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Cardiovascular Response to Exercise in Vertebrates: Update

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Abstract: Physical exercise is the greatest stress on the cardiovascular system, not only in humans but also in all vertebrates. Consequently, the cardiovascular response cannot be thought of as having only one "anthropocentric" interpretation. The modulation of cardiac output (Q) in response to exercise in the five major groups of vertebrates exhibits considerable variability. Moreover, the response of the heart rate (HR) and the stroke volume (SV), the fundamental factors that cause the rise in Q, is also highly variable. The difference in the range of HR is difficult to determine in many vertebrates, both at rest and at maximal effort. Additionally, the increase in SV varies among vertebrates. For example, while rainbow trout and leopards increase their SV by increasing end diastolic volume (EDV), humans do so at the expense of both increasing EDV and reducing end systolic volume (ESV). The variation in arterial pressure that arises during exercise varies notably among vertebrates, such as amphibians, whose blood pressure values do not increase as significantly as in mammals. Such differences in cardiovascular response among vertebrates may be linked to their habitat or living environment. This review aims to analyze the cardiovascular response of vertebrates to physical exercise as the most common stressor.

Keywords: vertebrates; arterial pressure; cardiac output; exercise; heart rate; stroke volume

1. Introduction

Human interest in sport medicine and exercise physiology began in the 19th century. Some decades later, other athletic mammals received some attention, such as racing horses, dogs, and camels. In general terms, exercise is the greatest stress on the cardiovascular system, not only for humans but for all vertebrates. For this reason, the cardiovascular response cannot be considered to have only one "anthropocentric" meaning [1–3].

Athletic performance relies on aerobic capacity to generate energy for the exercising muscles, facilitated by an increase in HR and SV (the ability to increase Q), among other factors [4,5]. However, research on the cardiovascular response in vertebrates has serious limitations since its study is conditioned and limited by the methods needed for its assessment, such as stress tests, and the different models of locomotion (aquatic, terrestrial, aerial, and their combinations) in the different groups of vertebrates. Therefore, various types of ergometers are used, such as treadmills, flight tunnels, swimming tunnels, and running wheels. Other ways to measure cardiovascular response to physical activity include thermal stress due to cold or the straightening reflex [6,7].

Vertebrates that undertake enormous migrations, lasting from a few days to weeks, need to increase their metabolism eightfold in birds [8,9], and up to fifteenfold in salmon [10]. They must adjust their cardiovascular system correspondingly to sustain such considerable metabolic activity. Migratory birds maintain a high level of cardiovascular activity equivalent to the energy cost of a marathon competition in humans, ranging between 62 and 100% of their maximal rate of oxygen consumption (VO_{2max}) [11].

The general characteristics of the cardiovascular system in vertebrates have previously been described [12]. Throughout the evolutionary process, all vertebrates have possessed a myogenic heart with evident intrinsic activity, although there are exceptions in fish that have more than one heart. This intrinsic activity of the heart has been demonstrated in vertebrate precursors, tunicates, and cephalochordates [13]. Blood flows from the heart to the head and the rest of the organism, and there are also one-way valves, which open and close, allowing only one direction of the blood to flow through them. The venous valves are considered a "passive" system [14,15]. The blood vessels exhibit vasomotor activity, such that changes in the degree of contraction of the smooth muscles alter the peripheral resistance, variations in blood pressure, and the storage of blood in the periphery [16,17]. Although with certain limitations, as occurs at the capillary level with the exchange of liquids, the cardiovascular system can be functionally considered a closed system [18].

Apart from the characteristics already mentioned, significant heterogeneity exists among the five principal groups of vertebrates, including fishes, amphibians, reptiles, birds, and mammals, in relation to their cardiovascular response to exercise [6,7,19,20].

In the closest living relatives of vertebrates, tunicates and cephalochordates, blood is transported in clear vessels to a range of vascular beds [21,22]. Differences are observed within the fish division; for instance, specific classes can breathe atmospheric air for a certain duration of time [23–25].

The amphibian heart consists of two anatomically separated atria, left and right, which receive blood from both the lungs and the systemic venous circulation, respectively. This blood then enters a ventricle that is highly trabeculated and undivided. The trabeculae, forming deep sacs, gather and retain blood during diastolic filling. This mechanism appears to enable a partial separation of the blood not only during this final phase but also while the blood is being expelled during systole [26–28]. There are also exceptions, such as tadpoles and some adult salamanders, which have pulmonocutaneous circulation. Nevertheless, notable differences exist between the two main classes of amphibians: Anura (frogs and toads) and Caudata (for example, the salamander) [15,29,30].

The differences among the classes of reptiles have been analyzed previously. The heart and central circulation in reptiles exhibit anatomical complexity, resulting in a parallel connection between the systemic and pulmonary systems. Furthermore, reptiles have a lower ratio of heart mass to body mass compared to mammals or birds. Extensive research has focused on the physiological implications of intermittent breathing patterns during both terrestrial and aquatic activities. Notably, reptiles demonstrate lower Q, which is a product of SV, mean blood pressure, and HR, when compared to mammals and birds [31–34].

The cardiovascular system of non-crocodilian reptiles is a paradigm of intracardiac shunting [12,35–37]. Cardiovascular shunts have been acquired as an adaptation associated with low metabolic activity and intermittent forms of apnea, especially in vertebrate ectotherms. The single ventricle of these vertebrates is partially divided by a muscular protrusion (homologous to the spiral valve of the amphibians heart) that partially separates flow and expels the blood from the ventricle according to the systemic and pulmonary vascular resistance Although there are two separate atria, the existence of a single ventricle with this valve device allows the pulmonary and systemic venous blood to be mixed [32,38–40].

Therefore, some reptiles with an undivided ventricle (except crocodilians, pythons, and monitor lizards) can perform right-left or left-right shunts. Possible theories regarding the functions of these derivations have been described by Burggren et al., giving them a holistic and integrative sense, and they may have several implications during exercise. In general, increasing exercise intensity results in cardiovascular bypass [38]. The right-left shunt allows the recirculation of venous blood to re-enter the systemic circulation and, consequently, a decrease in oxygen saturation, while the left-right shunt produces an increase in oxygen saturation and an improvement in tissue oxygenation in reptiles, aquatic anurans, and air-breathing fish. During exercise, amphibians and non-crocodilian reptiles have a left-right shunt [6,24,31,41–52].

Right-left shunts (Figure 1) would have a beneficial function in lowering metabolism, resulting in a decrease in blood flow at the pulmonary level and a decrease in the amount of oxygen in the body. The reduction of metabolism would reduce energy consumption when working conditions are

more exigent, such as prolonged periods of apnea. On the other hand, the left-right derivations (Figure 2) minimize the possible inequalities of the ventilation/perfusion ratio, allowing more oxygen to reach the brain and upper body in amphibians and reptiles [13,18,32,38,53].
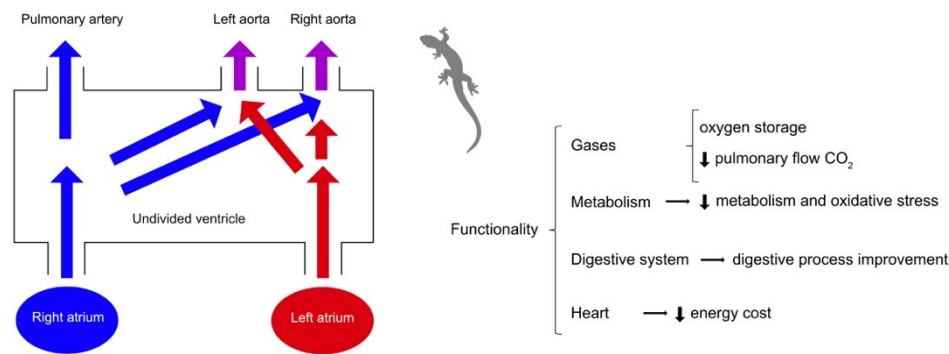

Figure 1. Right-left shunt and functionality in adult non-crocodilian reptiles. A right-to-left shunt occurs when oxygen-poor venous blood (right atrium) is diverted to the systemic circulation without being reoxygenated in the lungs. Cardiovascular shunts should be viewed as part of integrated systems with multiple functions. High vagal tone (typical of rest) promotes R-L shunting, whereas adrenaline reduces the R-L shunt. The reductions in R-L provide for an additional means to elevate systemic oxygen delivery during exercise. *Colours: red for oxygenated blood, blue for deoxygenated blood, purple for mixed blood.* Data: from different authors [31,32,38,41–43]
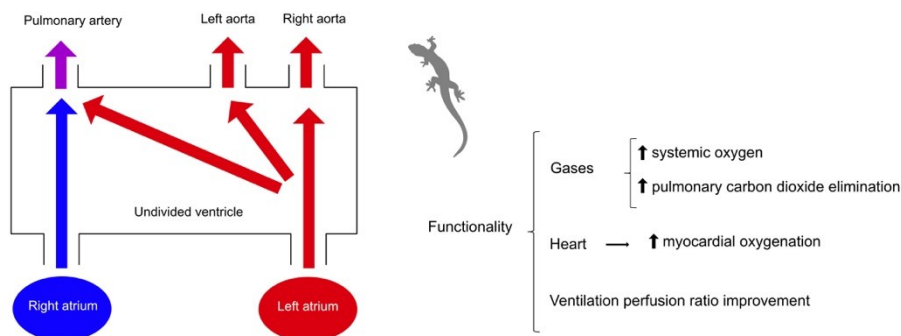

Figure 2. Left to right shunt and functionality in adult non-crocodilian reptiles. Left-to-right shunts occur when oxygenated blood (left atrium) is directly recirculated to the lungs and represent the recirculation into the pulmonary arterial circulation. Cardiovascular shunts are adaptions with multiple functions, selected for because of their favourable cost/benefit ratio. The increase in adrenaline during exercise may invoke a left-to-right shunt and a recirculation of pulmonary venous blood back into the lung. *Colours: red for oxygenated blood, blue for deoxygenated blood, purple for mixed blood.* Data: from different authors [31,32,38,41–43].

The heart of the crocodile is an example of extracardiac shunting, preventing the mixing of blood in the heart, which is common in other reptiles and amphibians, as cardiovascular shunting is produced outside the heart. The outflow tract is formed by the pulmonary and aortic components. The aortic component is double, with one aorta arising from the left ventricle and a second aorta taking its origin from the right ventricle, together with the pulmonary component [54,55].

Finally, the cardiovascular system of birds and mammals is completely divided into a pulmonary circuit, with low pressure, leaving the right ventricle to irrigate the lungs through the pulmonary artery, and a systemic circuit, with high pressure, originating from the left ventricle through the aorta to perfuse the rest of the body [56–59]. However, comparisons of the cardiovascular anatomy among genera and families, both of birds and mammals, reveal some differences [60–62].

Among them are the higher Q with the same body mass of birds compared to mammals, the more elongated heart of birds, and the greater cardiac mass compared to the body mass of birds in relation to mammals, finding significant differences between bird families. This may be due to the great need for aerobic power required to maintain flutter during flight [63].

HR in vertebrates is determined by the activity of the heart pacemaker and various factors, such us temperature, acetylcholine, adrenaline, or calcium, that modulate its electrical activity via nervous and hormonal pathways [64–68]. SV is determined by contractility and the characteristics of the ventricle, mainly regarding its filling capacity. Similarly, the control of the SV is accomplished by two different pathways, nervous and hormonal [7,17,69].

Although there are many common anatomic and functional characteristics in all vertebrates, the cardiovascular requirements in the five groups of vertebrates are highly dependent on the type of circulation and the environment. The domain of comparative physiology is inevitably linked to Laureate August Krogh (Nobel Prize) and adheres to the 'Krogh principle': "for many problems, there is an animal on which it can be most conveniently studied" [70]. By conducting comparative studies among various groups of vertebrates, research in exercise physiology in humans can be enriched.

The "amplitude" of the cardiovascular response is difficult to define because, except for vertebrates used in experimentation and some mammals, the values of rest and maximal exercise are not very precise. The knowledge and research on the cardiovascular response to physical exercise in various classes of vertebrates can assist in evaluating human cardiovascular responses during physical activity in diverse environmental conditions, including extreme temperatures, aquatic exercise, and high altitudes. Furthermore, this information may provide valuable insights into the interpretation of cardiovascular responses in humans engaging in physical exercise with disabilities or under pathological conditions. Previous reviews have focused on factors that limit physical exercise performance in vertebrates without emphasizing cardiovascular response [6,7]. A comparative analysis of cardiovascular parameters, together with an integrated description of the variables involved in the cardiovascular system's response to physical exercise in vertebrate groups, is essential. Focusing solely on the cardiovascular components is inadequate for understanding the adaptations in each vertebrate group, considering the diverse and individual variables attributed to each group.

The aim of this review is to examine the cardiovascular response in vertebrates based on hemodynamic parameters and the general hemodynamic equation, which establishes that the mean arterial pressure (MAP) equals Q divided by total peripheral resistance (TPR). Additionally, it aims to evaluate the integrated response of these cardiovascular variables, contributing to the adaptations to physical exercise across various vertebrate groups. The regulation of circulatory parameters during physical activity exhibits significant variation among vertebrates, attributable to their body structure and other determining factors affecting the regulation of Q and TPR. The parameters governing Q (the product of SV and HR) display substantial variability among the five groups of vertebrates, with some increasing Q via an increase in SV, while others achieve this solely through elevated HR.

2. Methodology

This paper constitutes a narrative review. The identification of research studies involved a comprehensive search across multiple databases, including PubMed, The Web of Science, Scopus, Google Scholar, and citation searches. The search terms included cardiovascular system, physical exercise, maximal effort, cardiovascular response, cardiovascular adaptations, exercise physiology, vertebrates, fish, amphibians, reptiles, birds, and mammals. These search terms were utilized in conjunction with the advanced tools provided by the search engines. The review did not set an arbitrary start date for the inclusion of studies. The searches were conducted up until September 2023.

3. Adjustment of the HR to exercise in vertebrates

All vertebrates have a pacemaker. The heart's activity is modulated by neural and hormonal factors. The intrinsic rate of the pacemaker shows important differences among the distinct groups of vertebrates [71–73]. Resting HR and maximal HR in ectotherm vertebrates are generally lower than

those of endotherms, although there are exceptions such as tuna and small reptiles [74,75].   Despite all the problems related to determining resting HR (such as temperature, ventilatory arrhythmia, and the definition of the resting state), the differences are related to phylogeny, body mass, temperature, and, to a certain extent, the capacity to perform exercise [71,76].

Evidence indicates an allometric relationship with an exponent of -0.25 between body mass and resting HR, reaching its maximum in birds and small mammals [12]. The significant contrast in HR between the smallest birds and the largest mammals, as shown in Table 1, is reflected in this relationship. The considerable variations may be attributed, at least in part, to differences in sodium (Na+) conductance, which determines the slope of the potential of slow depolarization in the pacemaker cells [71,77].

Although the data are scarce, there is an allometric relationship with a similar exponent in snakes and frogs [12]. Resting HR in fit horses, for example, ranges from 30 to 40 bpm [78] and from 50 to 60 bpm in athletic humans under similar conditions [79,80]. Based on limited data, the maximum heart rate (HR_{max}) during exercise for the majority of the lower vertebrates is 120 bpm [81]. Tuna is the only known exception to this generalization, as a HR_{max} of more than 200 bpm has been found [71].

The upper limit of HR in lower vertebrates appears to be unrelated to body mass, suggesting a phylogenetic constraint associated with the pacemaker rate or modulating mechanisms [71,77]. Given the recognized scale of HR to body mass, it is probable that the highest HR values are found in early development when the animal is a neonate or still relatively young. Other recent studies have found that in alligators and turtles, HR did not scale with body mass after injecting adrenaline. The lack of a scaling pattern contradicts prior studies on reptiles demonstrating HR decreases with body mass [82,83].

In the studied vertebrates, HR and its adjustment to physical exercise show notable differences and could be influenced by several intrinsic factors, such as age (as has already been evidenced in humans) [65,84–89]. As illustrated in Table 1, fish, amphibians, and reptiles show a limited range of HR. This may be because the environment in which they live do not require them to considerably alter their cardiovascular system, i.e., increase their Q. Another possible explanation could be that the adjustment of Q is produced by the Frank-Starling mechanism or contractility. Finally, the small increase in HR in response to exercise in these vertebrates may show the increase complexity of the control mechanisms that alter HR throughout evolution [7,56,74,90–96].

Table 1. Examples of resting and exercise heart rates in different classes of vertebrates. HR differ even among different animals in the same group of vertebrates.   Data: from various sources [56,74,92–95]. *Abbreviations: HR-heart rate; bpm-beats per minute; HR_{max}-maximal heart rate.*

Vertebrate	Resting HR (bpm)	Exercise HR_{max} (bpm)
Human	80	190
Rat (mammals)	320	600
Dog (mammals)	100	300
Horse (mammals)	38	207
Golden-collared manakins (birds)	250	1300
Tuna (fishes)	100	205
Salmon (fishes)	20	85
Frog (amphibians)	25	100
Rhinella marina (amphibians)	20	105
Ophisaurus (lizard) (reptiles)	20	60
Iguana (reptiles)	30	100

During strenuous physical exercise and VO_{2max} conditions, Thoroughbred horses can reach an HR_{max} close to 220 bpm, and maximum values ranging from 180 to 200 bpm have been found in humans at a similar exercise intensity. These data show the ability to increase the HR from rest to maximal exercise intensity by an order of five to eightfold and three to fourfold in the equine and human species, respectively [97–100]. Surprisingly, ventricular filling does not appear to be

compromised at maximal exercise, despite heart rates of 4 beats/s [101].These cardiovascular adjustments in response to exercise are one of the factors that may limit the VO_{2max} in some vertebrates [3,6,102].

The control mechanisms of the HR (endocrine and nervous control) seem to show an evolutionary tendency. Catecholamines are present in all vertebrates; however, adrenergic cardiac innervation is lacking in Cyclostomata and Elasmobranchii. Thus, from an evolutionary perspective, tachycardia mediated by adrenaline seems to have acquired greater importance in birds and mammals. The muscarinic receptors mediate cholinergic inhibition of heart rate (HR), influenced by a cardiac branch of the vagus nerve, and are present in all vertebrates except certain fish [68,103–107].

The resting HR is influenced by both autonomic and non-autonomic stimuli. Horses and young people are predominantly under parasympathetic control, which tends to shift to a sympathetic predominance as aging progresses. This modification could be due to decreased parasympathetic or increased sympathetic nervous system input, as well as an adjustment in plasma volume and cardiac filling pressure, or a combination of all these factors [68,108–112].

4. Adjustment of the SV to exercise in vertebrates

SV is under the control of the Frank-Starling mechanism and contractility. The participation of each of the mechanisms in different vertebrates depends on factors such as the Frank-Starling mechanism. The Frank-Starling curves, or the curves of ventricular function, have been established in several groups of vertebrates [14,71,113–115]. Figure 3 shows variations in SV with respect to cardiac pressure.
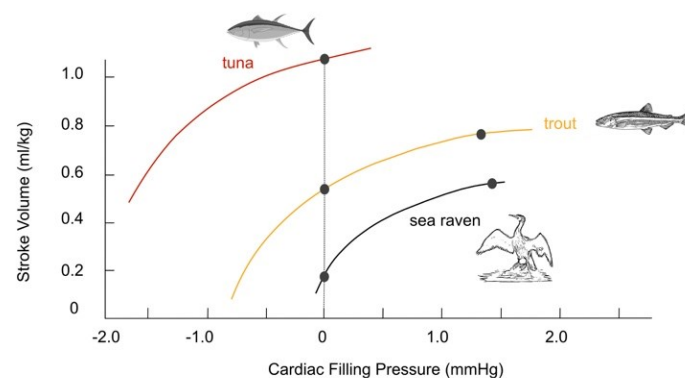

Figure 3. Importance of Frank-Starling's law in regulating stroke volume. An elevation in cardiac filling pressure leads to an augmented stroke volume through the Frank-Starling mechanism. Exercise is an extrinsic mechanism of cardiac stimulation that increase cardiac filling pressure and stroke volume. Tuna has less chance of improving ejection through the Frank-Starling mechanism since, at zero ventricular pressure, it reaches maximum stroke volume, unlike trout and sea raven, which maintain a lower stroke volume at higher cardiac pressures. *Abbreviations: ml-milliliter, kg-kilogram, mmHg-millimeters of mercury.* Data: from various authors [7,12,91,94,115,116].

The right ventricle of mammals is more sensitive to filling pressure than the left ventricle. It is not known if there are differences in the sensitivity of the right and left sides of the heart to filling pressure in amphibians and non-crocodilian reptiles, perhaps to help with intracardiac shunting [38,117].

Pulmonary arterial pressure in reptiles is several times higher than that in mammals when pulmonary blood flow increases, so there could be a different mechanism for adjusting SV during physical exercise [12].

Increases in SV of 10%-30% are observed in humans during exercise [116,118]. The relative increase in SV from rest to exercise for a racehorse and humans athletes has been measured and it can be doubled at high intensities [19,119]. Thoroughbred horses exhibit exceptional characteristics, doubling SV and tripling HR, resulting in an up to sixfold increase in Q. In these animals, it has been identified that there is an increase in SV from 1000 ml at rest up to 1700 ml at maximal exercise, consequent to an increase in blood volume, venous return, and filling pressures according to the Frank-Starling mechanism and it is highly enhanced by training [3,99,100,120]. The horse has evolved not only in accordance with the laws of nature like other vertebrates but also has been subjected to a thousand years of selective breeding based on athletic performance. This has created a disproportionate increase in the horse's heart size and, consequently, the SV, which increases sharply at the onset of the exercise from 2-2,5 ml/kg until around the 40% VO_{2max}. At maximal exercise, SV reaches 3-4 ml/kg and is determined principally by heart size [101]. This response is shown to a greater extent in the equine species than in humans, and it explains the enormous magnitude of the peak aerobic power in the horse compared to the elite human athlete [121,122]. Certainly, "athlete" horses are an exception among all vertebrates, so it is difficult to compare the results with other groups of vertebrates whose activity is limited to their ordinary lives.

In species where SV does not significantly rise during exercise, it is likely that the heart operates at the apex of the Frank-Starling curve under resting eupneic conditions. The Frank-Starling mechanism also maintains a long-term equilibrium between the Q of the right and left ventricles in mammalian hearts. Certain amphibians and reptiles exhibit slight reductions in SV during exercise, accompanied by increases in HR. The most notable alterations in SV in reptiles and amphibians occur as decreases associated with apnea. The greatest decrease in SV seen in these animals is associated with the apnea required during their physical effort in the water [7,17,53,66,69,86,123].

Unlike other vertebrates, certain fish species, including cyclostomata and teleosts, exhibit a twofold increase in SV during exercise [17,87,94]. The increase clearly underscores the functional importance of the Frank-Starling mechanism. In fact, fish appear to rely on HR modulation to achieve the augmented Q associated with aerobic exercise [65,67]. These differences in the SV response in fish may be a consequence of one of the following factors: greater sympathetic control of HR; the atria becoming less sensitive to filling pressure; a greater degree of sympathetic control of the tension in the vein walls; and a better shortening fraction [71,124].

Homeometric regulation is described as the capacity of the cardiac muscle to maintain blood flow independently of the development of pressure, in contrast to heterometric regulation (Starling's Law). This factor is thoroughly documented in the hearts of various fish classes and might explain why alterations in vascular resistance do not affect SV despite the changes associated with cardiac functioning [71,125,126].

Concerning the factors mentioned above, it is noteworthy that the sensitivity of fish hearts to filling pressure is nearly ten times higher than that of mammals (approximately 1-2 mmHg compared to 10-20 mmHg for a maximal response). This heightened sensitivity may be linked to the fact that the atrial chamber in fish has thinner walls and is more distensible [12]. Moreover, intracardiac shunting may require stricter regulation of the dimensions of the ventricle, thus limiting SV but not HR [38].

Contractility is an easily defined cardiac function that is difficult to assess. Contractility is defined as the change undergone by the ventricle or atria when the parameters that can affect myocardial performance (HR, filling volume and pressure and arterial diastolic pressure) are kept constant. The most accurate assessment is through the peak derivative of left ventricular pressure in relation to time (LV dp/dt), which seems to rise progressively with exercise intensity but remains unchanged with training [12,127,128].

Studies have demonstrated that the values for mammals and tuna are five times greater than those of teleosts (370-480 mmHg/s), whereas the values for cyclostomata (22 mmHg/s) and sharks (30 mmHg/s) are ten times lower. Intermediate values have been recorded for lizards (95-180 mmHg/s) and anura, including Rhinella marina (toad) (60 mmHg/s and 110 mmHg/s) [124].

These differences may be due to different factors such as HR (the phenomenon known as the "negative staircase" refers to the inverse relationship between contraction rate and maximum isometric tension (T_{max}); the increase in the frequency of electrical stimulation leads to a decrease in T_{max}), temperature (T_{max} decreases at high temperatures as a result of a shorter action potential duration), beta-adrenergic stimulation (in the cardiac strips of frogs and fish severely increases T_{max}), extracellular calcium (an increase in extracellular $[Ca^{2+}]$ within the range of 1-9 mM induces an elevation in the maximum isometric tension (T_{max}) of cardiac muscle), and inotropic agents (negative inotropic effects can be elicited by hypoxia, acidosis, and acetylcholine) [81,103,129–137].

Associated with contractile activity and the relationship between length and pressure, result of Starling's Law and ventricular performance, SV increases due to of the increase in EDV and decrease in ESV, as SV is the difference between them (EDV-ESV). The ventricular ejection fraction in the rainbow trout is usually around 100% [138,139], while that of the leopard shark is 80% [140]. Hence, the significant increases in SV observed in fish arise from the corresponding increases in EDV. In amphibians and reptiles, the duration of the systole is 50% of the cardiac cycle, which potentially leading to a small ESV, which can be fundamental for intracardiac shunting [38,141]. At elevated heart rates, there is a decrease in filling time, which may account for the observed reduction in perfusion in the rainbow trout heart [142]. Similarly, in dogs, an increase in HR from 120 bpm to 180 bpm has minimal impact on Q due to the decrease in SV [143].

Unexpectedly, the maximum SV in various fish and mammals shows little variation (approximately 0.5-1.5 ml/kg of body mass). This narrow range might signify an anatomical limitation, as hearts with a larger volume require a disproportionately thicker wall to uphold the same tension, as per Laplace's Law [71]. A thicker cardiac wall presents a challenge to O_2 diffusion. Therefore, the maximum SV is probably established as a compromise between the generation of wall tension and the adequate supply of myocardial O_2. The notion that animals with a substantial SV exhibit low arterial pressure aligns with this concept. For instance, amphibians and non-crocodilian reptiles have a greater SV (3-5 ml/kg of body mass) compared to fish and mammals [71]. Moreover, the hearts of Antarctic fish demonstrate an exceptionally high SV (2-10 ml/kg of body mass) and a notably limited homeometric capacity [144].

Figure 4 shows the differences between a rainbow trout's cardiac cycle and that of human. While the rainbow trout seems to depend only on the Frank-Starling mechanism, the human improves its ejective capacity by increasing the final diastolic volume (Frank-Starling's law) and decreasing the ESV (contractility increase).
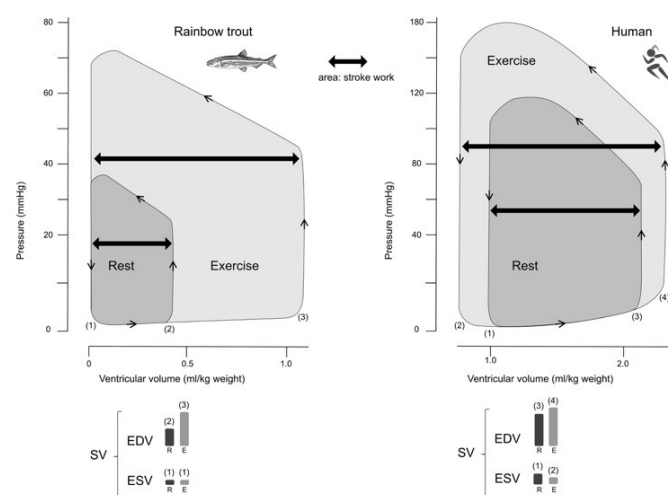

Figure 4. Comparative cardiac cycle between trout and human. The ventricular pressure-volume relationship can be described by a loop diagram with volume depicted on the x-axis and left ventricular pressure on the y-axis. Rainbow trout increase their stroke volume by increasing end diastolic volume, whereas human do so at the expense of both increasing end diastolic volume and reducing end systolic volume. *Abbreviations: SV-stroke volume, EDV-end diastolic volume, ESV-*

end systolic volume, ml-milliliter, kg- kilogram, mmHg-millimeters of mercury. Data: from various authors [6,7,12,71,91,94,116,124].

In most vertebrates, cardiac filling follows a vis-a-tergo (force from behind) pattern, where central venous blood pressure plays a crucial role in determining both cardiac filling and SV. In mammalian hearts, atria and ventricular filling occur simultaneously due to a favorable pressure gradient between the central veins and the heart chambers. As a result, filling pressure at the venous level serves as the primary determinant of both atrial and ventricular filling. Atria contraction alone contributes approximately 25% to ventricular filling, while a small portion results from the elastic recoil of the ventricle [17].

5. Adjustment of mean arterial pressure (MAP) to exercise in vertebrates

MAP is the product of Q and TPR. It is a parameter under the control of cardiovascular regulatory mechanisms, with the most important being pressure receptors (baroreceptors). In general, there is an evolutionary tendency towards an increase in pressure as progress is made from primitive circulatory systems to birds and endothermic mammals [12,145].

Species of fish adapted to fast swimming and high physiological performance have high levels of arterial pressure, exceeding 100 mm Hg in tuna and salmon [91]. The hearts of amphibians generally do not generate such high pressure. This could be linked to the single ventricle performing the function for both the pulmonary and systemic circuits [146].

Turtles have the lowest systemic arterial pressure, and terrestrial species have slightly higher pressure than the semi-aquatic species. Systemic arterial pressure at rest varies considerably among snakes, in part due to their diversified exposure to gravitational forces. There is an allometric relationship in snakes between arterial pressure and body mass (exponent = 0.15), probably because ventricular mass increases with the increase in body mass [147]. Resting systemic arterial pressure in crocodilians and lizards is similar to that of mammals, and is almost double in iguanas (finding mean blood pressure values in the iguana of 43.5 mmHg, in the varanus of 70 mmHg and in humans of 100 mmHg) [12,83].

The development of high arterial pressures is a feature of birds and mammals. The MAP is approximately 97 mmHg in the "average" mammal, whereas the "average" bird has a MAP of about 133 mmHg [148,149]. These variances appear to be associated with a higher Q (related to mass or metabolic rate) in birds rather than differences in peripheral resistance [150]. The literature describes a correlation between MAP and the vertical distance between the heart and brain in mammals; for example, giraffes would present a higher MAP to perfuse the brain [149]. However, compared to mammals, birds have larger hearts, a greater SV, and a lower HR. During exercise, MAP increases more than 50% above resting levels in these groups. As an example, MAP rises from 110 mmHg to 138 mmHg at rest to as high as 200 mmHg during maximal exercise [151].

Traditionally, books on physiology deal with mechanisms for regulating arterial pressure in the short, medium, and long term. In short-term regulation, the innervation of the heart is very varied [152]. In teleosts vagal innervation shows a higher tone at rest. The heart of amphibians has sympathetic and parasympathetic innervation, both in the caudata and anura. The activity of anura leads to an increase in both HR and arterial pressure. Initially, this rise is due to adrenergic effluents and is sustained by circulating catecholamines. In reptiles, there is considerable variation in blood pressure levels, influenced by differences among species, environmental conditions, and non-steady states resulting from various causes. In spite of the high HR in relation to many other vertebrates, the heart of birds is subject to an important cholinergic (vagal) and adrenergic tone. Walking increases blood pressure in several types of birds, particularly at high intensities, due to the increase in sympathetic tone and, to a lesser extent, to vagal inhibition [153].

All the mentioned data suggest that the baroreflex function in the immediate control of arterial pressure is very important in amphibians (anura), reptiles, birds, and mammals, with the latter being the group that has provided the most evidence about this issue. Moreover, the central nervous system (CNS) plays a role in mediating diverse cardiovascular responses across all vertebrates, including

those associated with excitement, emotions, and cognitive functions. Several of these responses are immediate, such as the defense reactions involving tachycardia and elevated blood pressure. Mammalian central nervous mechanisms can inhibit the baroreceptor reflex responses during exercise, and there is evidence suggesting that the brain can modify the reference point around which arterial pressure is controlled or stabilized over the long term. The CNS is crucial in integrating both the heart and circulation and controlling sustained sympathetic activity, which is essential for maintaining peripheral vascular tone and Q. Without sympathetic vascular tone, the reflex controls cannot effectively stabilize pressure at any moment. Skeletal muscle arterial and arteriolar vasodilation allow a fall in TPR in exercising mammals, facilitating an increase in Q related to a modest rise in MAP. The control of these events involves a complex array of mechanical, humoral, and neural mechanisms [154].

Blood volume in vertebrates hardly exceeds 10% of body mass. It is supposed that all mechanisms controlling blood volume reflect steady-state conditions, depending on factors such as hydration, activity, hibernation, and other factors. The regulatory mechanisms of vertebrates are summarized below:

The elevation in efferent nervous activity can induce renal vasoconstriction, significantly decreasing renal blood flow in turn. Renal regulation may be particularly important in amphibians, some fish, and reptiles [155].

Endocrine factors, such as arginine vasopressin, the renin-angiotensin system, and atrial natriuretic peptide, play a role in fluid balance. The retention of fluid at the kidney level is promoted by arginine vasopressin (AVP), and its primary physiological significance lies in its indirect effects on blood pressure. AVP is found in the neurohypophysis of all mammalian vertebrates. The neurohypophyseal peptides in reptiles and birds closely resemble those found in mammals [156]. Except in cyclostomata and elasmobranchii, the renin-angiotensin-aldosterone system (RAAS) is present in all vertebrates. It stands out as one of the most crucial hormonal systems for the long-term modulation of renal function and hemodynamics in mammals [157,158]. The involvement of angiotensin II in regulating blood pressure in fish becomes evident when pressure declines following the administration of angiotensin-converting enzyme inhibitors. Finally, the atrial natriuretic factor comprises a family of peptides synthesized in the atrial myocytes in response to the tension in the local wall (increase in intra auricular volume), and it is present in all vertebrates [159].

Factors derived from the endothelium. Numerous peptides produce vasoactive effects and are present in all classes of vertebrates [160].

Other factors. Various molecules with autocrine or paracrine effects (such us histamine, bradykinin, adenosine, or nitric oxide) are present in the cells and affect the cardiovascular system of vertebrates [161].

As observed, an integrated response to changes in blood volume is controlled by all the afore-mentioned factors. The most prevalent natural disturbance in terrestrial environments, involving dehydration through evaporation, convection, and irradiation, as well as in marine environments marked by dehydration through osmotic imbalances, is the reduction in volumes of blood and body fluids in most vertebrates. Generally, mammals are less tolerant to loss of blood than other vertebrates such as fish [162], amphibians [163], reptiles [164,165] and birds [166,167], which can tolerate a greater degree of loss of plasma volume and mobilize compensatory fluid more quickly than mammals.

6. Integrated response to exercise in vertebrates

Metabolic demand in all vertebrates during exercise requires some cardiovascular system adjustments that are not quantitatively proportional. While VO_2 can increase from ten to twentyfold, the changes in Q are smaller. The increased needs from muscle metabolism during exercise impose control by matching the delivery of VO_2 and VO_{2max}. This is due to two factors. First, the increase in oxygen extraction allows a greater supply of O_2 to musculoskeletal muscles without a necessary increase in blood flow. Secondly, the supply of VO_2 to tissues depends not only on the cardiovascular system but also on the respiratory apparatus [19,20].

Di Prampero [168] calculated the contribution of each element that contributes to an increase in VO_2 to its maximum value. In humans, the central component (respiratory apparatus and cardiovascular system) is responsible for 75%, minimizing the participation of the peripheral route (mitochondrial oxidation and use of energetic stores). Ventricular size is a limiting factor for the central contribution as it determines SV, Q, and hence aerobic capacity and exercise performance. In mammals, the heart constitutes the same fraction of body mass according to the size of the mammals, from mice to cows [81]. In horses, the heart size ranges between 0.9 and 2% of the body mass in elite individuals, which is greater than in other species [3].

Thus, the cardiovascular system of vertebrates during exercise requires an increase in Q and a variation in TPR. In general, the adjustment of these variables differs among the five major groups of vertebrates. The way in which Q is augmented during exercise varies across vertebrates, with the majority increasing Q to a level between 1.3 and 3.3 times higher than resting values [169,170]. Exceptions to this pattern include trained human athletes and Thoroughbred horses. The contribution of each parameter that determines Q depends on the class of vertebrate [69].

While maximum HR is crucial in the increase of Q during exercise as an allometric function of body mass, SV may be an extremely important determinant in vertebrates with a certain body weight. Flying pigeons can increase HR sixfold without changing SV [169]. The majority of amphibians, reptiles, birds, and mammals depend to a large extent on tachycardia, although the range varies considerably [91] (see Table 1) as SV changes relatively little [171]. For example, in the rainbow trout, the considerable increase in EDV during exercise rises from about 0.4 ml/kg to 1.1 ml/kg, that is, almost threefold. In the leopard shark, the rise of the EDV during exercise is only 1.5 times, bearing in mind that it weighs 50 times more than the rainbow trout. In contrast to fish, humans increase EDV to a lesser degree, but ESV decreases [12]. However, training in mammals increases the role of SV. In mammals, the maximum HR in goats and dogs, ponies, calves, and horses is almost identical for animals of the same size, despite a difference of 1.4 to 2.5 times in their VO_{2max} [172]. Tachycardia typically involves the withdrawal of vagal influence and, whenever feasible, adrenergic stimulation.

Central arterial pressure rises during exercise. Nevertheless, species with respiratory and systemic circulations in series, such as fish and mammals, generally exhibit slightly greater increases in systemic arterial pressure compared to species with two parallel circulations, such as amphibians and non-crocodilian reptiles [173]. The amplitude of the increase in arterial pressure is reduced because of the decrease in total vascular resistance. The most active mammals appear to have the ability to achieve a more significant reduction in vascular resistance. The overall outcome of the rise in Q and arterial pressure is an elevation in myocardial energy expenditure, which naturally necessitates a simultaneous increase in myocardial oxygen consumption. Another response involves directing blood flow preferentially to the actively engaged skeletal muscles. The regulation of these varied responses is not fully comprehended, particularly in the case of lower vertebrates. In mammals during exercise, the vasomotor center coordinates afferent information from active muscles (proprioceptors), arterial and cardiac mechanoreceptors, chemoreceptors, the cortex, and the hypothalamus to ensure appropriate autonomic output [12].

The change in the regional distribution of blood flow with exercise has been measured in several types of fish. In the rainbow trout and the big-mouthed trout, blood flow in red muscle constitutes 9% and 0.57% of cardiac output (Q) at rest, respectively. During exercise, these values increase to 42% and 13.2%, respectively [174,175]. Simultaneously, while blood flow to the skeletal muscles increases, it diminishes in the abdominal viscera [176]. The reduction in blood flow in the celiac, mesenteric, and intestinal arteries can be particularly significant, reaching approximately 30% in Atlantic cod [144] and 70% in Chinook salmon [177]. As systemic resistance diminishes, the impact of vasodilation in the skeletal muscles must surpass that of vasoconstriction in the visceral region. The regulation of these vascular responses remains poorly understood. The potential modulation of systemic alpha-adrenergic tone is considered, and the roles of locally produced metabolites [178], adrenergic and non-cholinergic fibers, particularly in the intestinal circulation, have yet to be thoroughly investigated [179].

Nevertheless, our knowledge regarding the regional distribution of Q during activity in amphibians and reptiles is extremely limited [180–182]. One of the scarce studies of this kind assessed the blood flows in the left pulmonary and aortic regions during both rest and swimming in the green sea turtle Chelonia mydas [183]. During exercise, it was hypothesized that Q would rise, primarily attributed to an increase in HR from 24 bpm to 40 bpm (at 28ºC). Both pulmonary and aortic blood flows showed significant increases during exercise, but there was limited evidence of a redistribution of Q, except for what is typically associated with intermittent pulmonary ventilation and breath-holding periods. Another more recent study shows that alligators, which during development have lower oxygen levels, also show long-term changes in cardiovascular response due to hypoxia during the embryonic period. Many of the changes were masked during exercise, probably due to differences in adrenergic activity. The authors conclude that it seems likely that changes in cardiovascular response have an evolutionary origin in vertebrates [86].

7. Limitations

One of the main methodological limitations in comparative studies of the cardiovascular response to physical exercise in vertebrates is the use of different models of locomotion. This leads to varying approaches for assessing the response to physical exercise. Whereas, treadmills have been used in mammals and reptiles, more sophisticated ergometers such as aerodynamic tunnels have been used in birds and aquatic tunnels in fish. It is important to note that this type of evaluation may not be applicable to all vertebrates [6,7]. For instance, in reptiles, the cardiovascular response to posture changes, made manually or by mechanical devices, has been studied. These posture changes that are achieved through the development of 'straightening reflexes' [38,42]. Additionally, evaluations of ectothermic animals include adjustments in their cardiovascular system in response to heat stress [184].

Other limitations include the study of vertebrates in their natural habitat, which poses methodological challenges, including the inability to control the timing of the highest demands on the cardiovascular system [6,7,19,20,69].

Therefore, it is evident that the limitations described pose significant obstacles to fully comprehending the cardiovascular response to exercise, which involves the threshold of demand among varying vertebrate groups.

8. Conclusions and Future Directions

In conclusion, the cardiovascular adjustments needed during exercise in all vertebrates, including changes in Q, TPR, and pressure gradient, are quantitatively smaller than the increase in oxygen consumption. Different types of circulation in vertebrates determine differences in cardiovascular response and regulation. The mechanism by which Q (either the SV or the HR) is enhanced during exertion varies significantly among vertebrates. The diverse physical exercise responses observed in arterial pressure and TPR can be attributed to the existing differences in the pulmonary and systemic circulation systems between vertebrates. "Athlete" vertebrates (e.g. horses) or those that have been genetically manipulated (e.g. rats with high exercise capacity) may represent models of maximum adaptation of the cardiovascular system. However, they do not reflect the typical response in vertebrates.

Exploring the examination of an integrated cardiovascular response and the elements that influence the diverse cardiovascular adaptations to physical exercise in varied vertebrate groups may be of significance for understanding the cardiovascular response of athletes in different conditions, including extreme temperatures, immersions, or high altitudes, as well as in individuals participating in physical exercise with different physical and functional disabilities. It is recommended to further research comparative cardiovascular physiology across vertebrate groups to comprehend previously described situations and develop mechanisms to support or improve the athletic population.

Supplementary Materials: Table S1. Example of resting and exercise heart rate in different classes of vertebrates. Figure S1. Right-left shunt and functionality in adult non-crocodilian reptiles. Figure S2. Left-right shunt and

functionality in adult non-crocodilian reptiles. Figure S3. Importance of Frank-Starling's law in regulating stroke volume. Figure S4. Comparative cardiac cycle between trout and human.

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