

EVOLUTION OF THE VERTEBRATE CARDIO-PULMONARY SYSTEM

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ABSTRACT

Vertebrate lungs have long been thought to have evolved in fishes largely as an adaptation for life in hypoxic water. This view overlooks the possibility that lungs may have functioned to supply the heart with oxygen and may continue to serve this function in extant fishes. The myocardium of most vertebrates is avascular and obtains oxygen from luminal blood. Because oxygen-rich pulmonary blood mixes with oxygen-poor systemic blood before entering the heart of air-breathing fishes, lung ventilation may supply the myocardium with oxygen and expand aerobic exercise capabilities. Although sustained exercise in tetrapods is facilitated by septation of the heart and the formation of a dual pressure system, a divided cardio-pulmonary system may conflict with myocardial oxygenation because the right side of the heart is isolated from pulmonary oxygen. This may have contributed to the evolution of the coronary circulation.

INTRODUCTION

Early in the 19th century, biologists used the presence of a lung to distinguish amphibians and reptiles from fish; fish used gills for respiration, whereas terrestrial vertebrates used a membranous internal sac, a lung. Hence, when lungfish were discovered, they were considered to be gigantic amphibians. Yet so many other traits placed them firmly among fish that they were eventually assigned to a new and distinct subclass of fish called the Dipnoi. This mosaic of features is reflected in the name of the South American lungfish, *Lepidosiren paradoxa*. Species from two other genera are known from Africa (*Protopterus*) and

Australia (*Neoceratodus*). Initially, lungs were considered an adaptation that enabled these “amphibious” animals to breathe when venturing onto land, but because lungfish kept in captivity never left the water, it soon became evident that terrestrial journeys were more myth than reality. The selection pressure for the evolution of lungs was then deemed to be aquatic hypoxia (38). Lungs were thought to be an adaptation that enabled fish to obtain oxygen from air when it was scarce in water.

Over the next century, support for this idea grew. Numerous fossils of lungfish were unearthed in a red layer of sediment, known as the Old Red Sandstone, that was laid down during the Devonian, some 350–400 million years ago. Along with these fossils, remains of early amphibians and numerous traces of amphibian footprints were found, which revived the idea that lungs were important for terrestrial forays. In 1916, Barrell (1) proposed that the depositional environments of these fossils indicated a semi-arid flood plain subject to alternation of wet and dry seasons. As drought reduced the river systems to hypoxic pools, natural selection favored animals that could breathe air as well as migrate from smaller to larger water sources (1). The distribution of extant air-breathing fishes, which are generally said to live in hypoxic fresh water, further buttressed these ideas (16). Because warm water contains less oxygen than cold water, and because stagnant or poorly stirred environments (e.g. swamps, ponds) tend to be poorly oxygenated, tropical freshwater ecosystems were considered more probable settings for the origin of lungs than marine environments, which are stirred by tides and currents (for an alternate view, see 68).

In the past 50 years the fossil record of early fishes has become much better known, improving our understanding of their phylogeny, or genealogy. During the early evolution of bony fishes (Osteichthyes), two groups emerged—the ray-finned fishes (Actinopterygii) and the lobe-finned fishes (Sarcopterygii). Because extant members of both major radiations have lungs, it is probable that they were inherited from a common ancestor, thus dating the origin of lungs to at least as early as the Late Silurian, over 400 million years ago (Figure 1) (20). This poses a significant problem for the idea that lungs are an adaptation to aquatic hypoxia because the depositional environments of these early bony fishes are marine, yet marine environments are not widely hypoxic (9, 12, 18, 19, 83–85, 90). Another problem with the idea that lungs are an adaptation to hypoxic water is that the putative correlation between hypoxic freshwater habitats and the character of air-breathing has been based in part on speculation. Field data of aquatic oxygen content and the distribution of air-breathers are sometimes at odds with this speculation (54). For example, although early authors believed that the Australian lungfish inhabited hypoxic water (38), a study of the oxygen content throughout their habitat revealed that it is not hypoxic, even during periods of drought (37). The discovery of many marine air-breathing species

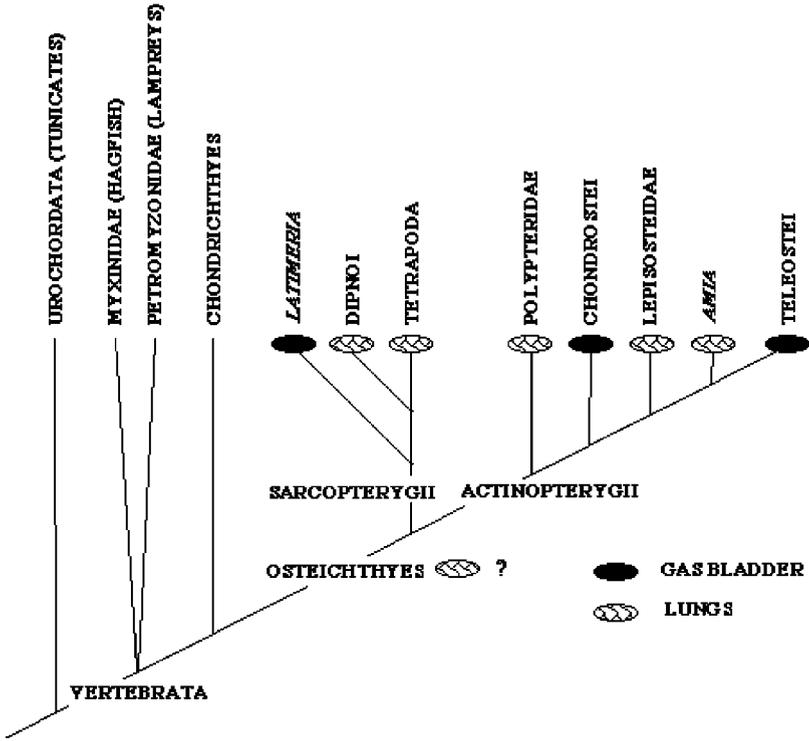


Figure 1 Hypothesis of the relationship of fishes showing the presence of lungs or a swim bladder (based in part on Lauder & Liem 1983) (57).

further erodes a correlation between warm, hypoxic freshwater habitats and the air-breathing habitus (35). Hence, in recent years it has become increasingly evident that numerous factors (e.g. buoyancy, hearing, etc) could have intertwined such that natural selection favored the evolution of air-breathing (34, 58).

One of these factors may have been the ability of lungs to supply the heart with oxygen. As vertebrates evolved from their protovertebrate ancestors, there was a shift in the primary site of gas exchange from the skin to the gills (30). Over the course of vertebrate evolution, this change, coupled with increases in body size and levels of activity, may have resulted in myocardial hypoxia.

LUNGS AS A SOURCE OF OXYGEN FOR THE HEART

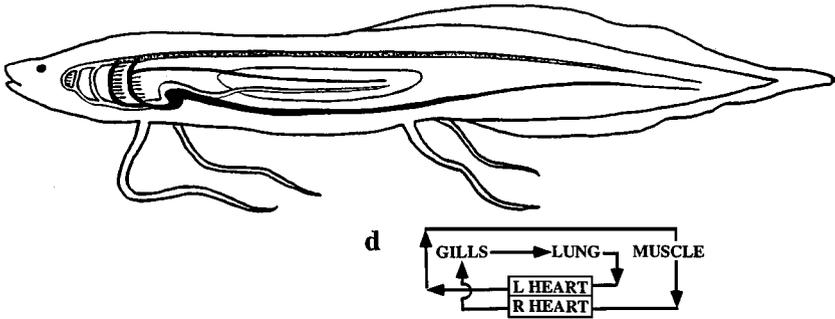
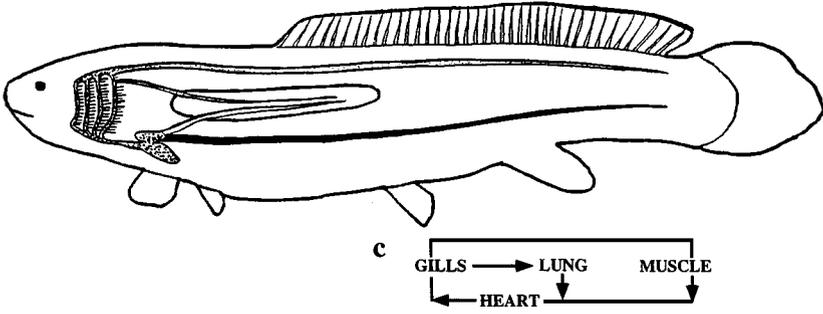
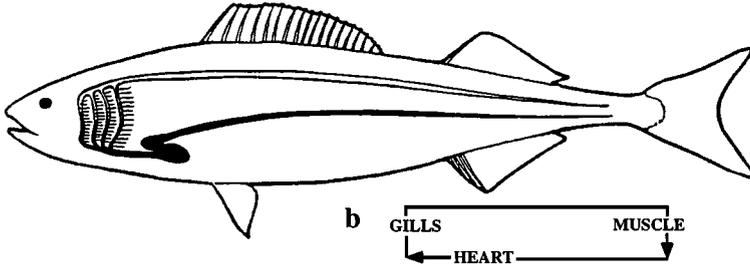
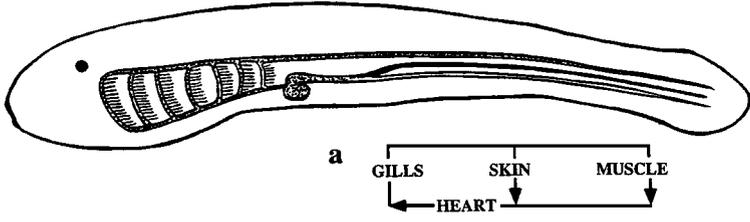
Soft tissues do not fossilize readily. Consequently, our knowledge of the cardiorespiratory system of protovertebrates and early vertebrates comes

primarily from comparing features found in extant cephalochordates with those of primitive vertebrates such as lampreys. The ancestors of vertebrates lived in the Cambrian, more than 500 million years ago. These animals were probably small, marine suspension feeders that relied upon the skin, rather than the gills, for gas exchange (30, 62). Ciliary tracts are used to obtain food in several chordate groups (ascidian tunicates, Amphioxus, and larval lampreys), suggesting that this feeding mode is representative of the protovertebrate pattern (Figure 1) (30, 62). In larval lampreys, the heart pumps blood through ciliated tracts in the pharynx, where thick strands of mucus trap food. This nutrient-rich blood flows to the tissues, including the skin, where carbon dioxide is unloaded and oxygen absorbed, and then returns to the heart (Figure 2a). The hearts of lampreys are distinct from mammalian hearts in that they do not contain a large lumen surrounded by a thick muscular wall. Instead, the heart is composed of an avascular, trabecular mesh of muscle cells (with a spongy appearance) that is encased by connective tissue, the epicardium. As the heart beats, blood flows to and fro through the spaces between the myocytes (referred to as sinusoidal channels or lacunae), and this blood supplies the muscle with oxygen. Ontogenetic studies and the phylogenetic distribution of avascular spongy myocardium indicate that it is the primitive condition for vertebrates (59). In larval lampreys, the heart is efferent to the gas exchanger, so this spongy myocardium is bathed in oxygen-rich blood.

As vertebrates evolved, gills lost their function as filter-feeding mechanisms and became the major site for gas exchange. When this happened, the spongy myocardium of the heart would have been bathed in oxygen-poor blood, as it is in extant gill-breathing fishes, because oxygen would have been unloaded to the other tissues of the body before entering the heart (Figure 2b). During the Ordovician and Silurian radiation, there arose both inactive (e.g. osteostracans and heterostracans) and highly active vertebrates (e.g. the bony fishes) (19, 62). In active animals, this circulatory design may have resulted in myocardial hypoxia and therefore may have been a selection pressure for the evolution of lungs and coronary circulation. Oxygen-rich blood from pulmonary respiration mixes with the oxygen-poor blood in the systemic venous return before entering the heart (Figure 2c). Therefore, pulmonary respiration could have functioned



Figure 2 Schematic of the cardiorespiratory design of (a) larval lamprey in which the heart contains an admixture of oxygen-rich and -poor blood; (b) gill-breathing fish in which the heart contains only oxygen-poor blood; (c) primitive air-breathing fish in which the heart contains an admixture of oxygen-rich and -poor blood; (d) *Protopterus*, the African lungfish that has nearly complete separation of oxygen-rich and -poor blood within the heart. Oxygen-poor blood, ■; admixture of oxygen-rich and -poor blood, ■; oxygen-rich blood, □.



ancestrally for myocardial oxygenation. This scenario for the evolution of lungs predicts that pulmonary respiration in extant fishes will continue to serve as a source of myocardial oxygen (24).

If pulmonary respiration is important for cardiac function, then it should be most useful during periods of activity. During exercise in fishes, when the work of the heart increases, the oxygen needs of the heart are elevated. But because working skeletal muscle extracts more oxygen from the blood than does resting muscle, the amount of oxygen in the blood entering the heart of gill-breathing fishes decreases (36, 50, 52). If the partial pressure of oxygen drops to a critical threshold, there will not be an adequate gradient to drive diffusion of oxygen throughout the ventricle (17). Hence, during exercise the supply of oxygen to the heart drops at the very time it is needed most. Although the myocardium of some vertebrates (e.g. turtles) is tolerant of hypoxia, this appears to be true at low work loads. At high work loads, myocardium has a primarily aerobic metabolism (13, 23, 27, 63, 76, 78). Because hypoxia directly inhibits myocardial function, an adequate supply of oxygen is essential for proper cardiac function during exercise (22, 32, 88).

Potentially exacerbating this decline in oxygen in the blood entering the heart is the acidosis that is routinely experienced by ectothermic animals during activity (5, 6). Acidosis inhibits myocardial power output, especially when combined with hypoxia (31, 33, 69). In addition, because acidosis decreases the affinity of hemoglobin for oxygen (the Bohr and Root effects), loading of oxygen in the gills becomes more difficult (6, 7). These factors may contribute to the lethal effects of intense exercise commonly observed in gill-breathing fishes, e.g. cod, dab, tench, salmon, bass, shad, haddock, and trout (6).

Although many gill-breathing fishes die from exhaustive exercise, the underlying cause of this mortality is unknown. A few electrocardiograms recorded from trout during periods of intense activity indicate that the heart stopped, leading Black (6) to suggest that the cause of death is circulatory failure, but Wood and colleagues disagree with this conclusion, asserting that trout die from a severe intracellular acidosis (95). However, exhaustive exercise in the bimodally breathing gar (*Lepisosteus*) produces a magnitude and pattern of blood acidosis similar to that observed in trout, but these fish survive as long as they have access to air (13a, 77). Furthermore, Black's data and hypothesis are consistent with electrocardiograms of resting fish subjected to severe environmental hypoxia, which indicate cardiac malfunction (e.g. increases in the p-r interval, inversion of the t wave) (70). Signs of cardiac malfunction (e.g. arrhythmia and decreases in pulse pressure concomitant with a reduced afterload) were observed when bowfin (*Amia*) swam in oxygen-rich water without access to air, but were not noted during exercise with access to aerial respiration (25). It is unresolved whether there is sufficient oxygen in the venous blood

of active gill-breathing fishes to maintain maximum cardiac performance or if there is circulatory failure from intense activity. Air-breathing may circumvent osmoregulatory or other unknown problems faced by gill-breathing fishes. However, the well-established sensitivity of myocardium to hypoxia and acidosis at high workloads increases the probability that the spongy myocardium of gill-breathing fishes can be oxygen limited during exercise. Because pulmonary respiration can circumvent these problems, air-breathing ought to be induced by activity.

Indeed, breathing air when active is important for many fishes and, in some circumstances, activity is a stronger stimulus for air-breathing than is aquatic hypoxia. For example, when subjected to aquatic hypoxia, rates of air-breathing decrease in *Polypterus*, but activity strongly induces air-breathing (60). Activity induces air-breathing in other fishes as well, e.g. *Amia*, *Lepisosteus*, and *Neoceratodus*, in spite of ample oxygen in the water (26, 37, 48, 77). If lungs are functioning to supply the heart with oxygen, then air-breathing should be stimulated by chemoreceptors that sense the oxygen in the blood before it has passed through the gills, since this is the blood bathing the heart. On the other hand, if air-breathing is important solely to provide oxygen to the systemic system, then the drive to breathe ought to arise from chemoreceptors that sense the oxygen in the blood that has passed through the capillaries of the gills, since this is what flows to the systemic vasculature. In both *Lepisosteus* and *Amia*, chemoreceptors have been found that sense the oxygen in the blood afferent to the gills (64, 79). Hypoxia at this site triggers air-breathing and, in *Lepisosteus*, a bradycardia (64, 79). *Lepisosteus* also have external chemoreceptors that sense the oxygen in the water and cause a reduction in gill ventilation and an increase in air-breathing when in hypoxic water.

These observations on the use of pulmonary respiration in extant fishes are consistent with fossil evidence indicating that early bony fishes were active animals that may have inhabited oxygen-rich water.

The fossil remains of early fishes show locomotor and feeding features indicative of an active lifestyle. Furthermore, as previously mentioned, the depositional environments are largely, and many times wholly, marine. Denison states that "they (early Osteichthyes) must be reckoned among the best swimmers of their time. The crossopterygians had powerful jaws and well-developed, pointed marginal teeth, indicating that they were predacious." He also points out that, as far as the geologic evidence is concerned, all early fishes could have been marine (19). Thompson's studies of the ecology and morphology of the lobe-finned fishes indicate that many of the earliest bony fishes were the dominant predators of their time (84). Furthermore, many of the fossil lungfishes, the majority of the fossil coelacanths, many of the Rhipidistia, and even some of the early amphibians were completely marine (84). It appears that only

a few genera, particularly in the late Devonian, were confined to freshwater habitats. Locomotor and feeding characters suggest that the lungfishes became specialized for a diet of plants and invertebrates, and the coelacanth became specialized for a more sedentary, stealthy approach to food, while the Rhipidistia (which contain the ancestors of tetrapods) remained active, cruising predators (84).

Why Don't All Fish Have Lungs?

If lungs are primitive and important in supplying oxygen to the heart, then why did the coelacanth, the Chondrostei, and the Teleostei convert the lung to a buoyancy device (Figure 1)? There are at least two circumstances that hinder aerial respiration in fishes, deep water habitats and aerial predation. Placement of food at progressively lower depths decreases air-breathing frequency (4, 55); trips to the surface for breaths of air may be too expensive for fishes occupying deep-water habitats. This may have contributed to the loss of lungs for gas exchange in the Chondrostei and the coelacanth, which occupy benthic and deep-water habitats (2, 29, 66).

A second factor that hinders breathing and that may bear on the loss of lungs in teleostean fishes is aerial predation. The fossil record indicates that the rise of teleosts is geologically contemporaneous with the origin of aerial vertebrate predators (pterosaurs and birds), many of whom ate fish (3). Some insight into the prehistoric impact predators may have had on their ecosystem is possible by the study of the historic impact of predators on extant ecosystems (21). Introduction of a new type of predator into an ecosystem can be devastating. For example, introduction of the brown tree snake (*Boiga irregularis*), which is native to Australia, to various Pacific islands has decimated or driven to extinction numerous species of birds and small mammals (73). Being totally naive to snakes, many of these birds seem to watch blithely as a snake approaches to eat them because they do not recognize the snake as a predator. For many millions of years, the predators of fish were other aquatic animals. Hence, fish were probably initially very naive to flying vertebrates, and it is possible that the evolution of flight had a significant impact on the aquatic ecosystem.

There are three lines of evidence from extant air-breathing fishes that indicate aerial predation is, and has been, a significant selection pressure. First, air-breathers show a strong diving reflex when they perceive a threat from the air. For example, placement of a stuffed heron over a tank of *Lepisosteus* caused the air-breathing interval to increase by 118% (80). Second, a large number of air-breathing fishes are nocturnal or crepuscular, a period when they are at less risk of aerial predation (e.g. *Neoceratodus forsteri*, *Lepidosiren* sp., *Lepisosteus* sp., *Amia calva*, *N. Notopterus*, *N. chitala*, *N. boreensis*, *Gymnarchus niloticus*, *Aspredinidae*, *Clarias lazera*, *Clarias batrachus*, *Callichthys*, *Hoplosternum*, *Brochis*, *Hypostomus*, *Ancistrus*, *Gymnotus*, *Electrophorus electricus*,

Loricaria) (34 and references therein; 84). Third, air-breathers tend to exhibit synchronous air-breathing behavior. In other words, they school, and when one fish surfaces to breathe they all do, reducing their risk of aerial predation (e.g. *Polypterus* sp., *Lepisosteus* sp., *Arapaima gigas*, *Heterotis niloticus*, *Megalops atlanticus*, *N. notopterus*, *N. chitala*, *Piabucina*, *Clarias batrachus*, *Hoplosternum thoracatum*, *Corydoras aeneus*, *Heteropneustes fossilis*, *Anicistrus spinosus*, *Hypostomus plecostomus*, *Colisa*, *Hoplerythrinus*) (34).

Specialists for Aquatic Hypoxia

Although the cardio-pulmonary system of the lungfish (Dipnoi) has received a great deal of attention from physiologists, this system is unusual and contrasts with the cardiopulmonary system of other lung-breathing fishes. Typically, fish hearts are composed of a series of four chambers that are curled into an S shape: the sinus venosus, the atrium, the ventricle, and a fourth chamber that is muscular and contractile in non-teleost fishes (the conus arteriosus) but is elastic in teleosts (the bulbus). In groups that use lungs for respiration (e.g. *Polypterus*, *Lepisosteus*, *Amia*), and in most groups that use a lung-like gas bladder, these chambers are not septated and contain largely or totally an admixture of oxygen-rich pulmonary and oxygen-poor systemic blood (11, 34). Because the pulmonary and systemic admixture is pumped by the heart to the gills, fish with this circulatory design can lose oxygen from the blood to the environment when in hypoxic water. In contrast, the circulatory system of the lungfish (*Lepidosiren*, *Protopterus*) circumvents this problem.

The three genera of lungfish show progressive cardiovascular specialization correlating with their dependence on aerial oxygen, and therefore they have been depicted as a sequence of transitional grades from water- to air-breathers (49). However, these features may not be adaptations to air-breathing per se but rather may be specializations for life in hypoxic water. The lungfish are aquatic animals; the African and South American genera can survive without water only by metabolic depression and aestivation. Although they do not use gills to acquire oxygen, they use gills for the elimination of carbon dioxide, pH regulation, and the excretion of nitrogenous wastes (reviewed in 34). Consequently, they retain gill filaments for these purposes yet live in habitats that are often hypoxic. To prevent loss of oxygen to the water, their gills have atrophied, and their cardio-pulmonary systems contain partial septa in the atrium and ventricle and a spiral valve in the conus. Oxygen-rich blood from the lung enters the left atrium, remains on the left side of the heart, and is sent through the gill arches that have lost their capillary bed so that oxygen from the blood is not lost to the water (Figure 2d). Oxygen-poor blood enters the right atrium, remains in the right side of the ventricle, and is ejected into gill arches that have a capillary bed so that carbon dioxide, nitrogenous wastes, and hydrogen ions can be unloaded to the environment (45, 74). In contrast, the Australian lungfish, *Neoceratodus*,

does not show the same degree of specialization. It does not aestivate, nor does it live in oxygen-poor environments. It has considerable mixing of oxygen-rich and -poor blood within the heart, a poorly divided conus that retains pocket valves, well-developed gills with all the branchial arteries subdivided into capillaries, and numerous other primitive features (e.g. large scales and dermal bones; big, fleshy, lobed fins; large opercular bone) (28, 37, 46, 61, 83). Hence, differences in these lungfish genera may not represent transitional grades from water- to air-breathers as much as transitional grades for progressively hypoxic aquatic environments. Identifying the factors that influenced the specialization of the lungfish cardiorespiratory system is useful when trying to sort out whether similar cardiovascular features found in tetrapods have resulted from convergent evolution or inheritance from a common ancestor.

THE TRANSITION TO LAND

Tetrapods probably descended from Rhipidistian fishes and inherited a spongy ventricle from these ancestors (59). With the transition to land came numerous changes in the cardio-respiratory system. In general, gills were lost, the lungs became the primary or only site of gas exchange, and separation of pulmonary and systemic blood was accomplished to varying degrees by subdivision of the ventral aorta into a pulmonary artery and systemic aortas and by subdivision of the heart into right and left sides [anatomically, the lumen of the ventricle was more nearly subdivided into dorsal and ventral than right and left chambers (42), but the description of right and left is used here for simplicity]. Although separation of oxygen-rich and oxygen-poor blood is advantageous in terms of the efficiency of gas exchange, it also results in very little oxygen in the right side of the heart. This may have posed a problem that was solved in various ways. In amphibians, oxygen-rich blood from cutaneous respiration enters the right side of the heart; in chelonians and lepidosaurs, the intracardiac shunt can carry oxygen into the right side of the heart; and in birds and mammals, the function of oxygenating the myocardium is carried out by a coronary circulation (this may also be true of crocodilians).

Amphibians have a full septum in the atrium; the left atrium receives oxygen-rich pulmonary blood while the right atrium receives systemic blood. Although amphibians lack a septum in the ventricle, the alignment of myocytes provides fairly good functional separation of pulmonary and systemic blood (47). Consequently, the right atrium and the right side of the ventricle, which are composed entirely of spongy myocardium, are isolated from pulmonary oxygen. However, the right side of the heart may receive oxygen from blood returning to the heart from the cutaneous and buccal circulation, which are oxygen-rich. Whether or not this occurs has not been investigated.

The heart of early amniotes also probably had a ventricle composed primarily of spongy myocardium, which has been retained in chelonians (turtles) and lepidosaurs (*Sphenodon*, amphisbaenids, snakes, lizards) (59). In turtles and lepidosaurs, the atrium is completely subdivided into two chambers, but the ventricle is generally subdivided into three chambers by two incomplete septa—the vertical and horizontal septa (42). Because the septa are incomplete, there can be mixing of blood between the chambers. When blood entering the ventricle from the right atrium is shunted from the right to the left side of the ventricle (the right-to-left shunt), oxygen-poor blood is ejected into the systemic aortas rather than into the pulmonary artery. When oxygen-rich blood entering the ventricle from the left atrium is shunted from the left to the right side of the ventricle (the left-to-right shunt), oxygen-rich blood is ejected into the pulmonary artery rather than into the systemic aortas. These shunts can constitute most of the cardiac output. Numerous studies have examined the function and mechanisms of shunts, and many have focused on the importance of the right-to-left shunt during diving (reviewed in 40). However, much cardiac morphology associated with shunts probably evolved in amniotes (42) along with features indicative of a terrestrial lifestyle (e.g. the amniotic egg, terrestrial locomotor features), suggesting an origin for this morphology unrelated to diving. Because the left-to-right shunt washes oxygen-rich blood into a region of the heart that would otherwise be oxygen-poor (41), it could function to supply oxygen to spongy myocardium (24).

As in fishes, myocardial oxygen demand in tetrapods is greatest during exercise. Furthermore, exercise induces an acidosis. Acidosis combined with anoxia is more debilitating for cardiac function than is either stress alone (43, 92). Hence, if the left-to-right shunt functions to supply the right side of the ventricle with oxygen, it should occur during exercise. Indeed, observations in turtles indicate that a left-to-right shunt occurs during exercise (56, 75, 93). The left-to-right shunt is also known to increase the oxygen content of the systemic arterial blood to levels that are equivalent to pulmonary venous values, suggesting that the shunt functions in systemic oxygen transport (39). However, this function does not exclude the left-to-right shunt from also serving as a source of myocardial oxygen. Indeed, myocardial electrical abnormalities (e.g. increase in the p-r interval, inversion of the t wave) that occur in turtles when effectively prevented from enriching ventricular blood with the left-to-right shunt during exercise suggest the function of myocardial oxygenation (25).

Archosaurs (birds and crocodylians) and mammals cannot shunt blood within the ventricle because it is completely subdivided by a septum. Nor do these animals enrich with oxygen the blood that enters the right side of the heart with cutaneous respiration. Consequently, another mechanism probably supplies oxygen to the myocardium. In birds and mammals, a coronary circulation

carries oxygen to the heart, but the situation in crocodylians is not fully known. Crocodylian ventricles contain more spongy tissue than do those of birds or mammals (53). However, overall their ventricles more closely resemble those of birds than those of snakes and lizards (89). The crocodylian ventricle contains a significant proportion of compact myocardium that is completely supplied with oxygen through a coronary circulation, and the spongy myocardium is also well-endowed with coronary vasculature (53, 71). Furthermore, injections of ink into the coronary circulation show anastomosis of coronary vessels with the sinusoidal channels of the spongy myocardium (53). Hence, spongy regions that are avascular could still obtain oxygen from coronary blood through these anastomoses. Finally, comparisons of the right and left atria (which probably have similar workloads) indicate that the right atrium contains more coronary vasculature than the left (CG Farmer, unpublished observation). All of these factors suggest that a coronary circulation is critical to the crocodylian heart.

In summary, the ventricles of many tetrapods (amphibians, turtles, snakes, and lizards) are composed primarily of spongy myocardium. The separation of pulmonary and systemic blood that occurs in these animals therefore could result in regional myocardial hypoxia. However, this hypoxia could be overcome with cutaneous respiration and/or a left-to-right intracardiac shunt. For lineages that neither rely on cutaneous respiration nor have the ability to shunt blood within the ventricle, the primary source of myocardial oxygen appears to be from a coronary circulation. There are two noteworthy observations regarding complete subdivision of the cardio-pulmonary system and the replacement of spongy myocardium with compact tissue that is supplied with oxygen through a coronary circulation: First, several lineages independently evolved such a system (Figure 3); second, the evolution of this system is correlated with the ability to sustain high levels of exercise.

Ventricular Morphology and Coronary Circulation

Cardiac morphology varies dramatically among vertebrates in terms of the shape of the heart; the alignment of the chambers, septa, and outflow tracts; the density and composition of the cardiac walls; and the mode of oxygenation, etc. It appears that foraging strategy is an important factor in shaping this morphology. A benefit of active foraging is the procurement of more food than is obtained by sit-and-wait predators (81, 82), but active foraging requires the aerobic production of adenosine triphosphate. This, in turn, mandates high rates of flow of oxygen from the environment to the mitochondria, i.e. the oxygen cascade. Consequently, the evolution of stamina entails numerous adaptations in the cardio-respiratory system that facilitate the flux of oxygen through the cascade. In many cases, similar structures are found that are almost certainly the result of convergent evolution rather than inheritance from a common ancestor.

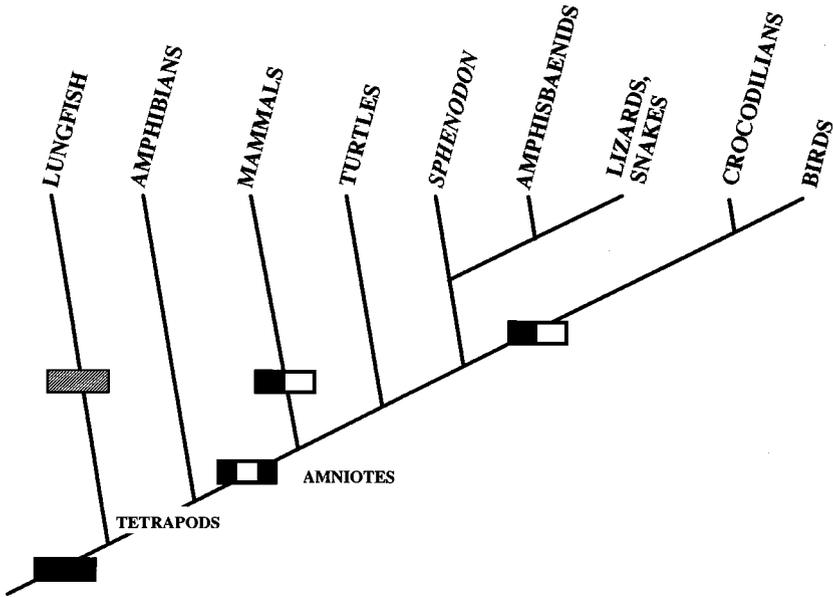


Figure 3 Hypothesis of the relationship of tetrapods, showing the number of chambers and the degree of subdivision of the ventricle. One ventricular chamber, no septum, ■; two ventricular chambers, incomplete septum, ▨; three ventricular chambers, incomplete septa, ▤; two ventricular chambers, complete septum, ▥.

The ventricular septa of lungfish and amniotes have an independent origin and serve different functions. Independent evolution of these structures is suggested by the embryological association of the lungfish septum with the atrial septum, and of the main amniote septum (generally called the horizontal septum) with the conus arteriosus (42). The function of the septum in lungfish is probably to prevent loss of oxygen from the blood to hypoxic water (see above) and is not related to the creation of a dual-pressure circulatory system or expanded aerobic capacities. Indeed, the African and South American lungfish are noted for having exceptionally anaerobic rather than aerobic metabolisms (34). In contrast, the function of a well-developed septum in amniotes is associated with the ability to sustain exercise by enabling elevated systemic arterial pressures without elevated pulmonary pressures, preventing excessive stresses in the pulmonary capillaries (51, 65). Among amniotes there is great variation in the degree of development of the horizontal septum that is correlated with the lineages' ability to sustain locomotion. The septum is poorly developed in turtles, more fully developed in snakes and varanid lizards, and complete in

archosaurs and mammals (Figure 3) (42). Evolution of a complete ventricular septum occurred independently in archosaurs and mammals. Likewise, a nearly complete septum evolved independently in varanid lizards (this septum totally divides the ventricle functionally but not anatomically) (65). Birds and mammals are well known for their endurance. Similarly, varanid lizards are noted among lepidosaurs for their ability to sustain exercise. Crocodylians, however, are better known for burst than sustained exercise.

The lifestyle of extant crocodylians might appear contradictory to the idea that a divided cardio-pulmonary system is an adaptation for sustained locomotion. Ancestrally, however, crocodylians were agile, terrestrial animals, and most of the specialized features found in the modern aquatic crocodylians were evolved in the late Triassic in highly terrestrial forms (15, 91). Hence, consideration of history is important in understanding these animals. Many extant crocodylian characters, including a fully septated ventricle, are probably vestigial. This idea is supported by similarities in the embryology of the avian and crocodylian ventricle that suggest the evolution of the septum took place early in the archosaurian lineage (42). Other characters of modern crocodylians were evolved later, probably as adaptations to an aquatic lifestyle, e.g. an ear lid that closes when the head passes through the air-water interface, preventing water from entering the ear (94). Cardiovascular features as unique to crocodylians as an ear lid may similarly have been acquired with the assumption of an aquatic lifestyle (e.g. an aorta originating in the right ventricle that enables a right-to-left shunt, the foramen of Panizza that enables blood flow between the right and left aortas).

Animals with a well-developed ventricular septum also tend to have a well-developed coronary circulation. In turtles, the coronary arteries often originate from vessels far from the heart (e.g. from the subclavians), and coronary support is nonexistent to the atria and minimal to the ventricle (about 10% of the muscle mass). In snakes and lizards, the coronary artery is confined to posterior regions of the aortas. In snakes and the varanid lizard, there is compact tissue in the atria as well as the ventricle and more extensive coronary support than in turtles or other lizards (10, 59). In archosaurs and mammals, the coronary arteries originate from the base of the aorta (right aorta in crocodylians) and play a dominant role in nourishing the heart (see above). In general, these changes are accompanied by other adaptations for elevated aerobic metabolisms, e.g. high afterload, high hematocrit, and high heart rate. Some of these features are also present in gill-breathing fishes (e.g. scombrid fishes) noted for endurance (e.g. active foraging mode, compact ventricles, coronary support, high heart rate, high cardiac output, high afterload, and high hematocrit) (14, 50, 59, 72, 87).

It remains for future research to determine whether and how these adaptations for endurance interact to affect the form and function of the heart. Mechanisms that influence mammalian coronary angiogenesis and ventricular remodeling

are complex and involve growth factors, extracellular matrix molecules, and inhibitory factors. Angiogenesis can be induced by thyroid hormones, hypoxia, dipyridamole or adenosine, and exercise. Exercise-associated angiogenesis is probably stimulated by mechanical stresses on the endothelial lining of the vasculature that trigger the release of growth factors and cause mitogenic, migratory, and tube formation of the endothelial cells (86). Exercise also induces ventricular remodeling that can vary with the type of exercise (44). An important bottom line to many of these changes is that sustained exercise confers great health benefits to humans, whereas a sedentary lifestyle is among the most significant risk factors for heart disease. The mechanisms by which an active lifestyle protects against disease are not fully understood (67). Although numerous potential mechanisms have been identified (e.g. improved lipoprotein profile, weight loss, lowered blood pressure), exercise confers health benefits that are independent of these mechanisms (8). Consequently, understanding how similar adaptations for endurance in groups as distantly related as birds, scombrid fishes, and mammals have resulted in similarities in cardiac form and function may prove important both for understanding the evolution of this system and for providing insight into the mammalian design.

SUMMARY

An adequate supply of oxygen to the heart is critical for proper cardiac function and probably has been a selection pressure during the evolution of the vertebrate cardio-respiratory system. The myocardium of essentially all vertebrates has primarily an aerobic metabolism that is depressed by hypoxia and acidosis; a combination of these factors inhibits the heart more significantly than either alone. Vertebrates have evolved two ways of oxygenating myocardium: (*a*) from channels that carry luminal blood to a spongy network of myocytes and (*b*) from a coronary circulation that carries oxygen-rich blood to compactly arranged myocytes. Ontogenetic studies and the phylogenetic distribution of these mechanisms indicate that spongy myocardium is primitive for vertebrates. The use of a coronary circulation and compact myocardium appears to have evolved convergently in several groups.

The cardiac performance of gill-breathing fishes may be limited by the fact that their spongy myocardium contains blood that is oxygen-poor. In air-breathing fishes that use a lung for respiration, there is mixing of oxygen-rich pulmonary and oxygen-poor systemic blood before it enters the heart. Hence, lungs may function to supply this myocardium with oxygen and could be an adaptation for an active lifestyle. Because both aerial predation and life in deep water preclude or diminish the usefulness of lungs, coronary support to the ventricle may have been requisite to an active lifestyle for fishes subject to these selection pressures.

With the transition from an aquatic to terrestrial life came numerous changes in the cardio-respiratory system. Subdivision of the cardiovascular system into a pulmonary and systemic circuit may have been a mixed blessing. Although improving the efficiency of gas exchange and enabling elevated systemic pressures, this subdivision isolates the spongy myocardium in the right side of the heart from oxygen-rich pulmonary blood. Cutaneous respiration in amphibians and the left-to-right shunt of chelonians and lepidosaurs could assuage this difficulty by enriching with oxygen the blood in the right side of the heart. Because a complete septum in the ventricle precludes this shunt, it may mandate coronary support to the heart in archosaurs and mammals. This idea is supported by the observation that progressive ventricular septation is accompanied by progressive coronary support to the heart and the replacement of spongy myocardium with compact tissue. Septation is important in the formation of a dual-pressure circulatory system and correlates well with lineages that have (or have had) an active foraging mode and therefore an aerobic exercise metabolism. Although numerous factors were probably involved in the evolution of compact myocardium and a coronary circulation, this selection pressure may have been among the most important. Along with this change in cardiac morphology are found other adaptations for sustained exercise (e.g. elevated hematocrit, heart rate, afterload).

It seems probable that many of these adaptations for sustained locomotion have interacted such that compact myocardium functions better for these organisms than spongy myocardium and therefore has been favored by natural selection. These interactions could involve changes in preload, afterload, blood viscosity, blood pH, heart rate, ejection fraction, etc, and are easy to imagine but have not been well studied. Consequently, comparative studies within an evolutionary context have potential to provide insight into basic mechanisms that may impact both the formation and the function of the coronary circulation. In humans, a sedentary lifestyle is among the most significant risk factors for heart disease, yet the mechanisms by which activity maintains the health of the coronary circulation are not fully understood. Research aimed at understanding the factors that have made a coronary circulation of importance in other groups of vertebrates that have experienced selection for an active lifestyle may not only be important for our understanding of vertebrate evolution but may also provide information important to understanding and maintaining the health of the mammalian coronary circulation.

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