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Similitude in the cardiorespiratory responses to exercise across vertebrates

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The anatomy of the heart and the respiratory organs differs enormously amongst vertebrates, and the absolute rates of oxygen uptake – both at rest and exercise — are several-fold higher in the endothermic birds and mammals when compared to fish, amphibians and reptiles (all ectothermic). Despite these large differences, all vertebrates can elevate the rate of oxygen consumption by 5–10 times when engaging in physical exercise. The increased oxygen delivery is attained by increasing the convective flows (i.e. increased ventilation and cardiac output) as well as increased extraction of oxygen from the blood leading that widens the arterial-venous oxygen concentration difference with an extraction of approximately 90%. All members of all vertebrate classes appear to exhibit some diffusive limitation for oxygen in the gills or lungs, whereas arterial PCO_2 tends to decrease due to hyperventilation.

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Introduction

The ability to perform muscular work is essential for any animal to forage, escape predators, procure mates or engage in any other type of physical activity [1•]. Given the relatively low yield of energy provided by anaerobic metabolism (lactate generation in vertebrates), it is hardly surprising that all vertebrates elevate the rate of oxygen consumption (VO_2) during physical activity with attending changes in oxygen and nutrient supply through appropriate ventilatory and cardiovascular responses [2,3]. As shown in Figure 1, the gas exchange structures, cardiac morphologies and resting metabolic rates differ enormously amongst vertebrates and have been modified by evolution through natural selection [4•,5]. In particular, the transition from water to air-breathing involved large cardiorespiratory modifications and the evolution of the four-chambered heart of mammals and birds is a requirement to sustain the high aerobic metabolism supporting endothermy (in contrast to the regional, myogenic thermogenesis observed in some fish and reptiles). Thus, fish rely on gills to extract oxygen from the water and utilise the double-chambered heart where the systemic and branchial circulation are arranged in series, whereas birds and mammals have complete division of the pulmonary and systemic circuits by virtue of their four-chambered hearts [4•,6]. In this context, amphibians and reptiles represent a transitional stage where the incomplete anatomical division of the cardiac ventricle allows for intracardiac shunting of blood between the systemic and pulmonary circulations [7].

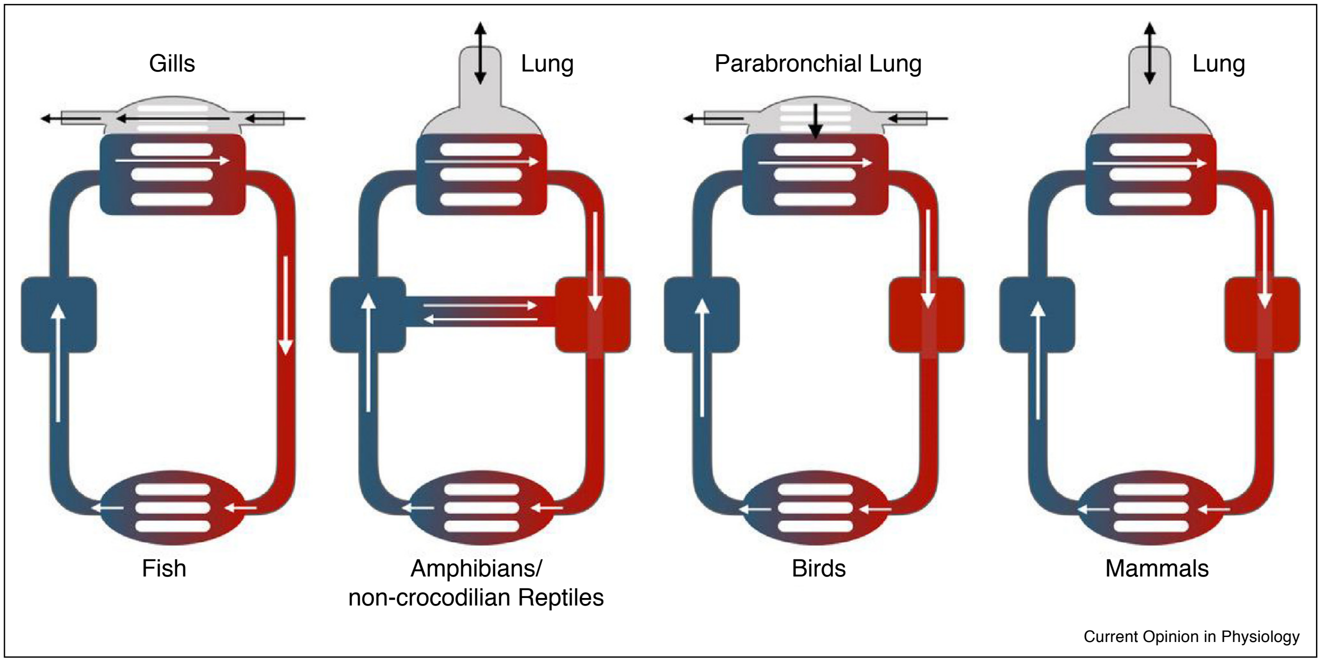
Despite the prominent anatomical and physiological differences, it is the same basic processes that drive oxygen delivery from the environment (whether water or air) to the mitochondria where oxidative phosphorylation takes place: i) convective movement of the respiratory medium to the respiratory epithelium where ii) oxygen diffuses passively into the blood, followed by iii) convective transport of the blood, by virtue of the muscular heart, to the capillaries where iv) oxygen diffuses passively to the mitochondria.

The goal of the present review is to emphasise the commonalities amongst vertebrate classes, and to highlight that these similarities prevail despite the considerable differences in cardiorespiratory morphologies and circulatory arrangements. In doing so, we will stress general patterns and will ignore specific adaptations of particular species. Before emphasising the similitudes in the four steps in oxygen transport, we briefly review the massive influence of endothermy, a trait that developed independently amongst birds and mammals from their common ectothermic reptilian ancestor some 240 million years ago [8].

The large difference in metabolism between ectothermic and endothermic vertebrates

The actual rates of metabolism vary substantially amongst vertebrate classes (e.g. fish, amphibians, reptiles, birds and mammals) and there are also considerable differences within each taxonomic group, so that athletic

Figure 1



A stylistic representation of the cardiorespiratory organs of the major groups of vertebrates. In fish, the oxygen-poor venous blood return to a heart that consists of sinus venosus, one atrium and one ventricle and is ejected towards the gills through the ventral aorta. The blood flow across the respiratory units of the gills, the secondary lamellae, is counter-current to the water flow, which provides for extremely efficient gas exchange as arterial blood gases can approach that of the inspired water. Amphibians and reptiles use a tidally ventilated lung for air-breathing, and the blood flows returning from the lungs and the systemic circulation reach the right and left atrium, respectively, before entering the single ventricle where cardiac shunts can occur, so oxygen-poor blood can bypass the lungs (right to left shunt shunt) or oxygen-rich blood can reenter the pulmonary circulation. The cutaneous gas exchange in amphibians is ignored in this representation because it contributes very little in exercise. Both birds and mammals have hearts with complete separation of the ventricular, such that cardiac shunting is avoided and allows for high systemic blood pressures while keeping low pressures in the lungs that provide for a much thinner blood–gas barrier than their reptilian ancestor. The lung diffusive capacity is considerable higher amongst mammals and birds compared to reptiles and amphibians. While the cardiac anatomy and physiology of the avian and mammalian hearts are strikingly the similar, birds have a unidirectional flow through the gas exchange unit of the lungs (the parabronchus) and the vascular arrangement provides for cross-current perfusion, which is more efficient that the mammalian lung.

species have considerable higher maximal rates of oxygen consumption (VO_2) than sedentary or sluggish species. For example, tunas are known to have very high VO_2 amongst fishes [9], and varanid lizards are renowned for their high aerobic capacity within reptiles [10,11]. Birds and mammals, the two clades where all species are endothermic and hence maintain high and stable body temperatures by virtue of metabolic heat production in all organs. This results in significantly higher rates of metabolism than measured in all ectothermic vertebrates (fish, amphibians and reptiles). Generally, the rates of oxygen uptake, a proxy for metabolism, are about 5–10-fold higher in mammals and birds compared to the ectothermic animals of similar body mass and similar body temperatures [12]. As an additional overall pattern, most animals can elevate VO_2 by approximately 5–10 times during activity [13•]. This commonality is independent of resting metabolic rate and implies very similar capacities to elevate oxygen delivery in all animals. As explained in more detail below, this is reflected in an extraordinary similarity in the proportional changes in heart rate (f_H), stroke volume (Vs) and arterial-venous oxygen extractions.

Aerobic versus anaerobic exercise

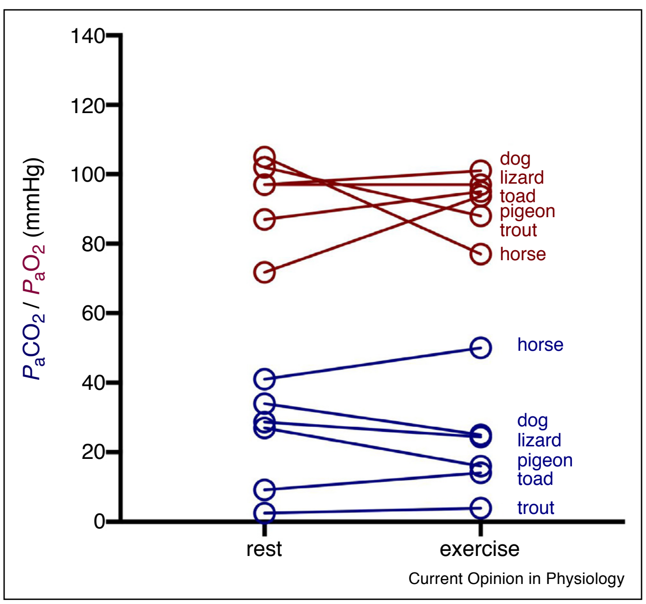
Vertebrates secure their ATP production by aerobic metabolism when at rest and inactive. Aerobic metabolism also suffices during moderate levels of exercise, but when metabolic demands in the working muscles exceeds the capacity of the cardiorespiratory systems to deliver oxygen deliver oxygen, they supplement ATP production by anaerobic metabolism with attending increases in lactic acid production [14•]. The proportion of anaerobic energy production is considerably larger in the ectothermic vertebrates where lactate production may contribute by as much as 50% of ATP generation. Lactate levels can increase to 20–30 mM in some species and can impose a severe metabolic acidosis with arterial (and venous) pH reductions in the order of 0.5 units (e.g. Ref. [15•]). The recovery from this lactic acidosis can be very prolonged, and may last many hours in ectothermic vertebrates, and can impose severe limitations to repeated bouts of activity [14•].

Ventilatory responses and arterial blood gases when metabolism increases

The anatomical arrangement of the respiratory structures differs amongst vertebrates. Fish rely on the gills for aquatic gas exchange where blood and water are brought in close contact in the small secondary lamellae. The counter-current flows of water and blood provides for very high gas exchange efficiency such that arterial PO_2 can be as high as in the inspired water, and the high rates of ventilation results in very low arterial PCO_2 levels [16,17]. The terrestrial vertebrates, including amphibians, use lungs and the diffusive capacities for both oxygen and CO_2 are highest in the alveolar lungs of mammals and in the specialised avian lung that provides for cross-current flows of air and blood [4•,18•,19]. Cutaneous gas exchange is significant in many resting fish and amphibians, but the rather limited conductance of the skin contributes little to gas exchange when metabolism increases during exercise.

Figure 2 shows a number of examples of $PaCO_2$ and PaO_2 at rest and during exercise in representative species within the vertebrates, and highlights the large interspecific variation in $PaCO_2$. It is evident that

Figure 2



Examples of the partial pressures of oxygen and CO_2 (P_aO_2 and P_aCO_2, respectively) in selected examples of fish, amphibians, reptiles, birds and mammals during rest and during strenuous exercise. Note P_aCO_2 is particularly variable, with fish having very low values due to the hyperventilation imposed the low oxygen solubility in the water. Data sources: Horse and dog [20], pigeon [37•], monitor lizard [11], toads ([59], CO_2 value; [67]; O_2), trout [65,66].

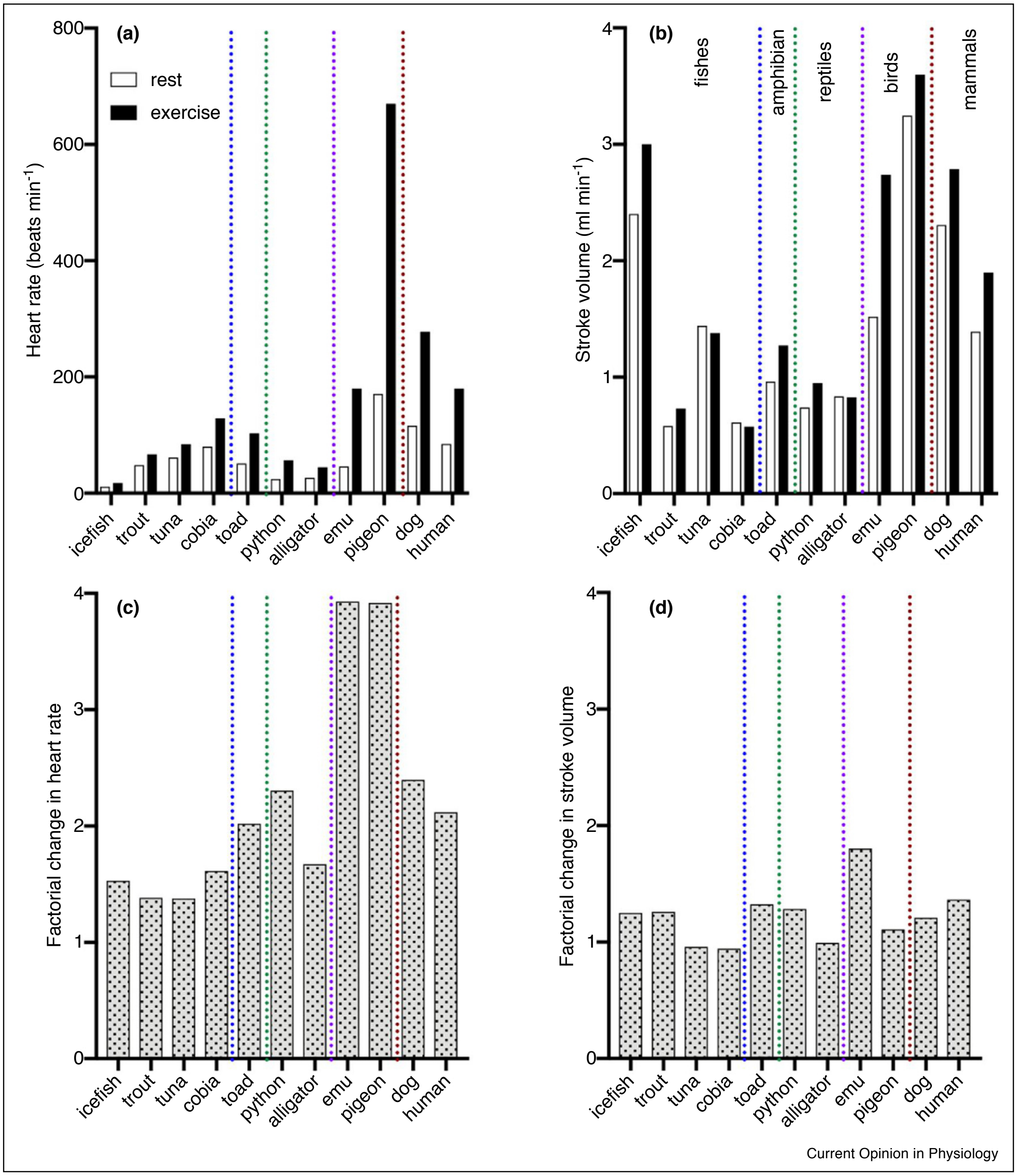
PaO_2 remains high during exercise, although some species experience a fall in PaO_2 with an associated desaturation of the haemoglobin. This is most likely due diffusion limitation, and it most prevalent in athletic species with high VO_2max, and associated with a widening of the alveolar-arterial PO_2 difference (A-a difference). That the lowering of PaO_2 during exercise is not due to hypoventilation is evident from the reduction of $PaCO_2$, which demonstrates most vertebrates hyperventilate (i.e. ventilation increase more than metabolism) during exercise. This ventilatory response serves to alleviate the diffusion-limitation for oxygen that arises from the large increase in pulmonary blood flow and the associate reduction in pulmonary transit time [18•,20,21•]. Lizards may represent a special case in terms of the ventilatory responses to exercise. Lizards lack a diaphragm and ventilation is achieved by the hypaxial musculature that provides stabilisation of the body to alleviate the bending of the body when the lizards move forward [71]. The severity of this constraint probably differs amongst species with different modes of locomotion, and some species such as varanid lizards, on the positioning of the legs. Varanids may also be uniquely assisted by 'gular pumping', a positive-pressure mechanism to assist ventilation [22•].

The regulation of the cardiovascular and ventilatory responses to exercise remains poorly understood in non-mammalian vertebrates. All vertebrates have peripheral chemoreceptors that respond to blood oxygen levels as well as pH/PCO_2, and all, with the reception of fish, have central chemoreceptors. However, given that $PaCO_2$ tends to decrease during exercise it is unlikely that the central chemoreceptors play a significant role and it is quite possible that feed-forward mechanism arose early in vertebrate evolution and that much of the exercise hyperpnoea arises as 'spill-over' within the central nervous system when the skeletal muscle is activated during locomotion. When anaerobic metabolism is recruited, increased circulating lactate may also serve as a respiratory stimulus, as has been demonstrated in fish [23•] and mammals [24] alike.

The cardiovascular responses to exercise

Cardiac output is the product of heart rate (f_H) and stroke volume (V_s). The rise in cardiac output during exercise is attained by an up to fourfold elevation in f_H, and, in some cases smaller, but appreciable elevations of V_s (Figure 3). The similitude in the proportional elevations of f_H are overwhelming considering the large differences in resting f_H. Thus, in the Antarctic icefish that lives at freezing temperatures without circulating haemoglobin, f_H increases from 11.5 to 17.6 beats min^{-1} when undertaking moderate activity [25]. This is accompanied by a proportionally similar increase in Vs, from 2.4 to 3 ml kg^{-1}. In active, tropical fishes such as tuna and cobia, similar relative (50%) increases in f_H have been reported during

Figure 3



The absolute heart rates and stroke volumes of various vertebrates at rest and during exercise **(a** and **b)**, as well as the relative changes in heart rate and stroke volume of the same species **(c** and **d)**.

swimming, despite these species having much higher resting heart rates (60–80 beats min^{-1}) [26–28]. In these athletic fish, V_s does not change with exercise. In the most intensely studied teleost fish, the rainbow trout, it has been strongly upheld that cardiac output is largely changed by V_s as opposed to f_H [9,29], but this is largely based on a classical study by Kiceniuk and Jones [30•], where trout showed an unusually small increase in f_H. More recent studies demonstrate much larger changes in f_H than V_s (e.g. Ref. [31]), and it now recognised that the fish studied in many of the older studies were tachycardia at rest due to disturbance or short recovery times following surgery (see Ref. [32]). The vast majority of investigations on reptiles (lizards, snakes, turtles and crocodilians) and amphibians have shown that cardiac output increases predominantly due to a tachycardia, with V_s remaining stable or increasing only slightly, during exercise [11,33•,34•,35,36]. This is also the case in birds [37•,38] and mammals [39–41], including humans [42].

The tachycardia is achieved by withdrawal of vagal tone and elevated sympathetic tone [43,44], and the rise in V_s stems from elevated venous return. At steady-state, cardiac output must equal venous return, meaning that V_s is largely determined by the peripheral vasculature [45,46]. The dependence of cardiac output on peripheral (vascular), as opposed to central (cardiac), factors is strikingly revealed by right-atrial pacing to raise f_H experimentally. In both mammals (dogs, humans) [42,47–49] and reptiles (alligators) [34•], increasing f_H by pacing has little direct effect on cardiac output at rest or during exercise, drawing us to the surprising conclusion that whilst f_H is *regulated*, it is not *regulatory* of cardiac output. Instead, the exercise tachycardia simply appears to be synchronised with the regulation of venous return to ensure that V_s remains relatively unchanged, presumably to ensure optimal cardiac function and to protect the heart from pressure overload. This effect is independent of the cardiac anatomy, and emphasises the underappreciated role of regulating the rate of venous return.

Despite large rise in cardiac output during exercise, arterial blood pressure typically only increases marginally, not at all, or may even decrease slightly [25,27,42,50]. This reflects that peripheral vascular conductance increases tremendously, which may be mediated by sympatholytic vasodilators such as adenosine and nitric oxide [51,52]. Indeed, such a peripheral vasodilatation has been experimentally demonstrated to directly increase cardiac output [47,53,54], and likely represents the major driving force for the increase in venous return that characterises exercise.

Elimination of cardiac shunts to increase systemic oxygen delivery during exercise

The undivided cardiac ventricle of amphibians and reptiles offer the possibility for intracardiac shunts [55,72], and crocodilians can have right-to-left shunts because the left aortic arch emanates from the right ventricle (along with the pulmonary artery; [73,74]). A right-to-left (R-L) shunts result in oxygen-poor venous blood bypassing the lungs and re-entering the systemic circulation. Typically, R-L shunts are often large in resting undisturbed reptiles [55,56], accounting for low arterial oxygen saturation [11,57–59]. The magnitude and the direction of cardiac shunts are regulated by the autonomic nervous system. High vagal tone (typical of rest) promotes R-L shunting [60], whereas adrenaline reduces the R-L shunt and may invoke a left-to-right shunt; recirculation of pulmonary venous blood back into the lung [25,68,69]. In swimming alligators, flow in the left aortic arch changes little from resting values, whilst right aortic arch and pulmonary blood flow increase [25,34•], providing evidence that the R-L shunt fraction decreases. The reductions in R-L provide for an additional means to elevate systemic oxygen delivery during exercise in amphibians and non-crocodilian reptiles (Figure 4; [11,58,59,61,62•,70]).

Similitude in the high extraction of oxygen from the blood amongst vertebrates

All existing studies with simultaneous measurements of venous and arterial blood gases in vertebrates demonstrate that all classes widen the arterial-venous oxygen concentration difference, which means that the mitochondria are capable of utilising the oxygen that is provided by the convective transport and that tissue capillary density and perfusion provides for almost complete unloading (venous haemoglobin oxygen saturation is typically below 20% during exercise (e.g. Refs. [30•,33•,37•,63]).

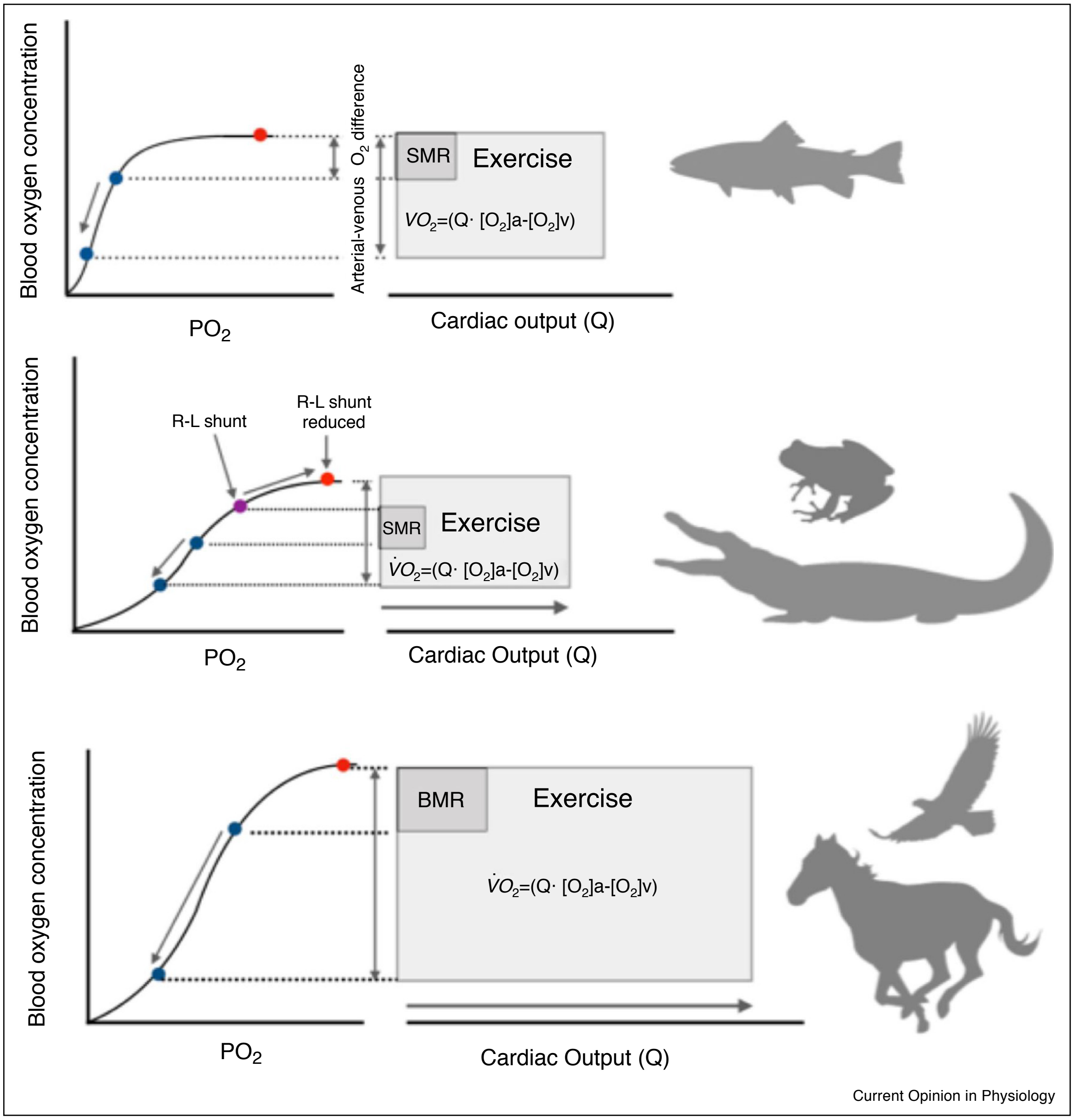
The integrated response to increased metabolism during exercise: graphical solution of the Fick principle

As originally outlined by Adolph Fick [64], VO_2 is given as the product of cardiac output (which is $Vs \times f_H$) and the oxygen extraction, that is, the oxygen concentration difference between arterial and venous blood ($[O_2]_a - [O_2]_v$):

$$VO_2 = Vs \times f_H \times ([O_2]_a - [O_2]_v)$$

This relationship is expressed graphically in Figure 4 where the left panels depict an oxygen equilibrium curve of the blood with arterial and venous PO_2 and O_2 concentrations, whilst the squares on the right-hand panel demonstrates the product of the A–V difference and cardiac output, that is, VO_2 at rest and during exercise. This representation illustrates the similitude in the changes delivery when vertebrates transition from rest to exercise, despite the large anatomical differences in their cardiorespiratory organs. Thus, endothermic vertebrates can accommodate the higher VO_2 max because i) ventilation is increased proportionally allowing for high arterial oxygen levels, ii) cardiac output, achieved primarily by tachycardia, and blood haemoglobin concentration is higher, and iii) the capillary density and the amount of the mitochondria provides for high extraction and resulting low venous oxygen levels. Interestingly, the similitude also applies to blood pressure because the increased cardiac output is proportional to the rise in systemic vascular conductance (due to capillary recruitment), such the blood pressure only increases modestly in most species.

Figure 4



A graphical solution to the Fick principle for oxygen uptake as calculated from the product of cardiac output (Q) and the arterial venous oxygen concentration difference (A–V difference). Note that all vertebrates maintain high arterial oxygen saturation, although arterial PO_2 may fall appreciably in athletic species with high VO_2 max, such that rise in the A–V difference is primarily due to increased extraction in the tissues. In amphibians and reptiles, arterial oxygen levels may actually increase during exercise because the reduction in right-left-shunts provides for a mechanism to elevate oxygen concentration that is independent of pulmonary ventilation. Also, note that the oxygen concentration of the arterial blood is higher in the endothermic birds and mammals due to a higher haematocrit than the ectothermic fish, amphibians and reptiles.

Summary

In the vertebrates, there are two basic metabolic strategies (ectothermy versus endothermy), significant variation of respiratory (gills and lungs) and cardiac (single chamber, three chamber, four chambered hearts) design, yet the strategies used to sustain locomotor activity are remarkably similar. When analysed within the context of standard mass transport equations and the oxygen transport properties of haemoglobin, this similitude is not surprising. The convective and diffusive conductance simply must increase and be fairly well matched insuring adequate delivery and extraction of O_2 and removal of CO_2. How these transport processes are regulated, particularly near the extremes of performance (VO_2max) or affected by environmental conditions (e.g. hypoxia and or temperature) remain fruitful areas of investigation. Ultimately, how diverse organisms respond to physiological and environmental challenges and how these responses are controlled and integrated over multiple levels of biological organization is exceptionally complex, but remains an area for the convergence of comparative omics and organismal physiology.

Conflict of interest statement

Nothing declared.

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