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The Evolution of the Cardiovascular System: A Hemodynamic Perspective

Kalp-Damar Sisteminin Evrimi: Hemodinamik Bir Bakış Açısı

ABSTRACT

The human cardiovascular system is a product of evolution that occurred over hundreds of thousands of years. During its long history, cardiovascular design has been shaped and reshaped by developing adaptations to the hemodynamic challenges it faced at every step. Although being momentarily beneficial for dealing with the problem they were first devised for, the evolutionary changes were built upon one another and culminated in the current scheme which may not necessarily be the ultimate or an immaculate design. Therefore, the analysis of the cardiovascular evolution provides a fascinating opportunity to spot the possible weak points of our cardiovascular system, to better understand the disease pathophysiology, and to formulate treatment alternatives. In this regard, this review tries to summarize the teleonomy of cardiovascular evolution from a hemodynamic perspective.

Keywords: Blood pressure, cardiac function, evolution, heart failure, hypertension

ÖZET

İnsan kalp-damar sistemi yüz binlerce yıl içerisinde gerçekleşen bir evrimin ürünüdür. Uzun tarihi boyunca kalp-damar sisteminin dizaynı, her aşamada karşılaşılan hemodinamik engellere yanıt olarak yeniden şekillenmiştir. Başta cevap oldukları sorunla mücadelede faydalı olsalar da evrimsel değişiklikler birbiri üzerine birikmiş ve eksiksiz ya da kusursuz olmayabilecek şu andaki şemayla sonuçlanmıştır. Bu nedenle kalp-damar sisteminin evriminin analizi; kalp-damar sisteminin olası zayıf noktalarını tespit edebilmek, hastalık patofizyolojisini anlamak ve tedavi alternatifleri geliştirmek için mükemmel bir fırsat vermektedir. Dolayısıyla bu derleme kalp-damar sistemi evrimini hemodinamik bir bakış açısıyla ele almaya çalışacaktır.

Anahtar Kelimeler: Evrim, hipertansiyon, kalp işlevi, kalp yetersizliği, kan basıncı

REVIEW
DERLEME

At the bedside of a deteriorating patient with circulatory failure, one might wonder if we really understood the basics of circulation enough for devising new treatment options that can be used for the patient's benefit. Should the circulation be the way it is? Is the current design of the cardiovascular system the ultimate best possible one? Or, is it one of the many possibilities that contain inherent flaws which should be accounted for when trying to understand or to treat a disease? In this review, I will try to summarize the teleonomy of cardiovascular evolution from a hemodynamic perspective to uncover its possible Achilles heels, compare it to other possible designs and analyze possible treatment targets.

From Single Cell to Vertebrates

More than 2.5 billion years ago, some microorganisms inhabiting the primeval ocean of our planet invented photosynthesis and started to pollute the atmosphere with a new, highly lethal waste product: oxygen. Only organisms who learned to harness this chemical for energy generation survived this catastrophe.[1] The hemodynamics is actually nothing else than a reiterative story that narrates the possible ways of providing the descendants of these cells with oxygen.[2,3]

For unicellular organisms, diffusion was adequate for oxygen delivery (Figure 1A). With the origination of multicellular organisms, however, this method became inadequate. First, new body designs permitting internal convective streams of the water among

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cellular masses were tried, as seen in sponges.[4] Then, a more organized scheme was invented some 700 million years ago with the emergence of bilateral symmetry. The success of this framework was in the utilization of consecutive copies of the same basic units along a craniocaudal axis. These fundamentally similar body segments had the potential to be remodeled for different purposes.[5] A new germ layer, *the mesoderm*, which is first seen in the bilaterians, gave rise to a cardiovascular system that follows this blueprint and created repeated vascular structures perpendicular to the body axis, connecting dorsal and ventral vessels around the gut with an opening at the head and the rear. The first heart-like organ is believed to have emerged from the fusion of the ventral main vessels over 520 million years ago.[6-8]

Although cells require a continuous flow of oxygen and nutrients, a continuous-flow pump that is capable of delivering constant propulsive torque is very hard to evolve. Indeed, the animal kingdom has never been able to invent the wheel mechanism, instead, developed a pulsatile pump from the primitive peristaltic vessel.[9] However, the preference of a pulsatile pump, instead of a continuous one, established the first (and somewhat disadvantageous) law of the hemodynamic constitution to be obeyed by all generations to come (Figure 2, Article 1).

At the beginning, the system was open at both ends and supported the circulation of the intracorporeal fluid.[10] Although this circulatory system is still being used by arthropods, mollusks and during embryogenesis,[11] open circulatory systems limit the size of the animal as it needs a high volume of circulating fluid approaching nearly half of the body mass and interstitial diffusion is only efficient over short distances.[12] Under this selection pressure, closed vascular systems evolved and the emergence of an uninterrupted vascular network established the second fundamental law of the universal hemodynamic constitution that governs tissue perfusion (Figure 2, Article 2). The main advantage of this closed system is that, as long as arterial and venous pressures are kept constant, tissues can regulate their individual blood flows simply by adjusting their vascular resistance. This makes the arterial compartment the primary reservoir of the hydraulic energy and reduces the heart to a secondary position as its recharger unit. To charge the arterial pressure reservoir, the heart has to transfer some volume from the venous compartment to the arterial compartment and thus create a prefusion pressure by lowering venous and increasing arterial pressure inversely proportional to their respective compliances (*arterio-venous integration*).[13] With a non-sucking pump and collapsible vessels, this is only possible when the venous compartment is already pressurized to enable the filling of the heart and to prevent vessels from collapsing while cardiac veins are being emptied. Therefore, the vascular system should have a positive pressure even before the heart starts to beat (mean systemic filling pressure, P_{msf}). Thus, P_{msf} sets a maximum limit to cardiac output as it is mandated for fluid transfer from the venous to the arterial side.[14,15] As a corollary, the organisms would choose to monitor the vascular pressures instead of directly measuring cardiac output, which will have implications in the future.

Equipped with this cardiovascular system, some ancient bilaterians developed a cartilaginous back (*noto-* in Greek) cord that serves as a site for muscle attachments and thus enables better locomotion.[16] In these primitive chordates, the pharynx had repeated slits that serve as a filter-feeding mechanism by allowing the movement of water in from the mouth and out from the slits. The blood in the pharyngeal vessels, directly arriving from the heart, absorbs these nutrients into the bloodstream and carries them to the tissues. The blood gets its oxygen and unloads its carbon dioxide during the passage through the skin. This oxygen-rich blood then arrives at the heart, which is a spongy trabecular network of muscle cells (Figure 1B).[17] In time, notochord gave rise to a more robust structure called the vertebral column that supports stronger muscles, a larger body size, and better locomotion.

From Fish to Amphibians

As vertebrates rapidly diversified and grew in size, skin respiration gradually became inadequate. Pharyngeal vessels around the pharyngeal slits showed extensive branching and gave rise to the gills.[18] A gill unit consisted of an individual arterial supply, gill filaments arising from that artery, and supporting cartilaginous elements. This delicate structure creates a large surface area ideal for gas exchange but has some prerequisites. It can only accommodate a low-pressure perfusion, because the fragile gas exchange surface can be endangered by high arterial pressures. Moreover, since air-saturated water contains a limited amount of oxygen, the cardiac output passing through gills must be much less than the flow of the water through gills to match ventilation with perfusion.[17-19] These prerequisites required 2 important cardiovascular problems to be addressed: (1) A limited cardiac output ultimately leads to a lower body mass and locomotor potential which is a disadvantage that nature has a strong selection pressure against; (2) With a circulatory design that the blood perfusing gills first, then tissues and then returning to the heart, the heart becomes afferent to the gas exchanger organ and receives oxygen-poor and acidotic blood from the tissues. This is particularly disadvantageous during exercise, as evidenced by the fact that many extant gill-breathing fish die from exhaustive exercise.[17]

For a higher cardiac output, mechanisms providing a higher gill ventilation should be provided in the first place. Ancestral jawless fish (Figure 1C) found a solution to this problem by repurposing the first 2 gill arches. First, the second gill cartilage evolved into the hyoid bone and its branchial muscles were employed for decreasing and increasing the volume of pharyngeal space. This offered a more efficient pump mechanism for sucking water in and blowing it out.[20] Second, as the gills were supported by hinged cartilages, evolving it into a jaw was not too far-fetched. Thus, the first gill cartilage formed the mandibula and jawed fish emerged (Figure 1D). Aside from yielding a powerful new weapon to be used for predatory purposes, this innovation also opened the way for gulping air. Gulping air from the surface provided a new way of getting oxygen. A predictable next step was to evolve an outpouching in the pharynx to store that air

ABBREVIATIONS

LV	Left ventricle
Pmsf	Mean systemic filling pressure
RV	Right ventricle

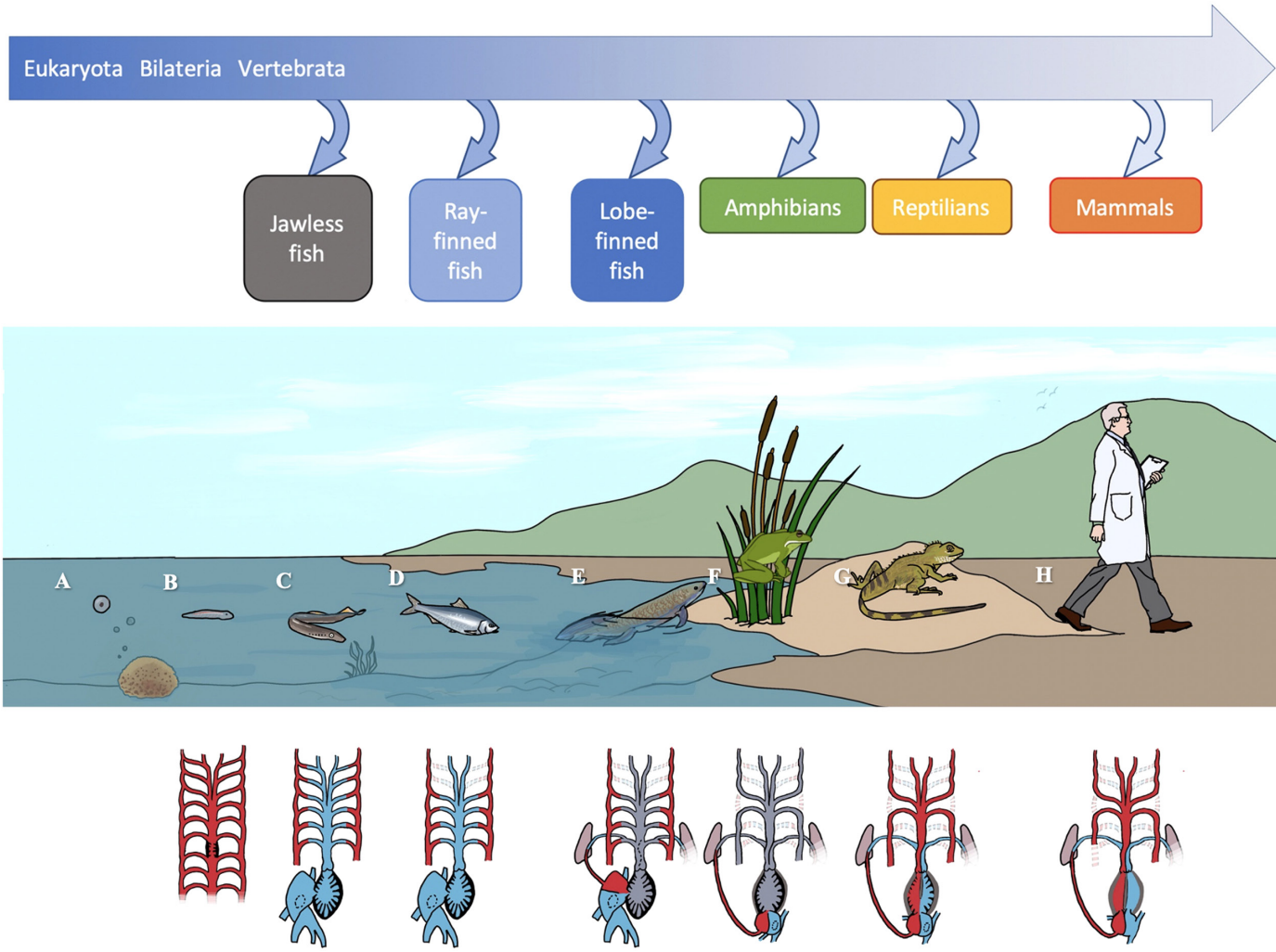

Figure 1. A-H. Evolution of cardiovascular system. (A) For single-cell organisms, no circulation is necessary as diffusion is adequate for oxygen delivery. (B) Ancient bilaterians used skin respiration and repeated vascular structures for segmental perfusion. (C) The primitive vertebrates repurposed the leading segmental arteries as gills. Their heart included a sinus venosus, a single atrium, a single ventricle, and a bulbus cordis. (D) With the evolution of the jaw, first 2 gill arches were lost. (E) The ancient lobe-finned fish developed a lung, a pulmonary circulation arising from the sixth pharyngeal arch, and a partially septate atrium. (F) The amphibians developed a 3-chambered heart with 2 atria and a single ventricle. (G) The reptiles developed a partial ventricular septum. The ventricle became more compacted. (H) The mammals (and the birds) completed the ventricular septation and developed a 4-chambered heart. The sinus venosus and the bulbus cordis incorporated into the right atrium and right ventricle, respectively. The mammals retained the left arcus while the birds retained the right arcus aorta.

and allow respiratory gas exchange.[21] A special subclass of fish (*Sarcopterygii*) evolved this outpouching into the lungs (*lung-fish*) and provided an arterial supply from the sixth pharyngeal arch (Figure 1E). In contrast to the general scheme, the venous return of this outpouching was not to dorsal aortae but directly opened to the adjacent atrium. This arrangement provided the heart with an extra oxygen source and helped to overcome the second limitation.[17,19,22,23]

The pulmonary venous return had effects on the heart anatomy. The entrance of the pulmonary vein to the atrium induced a pulmonary fold to form in the atrium that constitutes a partial atrial septum.[24] Also, a spiral-shaped ridge in the conus arteriosus created 2 functional outflows.[17,25] However, these were not the innovations that the sarcopterygian fish named after, they got their name because of their muscular (*sarco-*) fins (*-pterygius*). Equipped with an air-breathing organ and stronger extremities, they were ready to set their "foot" on an uncharted territory.[23,26,27]

From Amphibians to Mammals

The conquest of the land was promising. As green plants and arthropods had already invaded the land dozens of millions of years earlier, it provided an ecosystem to forage, shallow intertidal ponds to find trapped coastal preys, and a niche to escape from aquatic predators. Furthermore, when crawled onto the shores to raise their body temperature by basking in the sun, the animal boosts its metabolism and develops more power and speed. This was extremely advantageous for catching prey, escaping from predators, and for reproduction.[17] These factors gradually led to an amphibious lifestyle.

On the other hand, the transition to the land required many adaptations. The increased water loss from the skin and respiratory tract, the reduced access to the water, trauma, and blood loss on the dry land surface rendered the volume loss as the most feared risk of this migration. With a regulation mechanism already monitoring vascular pressures, any stress reaction would evolve to include fluid retention response in order to increase P_{msf} and cardiac output. An avidly water and salt sparing kidney was strongly favored, and the plasma protein concentration and oncotic pressure increased and even exceeded P_{msf} to keep fluid in the vascular space.[28] By abandoning the buoyancy of the water that offered practical weightlessness, the animals now had resistance to gravitational forces necessitating stronger bones and muscles, more energy, and oxygen requirement.[29] This needed a better separation of oxygen-rich and -poor blood, hence amphibians finalized atrial septation they inherited from sarcopterygian lungfish.[30]

The effects of gravity on hemodynamics were also profound. The weight of a 1-m water column creates a pressure of 73.5 mmHg (Figure 2, Article 3).[13] As hydrostatic pressure increases and decreases at the same amount in arteries and veins with height, the difference between the 2 remains constant and the Article 2 was still in force. However, when intravascular pressure drops below atmospheric levels while gaining height, the vessels collapse. Venous collapse does not stop the organ flow, only limits it by increasing vascular resistance, but arterial collapse shuts the organ circulation down. As fish and then amphibians had a systolic blood pressure of only 30-40 mmHg, and this level of pressure permits only 50 cm vertical distance between the heart and the brain before arteries collapse, amphibians and their first reptile offspring had to have a horizontal body posture.[31-35] Furthermore,

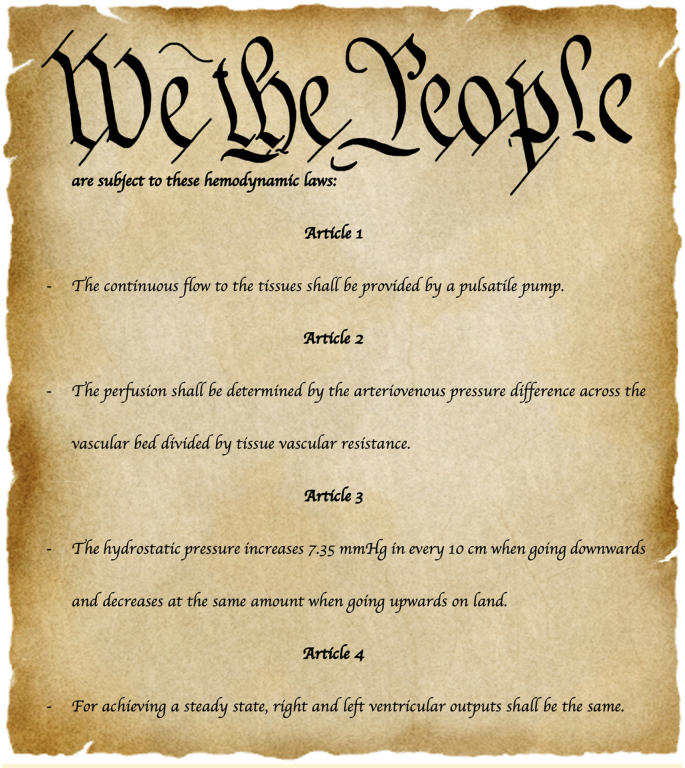

Figure 2. The Laws of The Hemodynamic Constitution.

a systemic pressure exceeding 50 mmHg is not likely with an undivided ventricle, as this higher pressure endangers the pulmonary blood-air interface.[36] Nevertheless, the spongy myocardium that predominates in fish is now gradually encased in a layer of compact myocardium that increased in thickness and proportion and enables higher pressures (Figure 1F).[10-12]

The reptilians were the first vertebrates sufficiently adapted for terrestrial habitation and utilize the lungs as the sole pathway for the acquisition of oxygen.[36] Under the strong selection trend towards ventricular septation, reptilians developed a partial ventricular septum and more compact myocardium (Figure 1G).[10-12] Debatably, those who developed a completely separated ventricle first and attained high arterial pressures were the dinosaurs, as supported by their towering heads reaching over 10 m, barely fitting under the ceilings of the museums they are exhibited today.[37] Of note, these giants seem to exploit Article 2 up to the physical limits for a cardiovascular system (Figure 3A). When they raised or lowered their heads, the transmural pressure in their cerebral vessels decreased or increased, therefore vessels tended to collapse or distend, respectively (Figure 2, Article 3). Despite these wild fluctuations in transmural pressure, the perfusion did not change because it is determined by the arteriovenous pressure difference (Figure 2, Article 2). Yet, with an erect neck posture, very high arterial pressures were still required, not only for preventing arterial collapse[35] but also for keeping the blood under the boiling point which is decreased to room temperatures when the blood is subjected to such negative pressures and preventing oxygen from dissociating from the hemoglobin under low pressure and coming out of solution to form bubbles.[37] It is still not clear how these dinosaurs managed to circumvent these limitations without incredibly huge left ventricles generating immense arterial pressures. Nevertheless, the presence of 2 separate circulations is associated with the ability to sustain exercise by enabling elevated systemic arterial pressures without elevated pulmonary pressures and a thinner and more efficient blood-gas interface.[3,12,31,36] With a higher systemic pressure reservoir, tissues can now increase their flow and oxygen delivery to much higher levels. The higher oxygen supply to the muscles enabled a higher exercise capacity and stamina, which enabled dinosaurs to dominate the planet for approximately 150 million years.[2,12,17]

The bliss of higher arterial pressures came at a cost, however. Higher vascular pressures need a more active thrombotic system to quickly control any possible hemorrhage. Vascular damage due to high pressures (including atherosclerosis and arteriosclerosis) and thrombotic complications would be the fate of the later generations to come.[38-41] Furthermore, dividing a single ventricle into 2 separate parts laid the foundations of another hemodynamic law (Figure 2, Article 4). Now, the right and left ventricles have to beat at the same heart rate and pump the same stroke volume and cardiac output, even though they have different contractile properties, and they are facing completely different vascular beds with different responses to various pathophysiological processes (Figure 4). If left ventricular output, even temporarily, falls short of right ventricular output (*interventricular disintegration*),[13] the excess volume created by the difference between these 2 outputs has to accumulate in the pulmonary vascular compartment that is tried to be protected by the evolution all along.

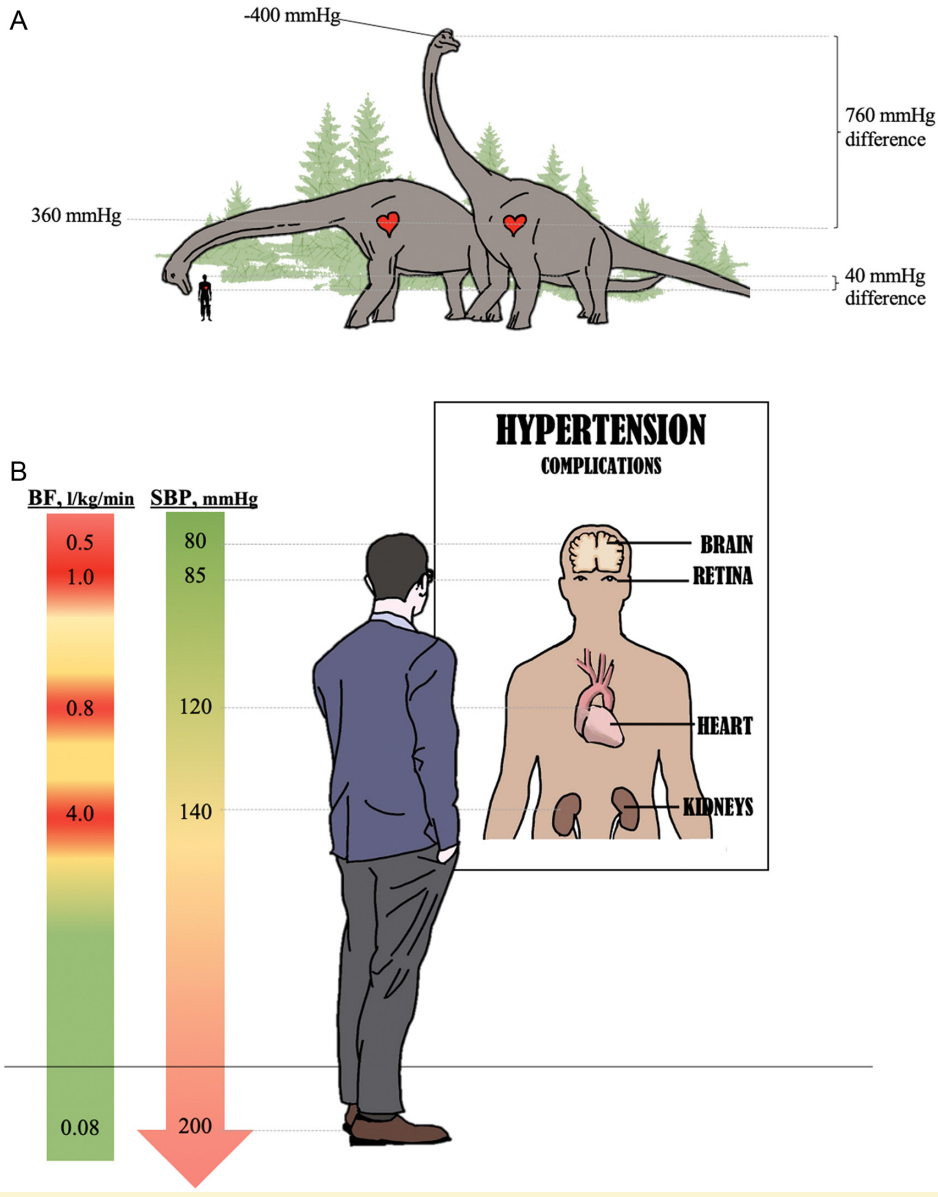

Figure 3. A-B. (A) Sauropod dinosaurs had a ~760 mmHg pressure difference between their hearts and brains when they kept their necks in an erect position. When they lowered their heads, there should have been an enormous change in cerebral arterial pressure, despite arteriovenous pressure, hence cerebral flow did not change. Although the pressure swings in humans are much more modest, this still means that in a lying normotensive man with a systolic blood pressure of 120 mmHg, the pressure in the cerebral vessels is equal to that in a standing hypertensive man with a blood pressure of 160 mmHg. (B) The ignorance of Article 3 of the Hemodynamic Constitution may have misled us into thinking that the pressure is the cause of "hypertensive" complications. However, the pressure in the vascular system changes vertically in an upright man, attains its lowest level in the brain, and reaches up to 200 mmHg at the level of toes. Yet, hypertensive involvement does not follow this craniocaudal pattern, rather it generally targets the organs with the highest flow. BF, blood flow; SP, systolic blood pressure.

While reptiles were reigning in the land, there was a small group of organisms called mammals hiding in the darkness of the night and waiting for something from the heavens to dethrone their reptilian oppressors. Their nocturnality selected several traits such as thermogenesis, encephalization associated with the development of sensory functions critical for the nocturnal existence,[42] miniaturization,[43] and finally endothermy. Endothermy simply means the production of endogenous heat that leads to independence from the ambient temperature and made invasion of several biological niches possible. However, endothermic animals consume 10 times more energy than their ectothermic peers for generating heat that will keep body temperature constant.[44,45] This is associated with an increased oxygen demand and cardiac output. As a corollary, the heart itself showed some adaptations. The level of ventricular compaction increased to the utmost degree. Because of the higher cardiac output, shorter systole, and longer ventricular diastole, the sinus venosus became obsolete and fused with the right atrium but

retained its sole function as the dominant pacemaker.[24,25] As an adaptation to longer gestational durations, a secondary foramen developed in the cranial part of the primary atrial septum during embryogenesis to enable continued shunting. While the sinus venosus is incorporating into the right atrium, a second septum developed from the right atrial roof as a thick fold, gradually overlapped this *foramen secundum*. This *septum secundum* serves as a valve mechanism that enables continued right-to-left blood passage in the embryo but prevents shunting after the birth. The sinus venosus also leaves its left horn as the coronary sinus and its valves as crista terminalis, Eustachian valve, and Thebessian valve.[24] The right-sided aortic arch regressed, probably due to the requirement for a large arterial duct connecting to the descending aorta and left the familiar left-sided arcus aorta as the principal highway of the mammalian vascular system (Figure 1H).

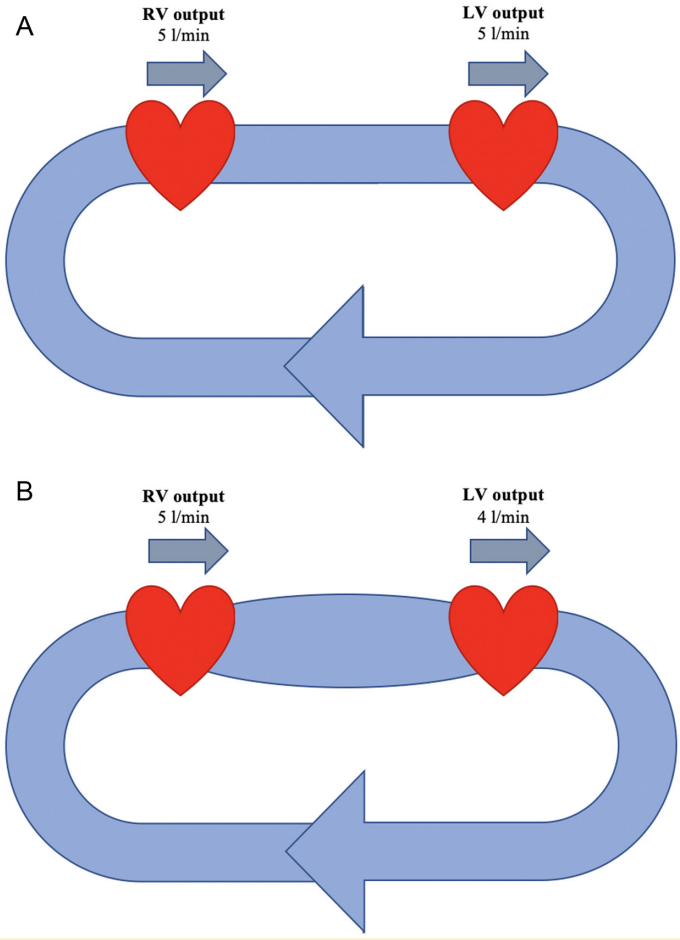

Figure 4. A-B. (A) In a serially connected 2-pump system, the output of both pumps should be equal to keep a steady-state. (B) When the output of the upstream pump (RV) temporarily exceeds the output of the downstream pump (LV), excess volume accumulates in the intermediary (pulmonary) vascular compartment, unless the outputs of the pumps could be regulated independently. This is not fully possible in the mammalian cardiovascular system, as the evolution created not 2 independent pumps but rather 2 half-pumps by dividing a single ventricle into 2 halves. Although increased pressure in the pulmonary vasculature in this situation is frequently explained with "diastolic LV dysfunction" that is transmitting backward, the source of excess pulmonary hydraulic energy is actually the RV. LV, left ventricle; RV, right ventricle.

Implications for Homo sapiens

Our cardiovascular system is a result of the abovementioned evolutionary process and it reenacts this evolutionary history during embryogenesis. The full-blown 4-chambered human heart develops after the successive stages of the single peristaltic tube, the 2-chambered fish heart with a spongy ventricular cavity, the 3-chambered more compact amphibian heart, and the three-and-a-half-chambered reptilian heart with a partly divided ventricle.[24,46] Six pairs of pharyngeal arteries develop and either regress or metamorphose into mature vascular structures as evolutionary history foretells.[47]

Although cardiovascular evolution sculpted our body and brought us many new organs while trying to stretch its physiological limits, our cardiovascular system is not a unique, ultimate design that is specifically planned to meet the requirements of the human organism. Neither it is flawless. Some of the adaptions gained during this evolutionary process are not necessary, even harmful, causing or contributing to disease processes. The diseases associated with high blood pressure and increased tendency to thrombosis are the leading causes of death not only in humans but also in other mammals and birds.[39-41] Unfortunately, these diseases escape from the elimination of natural selection, since they manifest in the post-reproductive ages. A higher "normal" blood pressure is a demanding obligation during other disease processes as well. In a patient with cardiogenic shock lying in a coronary care unit bed, neither high arterial pressures nor the adaption of costly endothermy is beneficial. If it was possible to induce a transient ectothermic state with a metabolic need 10 times lower than endothermy or lower arterial pressures not contesting the effects of gravity, the possibility of survival would be increased.

Even the hemodynamic constitution sometimes seems to work against us. The first article dictates the use of a pulsatile pump to provide continuous flow to the tissues. This requires a compliant arterial system that cushions pressure oscillations and converts the pulsatile output to a steady outflow with the Windkessel effect.[48] However, as the arterial system is not perfectly compliant, a pulsatile pump consumes more energy and is less efficient than a continuous pump. Since the pulsatile heart is positioned behind the main pressure reservoir, it has to consume a sizable portion of its energy to open its semilunar valves first, which explains why pressure-overload conditions are less tolerated than volume-overload conditions. The compliance of the arterial system also decreases with age and increases the pulsatile load on the left ventricle.[49,50]

The pulsatile flow has detrimental effects on the vascular system. The cyclic stress on conductance vessels prompts elastic fiber breakdown and decreases arterial compliance.[51] A decreasing arterial compliance causes wide pressure oscillations that penetrate into microvasculature and compromise the integrity of delicate capillaries.[52-54] Furthermore, phasic pressure waves reflect at all bifurcations and discontinuities of the vasculature.[55] The reflected waves come back to the proximal aorta

and if they coincide with systole, they cause an extra pulsatile load. However, as all mammals use a similar vascular map, none have a perfect *ventriculoarterial coupling* that minimizes these undesirable effects. For example, kangaroos have extensive vascular branching in their well-developed lower extremities which create strong wave reflections. These wave reflections return to the proximal aorta at late systole and generate a pulsatile load that diminishes the cardiac output. Although vascular reflections are mild and return in diastole in healthy humans, they become more pronounced and return at late systole with aging. This deranged ventriculoarterial coupling is a significant problem in hypertension and heart failure.[56,57]

A pulsatile pump also has the limitation of working in a fraction of its duty cycle. Since the mammalian ventricle does not have an effective sucking mechanism, its filling rate determines the volume that could be pumped. The balance between systole and diastole, which are governed and influenced by completely different processes, may also be compromised by simple physiologic perturbations, such as high heart rates, which in turn result in derangements in both functions (*systole-diastolic disintegration*).[13] All of the abovementioned limitations could be avoided if nature endowed us with a continuous pump.

The second article mandates that the arteriovenous pressure difference governs tissue perfusion, but the body predominantly monitors only 1 side of this equation. When the arterial pressure is used as a surrogate for cardiac output, any decrease in cardiac performance is misinterpreted as hypovolemia and leads to fluid retention and edema formation without any abolishing effect on the underlying pathology. On the other hand, as P_{msf} sets a limit for maximum cardiac output, no effort of the heart can compensate for hypovolemia, which would be possible if the pump was continuous and the veins were non-collapsible.[13] The arterial pressure-oriented autoregulation of the organ flow also fails in many disease conditions. In ischemia-reperfusion states, precapillary sphincters exposed to ischemic metabolites maximally dilate during ischemia and they become incapable of dampening the harmful effects of high arterial reservoir pressure penetrating into the capillaries when reperfusion occurs.[58] In heart failure, high venous pressures may decrease glomerular filtration rate, endanger renal flow, and can lead to renal failure.[59]

The third article seems to be frequently ignored altogether as if we had never transitioned to the land. Since we deliberately perform our pressure measurements in a flat posture reminiscent of our fish ancestors and eliminate the effects of hydrostatic pressure, we tend to misinterpret the pressure-related phenomena. The most obvious example is our approach to essential hypertension. Although data from observational studies indicate that the risk of cardiovascular complications doubles for every 20/10 mm Hg increase in blood pressure[60] and lowering it with virtually any drug significantly reduces adverse events,[61] this approach completely disregards the effects of hydrostatic pressure. Considering that the arterial pressure is ~40 mm Hg lower in the head and ~90 mm Hg higher in the lower extremity (Figure 3B), it is hard to explain why (1) the organ with the lowest blood pressure in the body, the brain, is the leading target of hypertension; (2) target organ involvement in hypertension does not fit into a craniocaudally increasing pattern; (3) hypertensive complications tend to cluster in organs with higher flow, such as the brain, the heart, and the kidneys, rather than the organs with vascular beds exposed to higher pressures. Correspondingly, we previously questioned the theory blaming the pressure as the cause of "hypertensive" complications and asked if the flow or any of its iterations, which may have escaped our attention because of its correlation with pressure and harder technical measurement, could be the real culprit.[62]

The ignorance of hydrostatic pressure leads to the generation of hypotheses not compatible with the basic principles of physics. The temporal coincidence of stroke with 24-hour variation in blood pressure, which shows the highest value around midmorning, led some authors to speculate a direct effect of increased blood pressure on vessels or atherosclerotic lesions.[63-65] But in reality, cerebral arterial pressure actually decreases upon waking up, as the magnitude of morning blood pressure surge is generally less than the decrease in hydrostatic pressure due to assuming an upright posture.[66] The studies exploring circadian rhythmicity of cardiovascular events show that myocardial infarction follows a similar pattern to the circadian rhythm of the stroke, which strongly argues against any genuine effect of the pressure since the heart is a nearly gravity-independent organ in contrast to the brain. Of course, it should not be ignored that hypertensive pathophysiology may and does include other factors in addition to the hemodynamics ones, including cellular, neural, and humoral factors.

Last, the fourth article can be, and is, easily violated by several diseases. In a serially connected 2-pump system, the output of both pumps should be equal to keep a steady-state and prevent fluid accumulation behind the pump with the lower output. If the output of the downstream pump (the left ventricle) falls short of the output of the upstream pump (the right ventricle), for example, the excess output accumulates in the intermediary (pulmonary) vascular compartment (*interventricular disintegration*),[13] unless there are regulatory mechanisms exclusively check the output of the upstream pump (the right ventricle) (Figure 4). However, no such mechanisms exist, on the contrary, both ventricles have to beat at the same rate, pump the same stroke volume, and respond similarly to the inotropic stimuli. In a patient with acute left ventricular infarction, the right ventricular output may exceed the output of the damaged left ventricle and leads to the patient's drowning in his own serum despite the patient is not fluid overloaded. A design with 2 completely independent pumps, with a separate right heart able to lower its rate or output to match the output of the diseased left heart, could have avoided this problem, but the evolution was only able to provide us with 2 half-pumps.

Conclusion

Our cardiovascular system evolved by formulating solutions to the challenges it faced by incrementally repurposing or remodeling the material at hand. Given each new branch of the evolutionary tree develops on an already existing one, human cardiovascular system is not a unique, flawless, or perfect design, instead, it is a complex product of a highly adaptable framework that has the

overtones of the past. Therefore, the analysis of cardiovascular evolution from a hemodynamic perspective provides a fascinating opportunity to spot the weak points of our cardiovascular system, to understand the disease pathophysiology, and to formulate possible treatment options.

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