theory constitutes the highest velocity that can be sustained for a prolonged duration, and a curvature constant termed W′ (187, 336, 452). CV represents the high-

est rate of energy utilization that can be maintained without mandating a continuous decrease in W′ and is thought to be linked closely with muscle oxidative capacity and pulmonary $\dot{V}O_2$max. W′ represents a finite intramuscular energy store, notionally similar to the O_2 deficit, that is composed principally of phosphocreatine and anaerobic glycolysis (rev. 187). Notice that W′ is the same for all exercise bouts performed above CV and that fatigue occurs when W′ is depleted.

In humans, exercise training acts to increase the capacity for high-intensity exercise by raising CV (104, 182, 183, 337), and if $\dot{V}O_2$ kinetics are speeded at the onset of high-intensity exercise (rev. 185), W′ will also be conserved by this mechanism. Both of these effects will serve to improve exercise tolerance and link the physiological adaptations detailed above to the improved work capacity and athletic performance seen after training in the horse. It has been considered that elevating O_2 transport has only a minimal effect on increasing athletic endurance performance (238). This viewpoint neglects the curvilinear shape of the velocity–time-to-fatigue relation evidenced in Figure 23. Consider that exercise training, or some other manipulation designed to elevate muscle O_2 delivery, elevates CV by shifting the curve upward by ∼10% (104, 182, 183, 337). The criterion running velocity that was more than CV in the initial instance might now be less than CV and the time-to-fatigue for that exercise bout will be substantially increased. Even if the pre- and posttraining bouts are more than CV, the posttraining condition will have increased time-to-fatigue as a hyperbolic function of the percentage improvement in CV (or oxidative function). This explanation for the interrelationship between increased O_2 transport (for which $\dot{V}O_2$max is an excellent indicator) and enhanced athletic performance is deserving of greater scientific attention.

Summary (Horse)

Centuries of selective breeding for athletic performance have produced a racehorse with an extraordinary O_2 transport system. The structure and function of those O_2 transport components exhibiting considerable plasticity (skeletal muscle, cardiovascular) have been specialized to facilitate huge O_2 fluxes, whereas the least plastic, the lungs, represent a major bottleneck in the O_2 pathway from atmosphere to mitochondria. Today, the competitive racehorse's body mass approaches 55% skeletal muscle and, whereas neither the structure (fiber type, capillary and mitochondrial volume density) nor function (mass specific blood flow, oxidative capacity) of that muscle differ markedly from that of other aerobically fit mammals, it is the sheer total mass of active mitochondria and associated RBC-supplied capillaries that is extraordinary and permits a massive diffusive O_2 flux. Because of the great muscle mass, the achieved mass-specific $\dot{Q}_m$ is relatively modest, thereby helping to avoid very short capillary RBC transit times and, combined with the physicochemical environment within the muscle (↑ P_{CO_2}, °C, H^+ → Bohr effect decreasing Hb–O_2 affinity), this facilitates more than 90% O_2 extraction. In turn, the skeletal muscle is supported by a cardiovascular system that facilitates a huge conductive O_2 flux. This O_2 flux may reach well above 110 liters/min and is driven by a very large compliant heart (up to 2% body mass) that can achieve a HR of 210 to 250 beats/min at a SV approaching 2 liters and is complimented by splenic contraction that elevates blood [Hb] and raises Ca_{O_2} above 25 ml/100 ml. In contrast, the capacity of the equine lung, constrained as it is by the thoracic dimensions, has been far exceeded by that of the cardiovascular-muscular systems and has been forced to accept much abuse (physical and verbal!). The equine lung is an amazing structure, with billions of extremely small alveoli providing a truly prodigious total surface area in excess of 2400 m^2 (>1700 m^2 of exchange surface), whereas the thickness of the blood-gas barrier remains modest at ∼1 μm. However, during maximal exercise, the enormous pulmonary $\dot{Q}$ raises vascular pressures to more than 120 mmHg and ruptures the blood-gas barrier causing EIPH. Equine respiratory muscles are large and highly oxidative, yet, despite this, and mechanisms emplaced to expand the tracheal airway on inspiration, not present in humans or dogs, the horse's airflow becomes mechanically limited. Indeed, as an obligate nasal breather during exercise, partial collapse of the unsupported nasal passageways exacerbates the negative alveolar pressures that must be generated to produce a given airflow. These pressures contribute to EIPH, and the horse's long neck and large airways increase dead space and the matching of stride and respiratory frequency mandates high dead space ventilation. Although there is little shunting of $\dot{Q}$ or $\dot{V}/\dot{Q}$ mismatch in the equine lung during exercise, the alveolar hypoventilation, extreme deoxygenation of the venous blood entering the pulmonary capillaries, and limitingly short RBC transit times conspire to produce a profound diffusion limitation and arterial hypoxemia (EIAH). In addition, the elevated body temperature (>42°C, 72, 256, 258, 266), arterial hypercapnia, and falling pH that help offload O_2 in the skeletal muscle reduce Hb–O_2 affinity and further impair O_2 loading in the lung. That the equine lung suffers from EIPH and allows arterial P_{O_2} to fall and that of CO_2 to rise during maximal exercise has often been regarded as "failure." From another perspective, it is, perhaps, unfair to condemn the equine lung for successfully achieving levels of gas exchange (>200 liters/min for O_2 and CO_2 combined) superior to those measured for any other animal.

The Athletic Dog

As the peregrine falcon (*Falco peregrinus*) is to birds, the cheetah (*Acinonyx jubatus*) to cats, and the Thoroughbred and the Quarter Horse are to equids, the Greyhound is to dogs. Pictures of Greyhounds etched on the walls of ancient Egyptian tombs support their enduring lineage (from between 8000 and 4000 BCE) and the notion that the Pharoahs rated them first among all animals as pets and hunters (127). Since

then, their athletic prowess, developed originally by the necessities of hunting gazelle, antelope, desert foxes, and hares in the flattish open terrain of the Middle East, has been lauded by the Persians, Arabs, and Greeks, among others. Indeed, the Greyhound is the only canine deserving mention in Scripture via the words of King Solomon (Proverbs 30: 29-31). Although this brief section focuses almost exclusively on the Greyhound in deference to its superior top speed (44-47 mph 71-76 km/h) and availability of rigorous scientific data (406, 407), one should not discount other superb canine athletes. For example, the Alaskan husky and other sled dogs, while towing a sled in the Iditarod 1000+ mile (1,600+ km) race, may have an average energy expenditure of well over 11,000 kcal per day, with some individuals exceeding 12,000 kcal per day (161; see also 117). This equates to a $\dot{V}O_2$ far exceeding 100 ml/kg/min for a 30-kg dog sustained for 10 to 12 hours per day!

Table 4 compares and contrasts the Greyhound with the Thoroughbred horse and also the superb human athlete with respect to key performance and anatomical and physiological attributes pertinent to our consideration of the O_2 transport pathway. Just as throughout this article where focus has been maintained on superior horses, these data reflect the same for the Greyhounds. As mentioned in the *Introduction*, most Greyhounds will not run on the treadmill: Out of over ten dozen animals evaluated, Ross V. Staaden was able to secure only three dogs that would do so adequately (406). Of these, two were available because of poor race performance and only one was a successful competitor whose pugilistic ways had him removed from the track. The data in Table 4 are almost exclusively from this latter animal, who, at the time of evaluation was, quite likely, aged beyond his peak.

Extraordinary though the 240 ml/kg/min $\dot{V}O_2max$ for the Greyhound undoubtedly is (Fig. 3A), values of up to ~170 ml/kg min have been reported for mongrel dogs (390,441) and Foxhounds (176, 285, 286). As a species, dogs are endowed with substantially larger hearts than humans, with measured values up to 1.7% body mass (51, 131, 242, 295, 386, 409). Maximal heart rate for the dog (i.e., 320 beats/min, Table 4; 77,377,407,432) is substantially higher than that for the horse or human and, combined with large maximal stroke volumes, can achieve cardiac outputs exceeding 1 liters/kg/min (286, 406). As for the horse, the dog utilizes splenic RBC discharge to elevate exercising hematocrit and thus CaO_2 (Table 4; refs. 73,180,289,404,406,421) and therefore splenectomy reduces exercising hematocrit and $\dot{V}O_2max$ (176, 241).

As for the horse and the human, the capacity for the dog to utilize O_2 (i.e., $\dot{V}O_2max$) does not seem to be limited by muscle oxidative capacity, at least in untrained mongrel dogs as evidenced by the elevated $\dot{V}O_2max$ found after pericardectomy increased $\dot{Q}$ and muscle O_2 delivery (412). This appears true also for the Foxhound in which exercise training increases $\dot{V}O_2max$ in the absence of adaptations in muscle capillarity or oxidative capacity (which are already very high, 299). Whether this is true for the Greyhound has not been established.

Table 4 Comparison Among Human (Superb Athlete), Horse (Thoroughbred and Quarter Horse), and Dog (Greyhound) for Principal Respiratory, Cardiovascular, and Muscle Structural and Functional (at $\dot{V}O_2max$) Attributes*

	Human (athlete)	Horse (Thoroughbred/ Quarter Horse)	Dog (Greyhound)
Running speed			
mph	**27**	**45-55**	**45**
kph	**43**	**72-89**	**72**
Body mass, kg	70-86	~500	~30
% Muscle	~40	55	58
Muscle mass, kg	28	275	~17
Maximal O_2 uptake, $\dot{V}O_2max$			
ml/min/kg	94	>220	240
liters/min	7.0	>110	7.2
Maximal CO_2 output, $\dot{V}O_2max$			
ml/min/kg	>105	>240	~270
liters/min	>8.4	>120	8.1
Maximal exercise *R* ($\dot{V}CO_2/\dot{V}O_2$)	1.2-1.4	~1.2	~1.2
$\dot{V}_E$, liters/min	>200	>2100	244
$\dot{V}_A$, liters/min	>180	>1400	~162
V_T, liter	>3	>16	~1.3
V_D, liter	>0.15	~3	0.096
f_b, breaths/min	<60	140-180	188
PaO_2, mmHg	70-100	<60-70	60-70
SaO_2, %	<90	<85	≤90
$PaCO_2$, mmHg	25-45	60-70	~43[a]
EIPH	Rare	Prevalent/ severe	Present/ mild
Heart mass			
% Body mass	>0.6	≤2.0	~1.7
kg	>0.5	~10	~0.5
$\dot{Q}_{max}$, liters/min	>40 to 48	>500	37
HR_{max}	~180	210-250	>320
SV, ml	>260	>2000	116
Hematocrit, %	~45	>65	>66
CaO_2, ml/100 ml	~20	>25	27.1
CvO_2, ml/100 ml	~3.0	~2.5	~4.0
$\Delta a\text{-}vO_2$, ml/100 ml	~17	>22.5	23
% Extraction	>85	>90	~86
Spleen, kg	NA	14	~1.8

*The foundation for these values is literature-based as indicated below and the reader should understand that the necessary encumbrances of the measurement apparatus (e.g., mask, catheters, probes) and the laboratory exercise equipment (treadmill) may have impacted the values presented. In addition, not all measurements were carried out in the same individuals. Thus, a composite is presented that, where possible, maintains internal consistency. Data from: human, based on 12,35,318; horse, see references in appropriate sections of the text; dog, see appropriate section in text). Note that the physiologic measurements presented for the Greyhound dog were essentially derived from one exceptional animal (NT) studied by Staaden (406).

[a]It should be noted that the Greyhound hyperventilates pre-race to ~28 mmHg $PaCO_2$ (314).

In the mongrel dog and also Foxhound running at maximal speeds, locomotory muscle blood flow is heterogeneous ranging from ~1 in the semitendinosus to 3 liters/kg/min or higher in the biceps femoris and semimembranosus (282, 284, 286). Although these $\dot{Q}$'s are somewhat greater than those measured in the Standardbred horse during maximal exercise (5), they are lower than in the human quadriceps (345). Thus, the high capillary density (and therefore volume density) in the Foxhound (299) will help preserve mean capillary RBC transit time such that one would not expect blood–muscle O_2 offloading to be limited by capillary RBC residence time (see 169). To our knowledge, no muscle $\dot{Q}$'s are available in the racing Greyhound. However, two facets of their design will help to prevent the high $\dot{Q}$ from reducing capillary RBC transit time: skeletal muscle capillarity is increased relative to other breeds (129) and the muscle mass relative to body mass is high (up to 58% body mass, 128).

Like horses, maximal running speeds in Greyhounds elicit blood lactate concentrations approaching 30 mMol (69, 128, 180, 314), which is appreciably higher than those reported for other dog breeds (e.g., mongrels, 283; Foxhounds, 175) and humans (rev. 12, 35). There is also breed-specific control of blood pressure. In association with their higher cardiac index, Greyhounds have a significantly higher MAP (118 mmHg) than mongrels (98 mmHg) at rest (56). Whereas exercising MAP does not increase much beyond ~140 mmHg in the Foxhound at maximal exercise (285, 286), whether, like the horse, MAP in the Greyhound reaches extremely high levels remains to be determined. The EIPH reported recently in the Greyhound, although mild, suggests that at least pulmonary artery pressures during racing become elevated sufficiently to rupture the blood-gas barrier (73) as seen to a greater extent in horses.

From the above, it is evident that there is considerable commonality between the elite athletes of the equine (Thoroughbred/Quarter Horse) and canine (Greyhound) species. Both have an extraordinary cardiovascular capacity that delivers a prodigious O_2 supply to a very large and highly oxidative musculature. But what of the pulmonary system? Less athletic breeds than the Greyhound such as mongrels and Foxhounds can exercise at $\dot{V}O_2$max's considerably above those achieved by humans, i.e., >>100 ml/kg/min, without evidencing overt EIAH or hypercapnia (283, 292).

Across mammalian species, the capacity for pulmonary gas exchange as assessed by lung diffusing capacity (D_L) is principally determined by body mass such that D_L determined by the size of the gas exchange apparatus scales to 1 power of body mass as opposed to metabolic rate that scales to 3/4 power (rev. 108). Notwithstanding this observation, highly oxidative animals such as the horse and the dog appear to have a greater D_L than might be predicted from body mass (52, 108, 192, 417, 439-441). From rest to maximal exercise, D_L (as determined for carbon monoxide) increases ~300% most likely due to the increased pulmonary $\dot{Q}$ and augmented vascular pressures recruiting additional capillaries and distending those already supporting flow (175). Increases in lung volume and capillary hematocrit may also contribute a minor proportion of the elevated D_L (~20%; ref. 41). Whereas this increased D_L, even in the face of elevated ventilation–perfusion mismatch (177, 388), is sufficient to defend blood gases during maximal exercise in lesser species, this is not true for the Greyhound. Specifically, the tongues of racing Greyhounds are often so blue immediately after racing that it was assumed that the dogs held their breaths during racing (406). Although a brief sojourn to the race track on a cold day to actually see them breathe with each stride will quickly dispel this myth (see Table 4), measurements during track racing and treadmill running demonstrate pronounced EIAH and mild hypercapnia (Table 4; refs. 314,406). One reason why the Greyhounds studied by Pieschl and colleagues (314) did not become more hypercapnic (like the horse) may have been their prerace strategy. Specifically, those Greyhounds hyperventilated immediately prior to the race and drove their $Paco_2$ down to 28 mmHg. Thus, during exercise, $Paco_2$ rose by ~15 mmHg, indicating that alveolar ventilation ($\dot{V}_A$) was insufficient to prevent substantial accumulation of CO_2 (presumably from mitochondrial CO_2 production and bicarbonate buffering of H^+).

Conclusions

The fastest horses and dogs have shared a common Middle Eastern heritage over millennia where survival, either as the hunter or intended prey, depended on great speed and, to a certain extent, endurance. During the past several centuries, both species have enhanced humankind's ability to hunt, prosecute war, and provide entertainment in the sports arena. The dependence of these physical traits on the development of a superior O_2 transport system has resulted in species that can increase O_2 utilization to prodigious levels (nearly three times greater per unit body mass than the best human athletes) with very rapid kinetics. Key elements to that O_2 transport system include the following: (i) Enormous hearts (1%-2% body mass) that can generate large stroke volumes and beat 250 (horse) to more than 320 (dog) times per minute sufficient to raise cardiac output to 1 liter or more per kg body mass. (ii) Highly contractile spleens that elevate systemic hematocrit to 60% to 70%, raising the arterial O_2 content (Cao_2) above 25 ml/100 ml. (iii) Increased muscle mass to more than 50% of body mass: Whereas neither the structure (fiber types, vascularity/capillarity, mitochondrial volume density) nor the function (blood flow/oxidative capacity) is extraordinary, *in toto* the capacity of this muscle mass for diffusive O_2 transport and utilization (fractional O_2 extraction >0.85) is spectacular. (iv) The ability to tolerate body temperature increases to more than 42°C (sled dog, 311; horse, e.g., 72, 256, 266). (v) Lungs that have frequently been maligned as the weak link in the O_2 transport pathway. Despite horse and dog lungs possessing far greater diffusing capacities than less athletic species of similar mass, at $\dot{V}O_2$max, the arterial blood is hypoxemic and hypercapnic and the blood-gas barrier is subject to

rupture. To some, this may be construed as failure. However, despite physical and functional constraints that include a long trachea, obligatory nasal breathing leading to partial airway collapse on inhalation (in the horse), locomotory-respiratory coupling (LRC) constraint to breathing frequency, physical dimensions of the lung that, combined with the prodigious $\dot{Q}$'s, lead to disappearingly short pulmonary capillary RBC transit times and diffusion limitation, elevated body temperatures (as well as hypercapnia/acidosis) that impair O_2 loading in the lung (rightward shift of O_2 dissociation curve), and blood leakage into the alveolar space, the lungs do a remarkable job of maintaining arterial O_2 saturation (Sa_{O_2}) above 80% in both species. In this regard, it is pertinent that exceptionally fit human athletes are also prone to EIAH albeit at far lower mass-specific $\dot{V}_{O_2}$'s than the athletically superior animals considered herein.

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