The evolution of the human heart and its relevance to congenital heart disease

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Abstract

The evolutionary history of the human heart is fascinating and highly relevant to an understanding of congenital heart disease. Our phylum Chordata goes back to ancient fish of the Ordovician and upper Devonian periods, 500 million to 345 million years ago.

These fish had a single ventricle, from which our left ventricle (LV) is derived.

Amphibia evolved 345 million to 325 million years ago during the Carboniferous period. They had lungs and so could breathe air, but they had no right ventricle. Some amphibia evolved into fully terrestrial animals, the Amniota, animals with an amniotic sac filled with amniotic fluid in which the embryo and fetus could float, like our piscine ancestors.

Some amniotes evolved into reptiles. Others evolved into birds – feathered reptiles like *archaeopterix*. Still others evolved into mammals – furry or hairy reptiles. Mammals evolved during the Jurassic period, about 180 million years ago. Although fish and amphibia do not have a right ventricle (RV), higher reptiles (crocodiles and alligators), birds, and mammals normally all do. The comparatively recently evolved RV is only about 36% as old as the LV (180 million vs. at least 500 million years old, respectively). Most human congenital heart diseases consist of anomalies of one or more of the four components that make up the RV. Malformations of the LV are relatively infrequent. Congenital heart disease is the commonest anomaly in live born infants (0.8%); it also accounts for more than 20% of all spontaneous abortions and for 10% of all still births.

Thus, we are still having trouble with our major cardiovascular evolutionary adaptations to air-breathing and permanent land-living: the development of the RV sinus (inflow tract), the embryonic aortic switch procedure, and septation to separate the systemic and pulmonary circulations. Recent molecular genetic data suggest that one or more mutations in the Nodal cascade may well be of great importance in anomalies of right-left asymmetry, such as the embryonic aortic switch process, and the heterotaxy syndromes. The embryonic first heart field gives rise to most of the myocardium of the cardiogenic crescent and the early heart tube and contributes only to the

Streszczenie

Historia ewolucji ludzkiego serca jest nie tylko fascynująca, lecz również ważna dla zrozumienia istoty wrodzonych wad serca. Strunowce wywodzą się ze starożytnych ryb okresu ordowiku i górnego dewonu, 500 do 345 mln lat temu. Ryby te posiadały pojedynczą komorę, z której pochodzi nasza lewa komora serca.

Płazy rozwinęły się 345 do 325 mln lat temu, w okresie karbonu. Posiadały płuca umożliwiające oddychanie powietrzem, lecz nie miały prawej komory. Niektóre płazy przekształciły się w zwierzęta w pełni lądowe – owodniowce. Zwierzęta te rozwijają się w worku owodniowym wypełnionym płynem owodniowym, w którym zarodek i płód pływają podobnie do rybich przodków. Niektóre płazy przekształciły się w gady. Inne w ptaki – upierzone gady, jak np. archeopteryks. Jeszcze inne przekształciły się w ssaki – futerkowe i owłosione gady. Ssaki rozwinęły się w okresie jurajskim, ok. 180 mln lat temu. Ryby i płazy nie posiadają prawej komory w przeciwieństwie do wyższych gadów (krokodyli i aligatorów), ptaków oraz ssaków. Stosunkowo niedawno wykształcona prawa komora ma zaledwie 180 mln lat, co stanowi 36% wieku lewej komory, liczącej przynajmniej 500 mln lat. Większość wrodzonych wad serca u człowieka składa się z anomalii jednego bądź więcej z czterech komponentów wchodzących w skład prawej komory. Malformacje lewej komory są stosunkowo rzadkie. Wrodzona wada serca jest najczęstszą anomalią u żywych noworodków (0,8%) i odpowiada za ponad 20% wszystkich aborcji samoistnych oraz 10% wszystkich porodów martwego płodu.

Tak więc wciąż mamy problemy z ewolucyjną sercowo-naczyniową adaptacją do oddychania powietrzem i stałego życia na lądzie: rozwój zatoki prawej komory (droga napływu), embrionalny proces „przełożenia" aorty oraz oddzielenie krążenia systemowego od płucnego. Niedawno uzyskane dane w dziedzinie genetyki molekularnej sugerują, iż jedna bądź więcej mutacji w kaskadzie Nodal mogą mieć wielkie znaczenie w anomaliach asymetrii prawo-lewej, takich jak embrionalny proces przełożenia aorty czy zespoły heterotaksji. Pierwotne pole sercotwórcze embrionu daje początek większości komórek grzebienia sercowego i wczesnej cewie sercowej; przyczynia się jedynie do po-

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embryonic LV. The embryonic second heart field contributes to the "recently" evolved RV. The embryonic anterior heart field, which is a subdomain of the second heart field, contributes to the development of the subarterial outflow tract (conal) free walls, that are important in the development of normally and abnormally related great arteries. Empedocles, an ancient Greek pre-Socratic physicist who lived in the 5th century BC, understood and promoted the concepts of evolution, natural selection, and survival of the fittest 2300 years before their rediscovery by Charles Darwin and Alfred Russel Wallace in the mid-19th century (1858). The primacy of Empedocles is proved by the surviving work of Aristotle (384-322 BC), who quoted Empedocles at length in order to disagree with him.

Key words: evolution of the human heart, normal right-left developmental asymmetry, the human right ventricle is only one-third as old phylogenetically as the left ventricle, the embryonic aortic switch process, the evolution of the right ventricular sinus (inflow tract), the development of cardiac septation, the genetic Nodal cascade, first heart field, second heart field and anterior heart field, Empedocles understood evolution and natural selection in the 5th century BC.

wstania embrionalnej lewej komory. Wtórne pole sercotwórcze embrionu przyczynia się do „niedawno" wytworzonej prawej komory. Przednie pole sercotwórcze embrionu, stanowiące podobszar wtórnego pola sercotwórczego, przyczynia się do rozwoju wolnych ścian stożków podtętniczych, ważnych w rozwoju prawidłowo i nieprawidłowo ułożonych wielkich tętnic.
Empedokles, starożytny grecki lekarz żyjący w V w. p.n.e. rozumiał i promował koncepcję ewolucji, naturalnej selekcji oraz mechanizm doboru naturalnego już 2300 lat przed jej ponownym odkryciem przez Karola Darwina i Alfreda Russela Wallace'a w drugiej połowie XIX w. (1858 r.). Wyższości Empedoklesa dowodzą zachowane prace Arystotelesa (384–322 p.n.e.) obszernie cytującego Empedoklesa, z którego opiniami się nie zgadzał.

Słowa kluczowe: ewolucja ludzkiego serca, rozwój prawo-lewej asymetrii, rozwój filogenetyczny komór serca, proces embrionalnego przełożenia aorty, ewolucja zatoki prawej komory serca, rozwój przegród serca, kaskada Nodal, pola sercowe, Empedokles.

Congenital heart disease is the commonest malformation in live born babies – almost 1% (0.8%). Cardiac anomalies also account for more than 20% of spontaneous abortions, and for 10% of all still births [1, 2]. The cardiovascular system is the first bodily system that must become functional in the embryo to facilitate the rapid growth of a multi-celled animal such as ourselves. The human heart beat is thought to begin at about 20 days of age in utero, at the early D-loop stage of cardiac development, before the mother knows that she is pregnant.

Hence, an understanding of the etiology and morphogenesis of congenital heart disease is of great importance, not only to pediatric cardiologists and cardiac surgeons, but also to the general public.

In a recent paper [3], the evolution of the human heart was traced in our phylum (phylum Chordata) from ancient fish of the Ordovician and upper Devonian periods, 500 million to 345 million years ago. These fish had a ventricle, that would become our left ventricle because of ventricular D-loop formation – the later folding of the straight heart tube in a rightward or dextral direction (hence the term dextral-or D-loop).

Consequently, our left ventricle (LV), in view of our phylogeny, is believed to be at least 500 million years old [4]. These ancient ancestral fish had gills, but no lungs, and no right ventricle (or lung pump).

Amphibia evolved 345 million to 325 million years ago during the Carboniferous period [4]. They had lungs and so could breathe air. But they had no right ventricle and like modern frogs they had to breed in the water.

Some of these amphibia evolved into fully terrestrial animals that did not need to breed in the water. These were the *Amniota,* animals with an amniotic sac containing amniotic fluid. The amniotes thus had a little *mare internum* (internal sea, Latin) of amniotic fluid in which the embryo and, later in development, the fetus could float – like our aquatic ancestors.

Some of the terrestrial Amniota then evolved into reptiles, birds – feathered reptiles such as *Archaeopterix,* and mammals – furry or hairy reptiles.

Mammals evolved about 180 million years ago during the Jurassic period when reptiles, including the giant dinosaurs, were lords of the Earth.

Although fish and amphibia do not have a right ventricle (RV), higher reptiles such as crocodiles and alligators, birds, and mammals all do.

Aquatic and semiaquatic vertebrates have a single circulation – the systemic – that supplies the body and the organs of respiration (gills, lungs, and skin).

Terrestrial vertebrates – higher reptiles, birds, and mammals – evolved a double circulation that was both systemic and pulmonary. The evolution of the right ventricular sinus (inflow tract) [5] and the embryonic aortic switch procedure [3] (in which the developing ascending aorta is switched from above the RV to above the LV) made possible a double circulation.

Why does the evolution of the vertebrate cardiovascular system matter to us as pediatric cardiologists and cardiac surgeons? Because most human congenital heart diseases consist of anomalies of one or more of the four components of the RV – the comparatively "recently" evolved ventricle that is only about 36% as old as the LV: 180 million years old versus at least 500 million year old, respectively. Malformations of the LV *per se* are comparatively infrequent. These data indicate that we are still having trouble with our major cardiovascular evolutionary changes that made possible air-breathing and permanent land-living, namely, the development of the RV sinus or inflow tract, the embryonic aortic switch procedure, and septation to separate the systemic and pulmonary circulations [3].

All of the foregoing has been published previously [3] and hence will not be presented again in detail here. But the foregoing is the essential background to what else needs to be understood.

What's that?

It includes:

1. the work of the molecular geneticists and embryologists [6-8] that appears to fit very well with the evolutionary history of the human heart; and
2. the true story of the discovery of the concepts of evolution and natural selection.

Molecular genetics and embryology

1. The molecular genetic evidence supporting the view that one or more mutations in **the Nodal cascade** may well be of great importance in anomalies of right-left asymmetry such as the embryonic aortic switch, and the heterotaxy syndromes has been noted previously [3].
2. What also merits emphasis is the probably great importance of the recent work of molecular geneticists concerning **the first heart field**, and **the second heart field**, and **the anterior heart field** which is part of the second heart field [6-8].

- **The first heart field** gives rise only to the embryonic LV. This first lineage gives rise to most of the myocardium of the cardiogenic crescent and to the early heart tube [7]. *Hypothesis:* Is this what our ancient piscine ancestors had 500 million to 345 million year ago? To my knowledge, this possibility has not as yet been investigated at the molecular genetic level in fish – that have only one ventricle, analogous to our LV.
- **The second heart field** gives rise to that "Johnny Come Lately" – the RV [8], that is only about one-third as old as the LV.
  Hypothesis: Is something similar or identical to the murine second heart field what evolved in higher reptiles, birds, and mammals, making possible the evolutionary development of the RV? Again, I am not aware of experimental data bearing on this question.
- **The anterior heart field**, which is a subdomain of the second heart field, is very important in the development of the subarterial conal free walls [7]. Complete right-left asymmetry in the development of the subarterial conal free walls – resorption of the right-sided subaortic conal free wall, and growth and expansion of the left-sided subpulmonary conal free wall – results in the normal embryonic aortic switch, and in normally related great arteries [3]. Any other development of the subarterial conal free walls results in a conotruncal malformation [3].

To the best of my knowledge, this is the first time that the first heart field, the second heart field, and the anterior heart field [6-8] have been potentially correlated with the phylogenetic history of the human heart – from fish to mankind [3, 9]. Much more work needs to be done to clarify the embryology and the molecular genetics of these potential correlations.

It is now known that the myocardium of the outflow tract (conus arteriosus) is derived from the pharyngeal mesoderm called the anterior heart field. The anterior heart field also contributes to the myocardium of the RV. Ablation of the anterior heart field leads to tetralogy of Fallot with pulmonary atresia [6].

Cardiac neural crest cells participate in aorto-pulmonary septation. Cardiac neural crest ablation in the chick leads to tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, and interrupted aortic arch. Neural crest cell migration defect in mice (Splotch mutations due to disruption or ablation of the Pax 3 gene) leads to similar outflow tract anomalies [6].

Pitx2c mutant mice also have conotruncal defects. Pitx2c is important in embryonic left-right signaling in asymmetrically developing organs [6] – such as the subarterial conal free walls [3].

Rapid rotation of the conotruncal junction in a counterclockwise direction (looking downstream) normally occurs in mice between Carnegie stages 15 and 19, but fails to occur in mouse models of truncus arteriosus, double-outlet right ventricle, and transposition of the great arteries [6].

In humans, this is exactly what one sees on comparing conotruncal anomalies with normally related great arteries [3]. Conotruncal malformations typically have a great deficiency in counterclockwise (or dextral) rotation at the semilunar valve level on comparison with normally related great arteries. The "engine" of these morphogenetic semilunar valve movements – be they normal or abnormal – is considered to be the development of the subarterial outflow tract (conal) free walls [3].

The dream of our field has long been to build a bridge from the operating room to the genome. Although we still have much to learn, the data are coming together from many different directions (e.g., man, mouse, chick) and they make sense.

Evolution, natural selection, and survival of the fittest

The concepts of evolution, natural selection, and survival of the fittest were known to **Empedocles** (490-430 BC), a pre-Socratic physicist from Agrigas (now Agrigento) in Sicily, which at that time was part of Magna Grecia (Great Greece) [10]. Thus, these concepts were known at least 2300 years before Darwin and Wallace's rediscovery of them in 1858-1860. Aristotle quoted Empedocles at length, in order to disagree with him.

Empedocles (quoted by Aristotle) wrote [10, 11]: *So here the question arises whether we have any reason to regard Nature as making for any goal at all, or as seeking any one thing as preferable to any other. Why not say that Nature acts as Zeus drops the rain, not to make the corn grow, but of necessity – for the rising vapor must be condensed into water by the cold, and must then descend, and incidentally, when this happens the corn grows – just as, when a man loses his corn on the threshing floor, it did not rain on purpose to destroy the crop, but the result was merely incidental to the raining?*

Thus, Empedocles is saying that the purpose of the rain is not to make the corn grow, nor to spoil the grain as it sits on the floor waiting to be threshed. Rather, the rain falls for other reasons altogether, that have nothing to do with the corn. Instead, the rain falls of necessity, because it must – because the rising water vapor is condensed by the cold into water, which then must fall as rain. The corn is not the cause of the rain, says Empedocles, correctly.

Empedocles is pointing out what today is called **the error of teleology**, which Empedocles did not make, but which Aristotle did.

Then Empedocles applies his disbelief in teleology to anatomy (again quoted by a contrary-minded Aristotle): *So why should it not be the same with natural organs like the teeth? Why should it not be a coincidence that the front teeth come up with an edge, suited to dividing the food, and the back ones flat and good for grinding it, without there being any design in the matter? And so with all other organs that seem to embody a purpose. In cases where a coincidence brought about such a combination as might have been arranged on purpose, the creatures, it is urged, having been suitably formed by the operation of chance, survived: otherwise they perish, and still perish* [10, 11]...

Thus, Empedocles repudiates teleological purpose, invokes chance, and then states that if the workings of chance happen to be favorable, the animal will survive. If not, it will die.

Then, Aristotle goes on to disagree with Empedocles. Aristotle wrote [10, 11]: *But it is impossible that this should really be the way of it. For all these phenomena and all natural things are either constant or normal, and this is contrary to the very meaning of luck or chance.*

So Aristotle favored the contrary idea of the constancy or immutability of animals and species. He believed that *there is purpose then, in what is, and in what happens, in Nature* [10].

Thus, the insight that purpose could be achieved by chance and preserved by natural selection, leading to survival of the fittest was evident to Empedocles, but not to Aristotle [11].

No one is perfect. Please do not misunderstand me. Aristotle was a towering genius, a one-man university for medieval Europe. For early Christianity, Aristotle was an acceptable barbarian because he believed in God, the soul, and purpose (teleology). As a biologist and philosopher, Aristotle also lent medieval Europe some much needed intellectual sophistication [10]. This is why so much of Aristotle has been saved – because he was made to order for the medieval Christian church. Ironically, scholars also think that without this disapproving quotation by Aristotle, the above-cited work of Empedocles might not have been saved.

A century before Empedocles, **Anaximander** (c. 611 – c. 547 BC) also thought that man evolved from other animals. Anaximander, who was born in Miletus and was a student of Thales, reasoned that *in the beginning, man was born from creatures of a different kind. Other creatures are soon self-supporting, but man alone needs prolonged nursing. For this reason, he would not have survived if this had been his original form* [10, 12].

Anaximander stated that before him, **the Syrians** worshipped fish as the human ancestor [10, 12]. We now know that in this respect, the Syrians were right.

What is so impressive about the understanding of Empedocles is not just that he understood the concept of evolution in the fifth century BC, but also that he grasped the concept of what Darwin called natural selection more than 2300 years later. The true story of the discovery of evolution and natural selection is almost never told in books or articles written in English. Since the present paper is about the evolution of the human heart, I also hope to set the record straight concerning the larger story of the discovery of evolution, natural selection, and survival of the fittest.

Why is an understanding of human cardiovascular evolution relevant to comprehension of congenital heart disease?

It is widely understood that pathology helps to make diagnosis more accurate, and catheter-based intervention and cardiac surgery more successful. Similarly, embryology helps to make pathology more comprehensible. Molecular genetics helps to explain the basic causes of normal and abnormal embryology and pathologic anatomy.

Similarly, it seems likely that an understanding of human cardiovascular evolution from fish to mankind [3, 9] will help to make human molecular genetics, embryology, and cardiac anatomy – both normal and abnormal – more comprehensible.

For example, fish normally have a single ventricle, which is analogous to our LV, without our RV sinus (inflow tract). Thus, fish normally have single LV [13, 14]. However, single RV [13, 14] in humans, with absence of the LV, is very different from the normal fish heart. It is sobering to realize that no animal known has ever normally had a single morphologically RV, with absence of the morphologically LV. This is a disturbing realization relative to the Norwood procedure for patients with the hypoplastic left heart syndrome.

Do fish and people with single LV (absence of the RV inflow tract) just have a first heart field, but with no (or an abnormal) second heart field? Is this why conotruncal malformations are so common in human single LV [13, 14] – remembering that the anterior heart field is part of the second heart field [13, 14]? Do patients with a Holmes heart, i.e., single LV (absent RV sinus) with normally related great arteries [15], have a normal anterior heart field within an abnormal second heart field?

Although the answers to these questions are unknown at the present time, clarification of the etiologies (molecular genetic and environmental) are important because etiologic understanding may well facilitate prediction and prevention of congenital heart disease. Evolutionary insight may well prove helpful in view of our connection with other vertebrate life forms.

At the present time, most cardiologists and cardiac surgeons do not know that the RV is only about one-third as old as the LV, and that the LV is the ancient systemic pump of the vertebrates. This evolutionary understanding helps to explain why most of human congenital heart diseases involve the RV – inflow tract, outflow tract, and septation. Much remains to be learned.

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