The Cardiovascular Keys to Air-Breathing and Permanent Land-Living in Vertebrates: the normal human embryonic aortic switch procedure produced by complete right-left asymmetry in the development of the subarterial conal free walls, and the evolution of the right ventricular sinus

Przystosowanie układu sercowo-naczyniowego kręgowców do oddychania powietrzem i stałego życia na lądzie: naturalne przemieszczenie aorty w życiu embrionalnym człowieka spowodowane całkowitą asymetrią rozwoju wolnych ścian stożków podtętniczych oraz ewolucją zatoki prawej komory

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Abstract

The subarterial conal free walls in *Homo sapiens* normally perform an embryonic aortic switch procedure by 38 to 45 days of age in utero. The right-sided subaortic conal free wall normally undergoes complete resorption. Simultaneously, the left-sided subpulmonary conal free wall grows and expands, elevating the pulmonary valve superiorly and anteriorly – above the developing right ventricle, away from the interventricular foramen. Resorption of the right-sided subaortic conal free wall permits the aortic valve to move posteriorly, inferiorly, and leftward – through the interventricular foramen to above the developing left ventricle. This asymmetric or opposite right-left development of the subarterial conal free walls results in normally related great arteries (solitus and inversus). There is only one way of doing the embryonic aortic switch right (with solitus and inversus isomers), and many ways of doing it wrong. All of the conotruncal malformations have anomalies of right-left conal free wall asymmetry. Molecular genetic evidence suggests that malformations of right-left development may be caused by one or more mutations in the Nodal cascade.

The heterotaxy syndromes, often misunderstood as malformations of bilateral symmetry (bilateral right-sidedness or bilateral left-sidedness), are also anomalies of right-left asymmetry. The other important evolutionary development was the appearance of the right ventricular sinus (inflow tract) beneath the proximal or apical part of the conus. The right

Streszczenie

Stożki podtętnicze (ich wolne ściany) u człowieka (*Homo sapiens*) zmieniają swoją pozycję (wykonują embrionalny proces przełożenia) między 38. a 45. dniem życia płodowego. Położona po stronie prawej wolna ściana stożka podaortalnego ulega resorpcji. Jednocześnie położona po stronie lewej wolna ściana stożka pod tętnicą płucną rośnie i powiększa się, podnosząc zastawkę pnia płucnego ku górze i do przodu, nad rozwijającą się komorę prawą (w oddaleniu od połączenia międzykomorowego). Jednocześnie resorpcja zlokalizowanego po stronie prawej stożka podaortalnego pozwala na przemieszczenie zastawki aortalnej ku tyłowi, dołowi i na lewo ponad otworem międzykomorowym, nad rozwijającą się komorę. Asymetryczny rozwój prawego i lewego stożka podtętniczego prowadzi do normalnej relacji dużych naczyń (w konfiguracji prawidłowej lub odwróconej). Jest tylko jeden właściwy (w konfiguracji prawidłowej i odwróconej) i wiele wadliwych sposobów przebiegu tego procesu. Wszystkie wady dotyczące okolicy stożka i pnia serca charakteryzują się zaburzeniem rozwoju asymetrii wolnej ściany stożków podtętniczych. Odkrycia genetyki molekularnej sugerują, że zaburzenia rozwoju asymetrii lewo-prawej mogą być powodowane pojedynczą lub wieloma mutacjami w kaskadzie *Nodal*. Zespoły heterotaksji, często nieprawidłowo rozumiane jako wady z obustronną symetrią (obustronna „prawostronność" lub obustronna „lewostronność"), są również nieprawidłowościami rozwoju asymetrii prawo-lewej.

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ventricular sinus is the lung pump. Hence, a double circulation – systemic and pulmonary – evolved in fully terrestrial vertebrates. The cardiovascular system is the first system that must become functional in the human embryo to permit the rapid development of multicelled animals such as ourselves. Congenital heart disease is the commonest congenital malformation in live-born humans – almost 1% (0.8%). Most human congenital heart disease consists of anomalies of one or more of the four components that make up the right ventricle. Anomalies of the left ventricle are comparatively infrequent. In our phylum Chordata, the morphologically left ventricle is at least 500 million years old. By contrast, the morphologically right ventricle is only about 180 million years old, i.e., only about 36% as old as the left ventricle. We are still having trouble with our comparatively recent cardiovascular evolutionary adaptations to air-breathing and permanent land-living: the development of the right ventricular sinus and the embryonic aortic switch. These two cardiovascular evolutionary developments helped to make possible our long terrestrial prehistory, our history, our cultures, our science, our "everything".

Key words: conotruncal malformations, anomalies of right-left asymmetry, embryonic aortic switch procedure, evolution of the left and right ventricles, air-breathing and land-living, the Nodal cascade.

Innym bardzo ważnym przystosowaniem ewolucyjnym było wykształcenie się zatoki prawej komory (droga napływu) poniżej bliższej lub szczytowej części stożka. Zatoka prawej komory jest pompą płucną. Dwa obiegi krążenia (płucne i systemowe) wykształciły się definitywnie u kręgowców lądowych. Układ sercowo-naczyniowy jest pierwszym układem, który zaczyna funkcjonować u zarodka, umożliwiając gwałtowny rozwój organizmów wielokomórkowych takich jak my. Wady wrodzone serca są najczęściej spotykanymi wadami u żywo urodzonych noworodków – w odsetku prawie 1% (0,8%). Większość z nich obejmuje jeden lub kilka z czterech elementów budujących prawą komorę serca. Wady komory lewej są stosunkowo rzadkie. W obrębie naszego podtypu – tj. kręgowców – lewa komora serca ma co najmniej 500 milionów lat. W przeciwieństwie do tego morfologicznie prawa komora liczy ok. 18 mln lat, co stanowi ok. 36% wieku komory lewej. Ciągle mamy kłopot z dostosowaniem się układu sercowo-naczyniowego do oddychania powietrzem i życia w środowisku lądowym: rozwojem prawej komory i prenatalnym procesem przemieszczenia się dużych naczyń. Te dwa mechanizmy ewolucyjne układu sercowo-naczyniowego umożliwiły naszą długą prehistorię lądową, naszą historię, naszą kulturę, naukę, nasze „wszystko".

Słowa kluczowe: wady stożkowo-pniowe, zaburzenia asymetrii prawo-lewej, embrionalny proces przełożenia wielkich pni tętniczych, ewolucja lewej i prawej komory, organizmy lądowe, kaskada *Nodal*.

The evolution of the cardiovascular system

One of the salient differences between relatively large plants and animals is that most large plants and multicelled animals have a vascular system [1, 2], but only animals have a heart [2]. In other words, only relatively large animals have a *cardio*vascular system, as opposed to a vascular system.

Why do animals have a heart? Diffusion (without a heart beat) is effective over only a few millimeters for the delivery of oxygen and metabolites and for the clearance of waste products in a rapidly growing animal embryo. This is thought to be why the cardiovascular system is the first to become functional in the human embryo. The human heart beat begins in the early D-loop stage of cardiovascular development (20 to 22 days of age in utero).

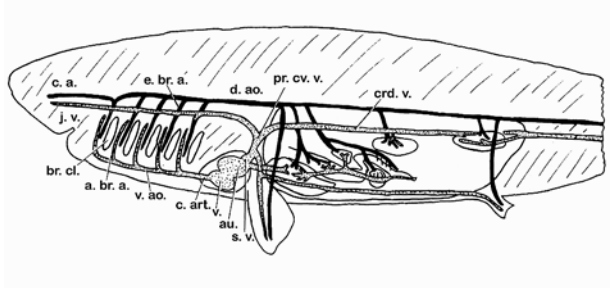

Fig. 1. Diagram of the cardiovascular system of a fish, left lateral view, head to the viewer's left, tail to the viewer's right. Vessels containing oxygenated blood black, those containing deoxygenated blood stippled. A.br.a. – afferent branchial artery; au – auricle; br. cl. – branchial clefts; c.a. – carotid artery; c. art. – conus arteriosus; crd. v. – cardinal vein; d.ao. – dorsal aorta; e.br.a. – efferent branchial artery; j.v. – jugular vein; pr. cv.v. – precaval vein; s.v. – sinus venosus; v. – ventricle; v. ao. – ventral aorta. Reproduced with permission from Robb [3].

Our remote ancestors were the fish of the Ordovician and upper Devonian periods that evolved some 500 million years ago. We humans belong to the phylum Chordata. Chordates are animals whose embryos have a notochord (back cord, Greek).

Fish have a single heart in which the ventricle pumps blood to the systemic circulation and to the organs of respiration, the gills (Fig. 1) [3].

Later in the Carboniferous period some 345 million years ago, amphibians evolved. They had lungs and could breathe air, but they did not have a right ventricle. The single ventricle of these amphibians supplied the systemic circulation and the organs of respiration – the lungs and skin. Like modern frogs, these amphibians were quasi-aquatic and quasi-terrestrial, but they had to return to the water to breed.

Some of these amphibians then evolved into the Amniotes, animals with an amniotic sac that contained a little internal "sea" of amniotic fluid in which the embryo and the fetus floated, mimicking the sea of our ancestral fish.

The amniotes then evolved into fully terrestrial reptiles. The higher reptiles such as crocodiles and alligators had both a left ventricle – the ancient chordate systemic ventricle – and a more recently evolved right ventricle

that was only partially developed in lower reptiles such as turtles, but was fully developed in the higher reptiles such as crocodiles and alligators.

Some higher reptiles then developed feathers, such as *Archaeopteryx*, evolving into birds. Other reptiles developed fur or hair, evolving into mammals.

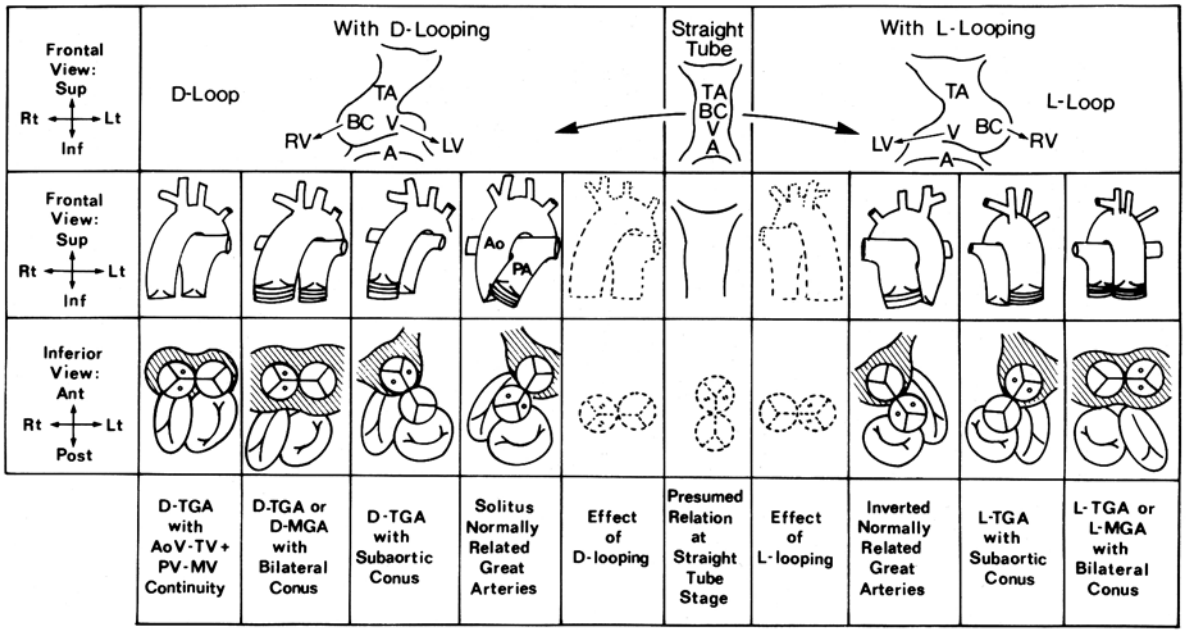

Fig. 2. The morphogenesis of normally and abnormally related great arteries with bulboventricular D-loops and L-loops. *Top row*: The cardiogenic crescent of precardiac mesoderm normally reaches the straight tube or pre-loop stage by 20 days following fertilization in humans. The truncus arteriosus (TA) is the most cephalic part of the straight tube; this is where the great arteries will develop. Beneath the TA is the bulbus cordis (BC), which will later form the conus arteriosus (infundibulum) and the morphologically right ventricle (RV). Beneath the BC is the ventricle, which will later develop into the morphologically left ventricle (LV). Beneath or caudad to the V is the atrium (A), which will develop into the morphologically right atrium (RA) and the morphologically left atrium (LA). Caudad to the A is the sinus venosus (not labeled). As time-lapse cine photomicrography shows, the cells of all of these areas are migrating toward their definitive locations. So these labels are an intentional oversimplification to indicate presumptive regions.
Between 20 and 22 days of age approximately, cardiac loop formation occurs, normally to the right forming a D-loop (*dextro* or D meaning right, Latin). D-loop formation places the BC and the developing RV to the right of the V (ventricle) and the developing LV. Hence D-looping is associated with solitus or noninverted ventricles. In D-loop ventricles, the RV is right-handed (Fig. 9) [24, 25] and the LV is left-handed. Abnormally, cardiac looping can occur in a leftward direction, forming an L-loop (*levo* or L meaning left, Latin). L-loop formation places the BC and developing RV to the left, and the V or developing LV to the right. Thus, L-looping results in ventricular inversion or mirror imagery, the L-loop RV being left-handed (Fig. 10) [24, 25] and the L-loop LV being right-handed. Chirality (handedness) (Fig. 9 and 10) [24, 25] can be very helpful in diagnosing which ventricular isomer (solitus or inversus) is present, particularly when ventricular spatial relations are unusual, as with superoinferior ventricles or crisscross atrioventricular relations. Although only the RV is diagrammed (Fig. 9 and 10), chirality applies just as well to the LV, and to both atria. Chirality is a fundamental property of matter; for example, neutrinos are left-handed and antineutrinos are right-handed [24]. We are not talking about ventricular topology; instead, we are dealing with ventricular situs (Fig. 9 and 10) [24, 25].
The second and third rows show some of the variations in the relations between the great arteries and in the development of the conus arteriosus (cross hatched), with D-loops and L-loops. The second row from the top (row 2) is shown from the front. The third row from the top (row 3) is seen from below, as in a subxiphoid 2D echocardiogram. Broken lines indicate that the ascending aorta (Ao) and the pulmonary artery (PA) are not really septated at this early stage following D-or L-looping. The aortic valve is indicated by the coronary ostia. Looping brings the future semilunar valves from a presumed anterior-posterior relationship to a side-by-side or right-left relationship.
Solitus and inversus normally related great arteries have a subpulmonary muscular conal free wall (and no subaortic conal free wall, permitting aortic-mitral fibrous continuity).
D- and L-TGA (transposition of the great arteries) have a subaortic conal free wall (and typically no subpulmonary conal free wall, permitting pulmonary-mitral fibrous continuity).
Double-outlet right ventricle (DORV) with either D- or L-malposition of the great arteries (D-MGA or L-MGA) often has a bilateral conus (subaortic and subpulmonary), permitting no semilunar-atrioventricular fibrous continuity. A bilateral conus also can be associated with TGA (D- or L-).
Bilateral absence of the subarterial conal free walls rarely can be associated with **D-TGA, with aortic-tricuspid and pulmonary-mitral fibrous continuity** (leftmost panel). When this diagram was made (1966) [5], we still had not seen **double-outlet left ventricle (DOLV)** with bilateral absence of the subarterial conus and with aortic-mitral and pulmonary-mitral fibrous continuity; this did not happen until just before 1970 [10]. This diagram is data-based, not hypothetical. Reproduced with permission from Van Praagh and Van Praagh [5].

Mammals appeared during the Jurassic period some 180 million years ago when reptiles, including dinosaurs, were the lords of the Earth.

The more recently evolved ventricle – the lung pump – became the *right* ventricle because of D-loop formation. In craniate tetrapod vertebrates, the straight heart tube normally loops or folds to the right, placing the more recently evolved lung pump to the right of the ancient systemic pump of our phylum Chordata. Consequently, in the higher reptiles, birds, and mammals, the more recently evolved pulmonary ventricle became the *right* ventricle relative to the ancient systemic pump of our phylum, which in turn became the *left* ventricle.

The embryonic aortic switch procedure

In *Homo sapiens sapiens*, the subarterial conal (infundibular) free walls normally perform an aortic switch procedure to achieve normally related great arteries by 38 to 45 days of age in utero.

How is the embryonic aortic switch normally performed? The salient developmental steps are as follows:

The cardiogenic crescent of precardiac mesoderm forms a straight heart tube that normally starts to loop to the right by 20 to 22 days of embryonic age (Fig. 2) [5]. This is also thought to be when the human heart beat begins.

D-loop formation places the truncus arteriosus (both developing great arteries) above the proximal bulbus cordis (the developing right ventricular sinus) (Fig. 2).

This is a critical point in normal cardiogenesis. If a developmental arrest occurs at this point, the result will be double-outlet right ventricle (DORV) of the Taussig-Bing type [6, 7]. So the developmental problem is: How to avoid the Taussig-Bing malformation, i.e., DORV {S,D,D} with a bilateral conus (subaortic and subpulmonary), and a subpulmonary ventricular septal defect (VSD) [6, 7]?

Normally, "Mother Nature's" answer is as follows:

1. Resorb the right-sided subaortic conal free wall (Fig. 3, not stippled) [8].
2. Grow and expand the left-sided subpulmonary conal free wall (Fig. 3, stippled) [8].

Growth and expansion of the left-sided subpulmonary conal free wall elevates the pulmonary valve superiorly and protrudes it anteriorly. This morphogenetic movement gets the pulmonary valve and the main pulmonary artery out of the way, i.e., away from the interventricular foramen or ventricular septal defect (VSD) through which the aortic valve must pass to reach the developing mitral valve and left ventricle. The superior and anterior pulmonary valve remains above the right ventricle.

Simultaneous resorption of the right-sided subaortic conal free wall makes it possible for the developing aortic valve and ascending aorta to move inferiorly, posteriorly, and leftward and to pass mostly through the interventricular foramen and to come into direct fibrous continuity with the developing mitral valve, above the left ventricle.

The final step in the normal embryonic aortic switch procedure is closure of the interventricular foramen (the VSD) at its rightmost or tricuspid valve end, typically between 38 and 45 days of age in utero.

Thus, asymmetrical (opposite) right-left development of the subarterial conal free walls results in normally related great arteries. In other words, **complete right-left asymmetry in the development of the subarterial conal free walls results in normally related great arteries**.

When the conotruncus (infundibulum and great arteries) is (are) inverted, the same complete right-left asymmetry in the development of the subarterial conal free walls occurs, but in mirror image, to result in inverted normally related great arteries (Fig. 3, right). In other words, **there is only one way of doing the embryonic aortic switch procedure right, i.e., only one successful mechanism, with two isomers (solitus and inversus normally related great arteries).**

There are many ways of doing the embryonic aortic switch procedure wrong, and they all involve anomalies of right-left asymmetry in the development of the subarterial conal free walls:

Transposition of the great arteries

If the subarterial conal free walls develop asymmetrically, but in a way that is the opposite of the normal right-left asymmetry, then transposition of the great arteries (TGA) results (Fig. 2 and 3):

1. Expansile growth of the right-sided subaortic conal free wall elevates the aortic valve and the ascending aorta superiorly and protrudes them anteriorly above the anterior right ventricle (RV) (Fig. 3).
2. Resorption of the left-sided subpulmonary conal free wall permits the pulmonary valve and the main pulmonary artery to move inferiorly, posteriorly, and leftward. The pulmonary valve passes through the interventricular foramen, above the left ventricle (LV) and into direct fibrous continuity with the developing mitral valve.

Thus, an embryonic arterial switch procedure is performed, but the wrong great artery is switched into the LV: the main pulmonary artery, instead of the ascending aorta. Why did this happen? We think that the answer is: because of the anomaly in right-left asymmetry of the development of the subarterial conal free walls that is the opposite of normal:

1. the right-sided subaortic conal free wall grows and expands, instead of undergoing normal complete resorption; and
2. the left-sided subpulmonary conal free wall undergoes resorption, instead of normal growth and expansion.

Typical D-TGA results from asymmetrical right-left subarterial conal free wall development that is the opposite of normal, i.e., the opposite of what normally happens with solitus normally related great arteries; and typical L-TGA results from asymmetrical right-left subarterial conal free wall development that is the opposite of what happens with inverted normally related great arteries (Fig. 2 and 3). It is understood that L-TGA occurs both with discordant L-loop ventricles, as in physiologically corrected TGA {S,L,L}, and with concordant L-loop ventricles, as in physiologically uncorrected TGA {I,L,L}.

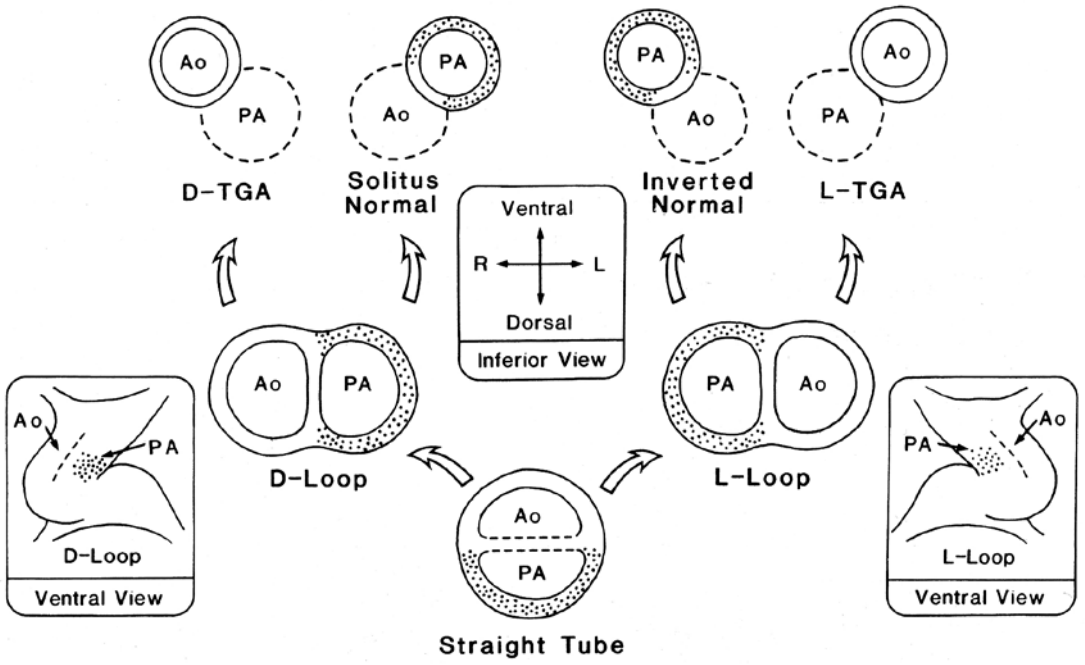

Fig. 3. The morphogenesis of normally related great arteries (NRGA) versus that of transposition of the great arteries (TGA).
The morphogenesis of the right-left subarterial conal free walls in TGA is the opposite of normal. Let us consider what happens with a D-loop first (left half of the diagram). With **solitus NRGA**, following D-loop formation, the left-sided subpulmonary conal free wall in the lesser curvature of the D-loop (stipples) grows and expands, carrying the pulmonary valve and the pulmonary artery (PA) superiorly and anteriorly – away from the interventricular foramen and above the developing right ventricle (RV). Simultaneously, the subaortic conal free wall on the greater curvature of the ventricular D-loop (no stipples) undergoes resorption, probably by apoptosis (programmed cell death), permitting the aortic valve and the ascending aorta (Ao) to move inferiorly, posteriorly, and leftward. The movements of the pulmonary valve and of the aortic valve are reciprocals, i.e., the opposites of each other. The aortic valve passes through the interventricular foramen (IVF) from above the RV to above the developing left ventricle (LV). Resorption of the subaortic conal free wall (broken circular line) facilitates aortic-mitral fibrous continuity. The IVF then is closed at its rightmost or tricuspid valve end, typically between 38 and 45 days of age in utero, thereby completing *the normal embryonic aortic switch process*.
In D-TGA, following D-loop formation, the right-sided subaortic conal free wall on the greater curvature of the D-loop (no stipples) undergoes expansile growth, elevating the aortic valve and the ascending Ao superiorly and protruding it anteriorly, above the RV. Simultaneously and reciprocally, the left-sided subpulmonary conal free wall in the lesser curvature of the D-loop (stipples) undergoes resorption, causing the pulmonary valve and the PA to move inferiorly, posteriorly, and to the left and to pass through the IVF from above the RV to above the LV, and typically to come into fibrous continuity with the developing mitral valve via the intervalvar fibrosa. Thus, *the wrong embryonic arterial switch procedure* has been performed: the PA has been switched into the LV (instead of the Ao).
When a ventricular L-loop occurs (the right half of the diagram), inverted NRGA and L-TGA can occur. The mechanisms are the same as with D-loop ventricles, except that they are inverted or in mirror image. Reproduced with permission from Van Praagh [8].

Double-outlet right ventricle

Following D-loop or L-loop formation, if both subarterial conal free walls (subaortic and subpulmonary) undergo growth and expansion, and if neither undergoes resorption, then double-outlet right ventricle typically occurs, with no semilunar-atrioventricular fibrous continuity (Fig. 2), as in the Taussig-Bing malformation [7, 8] mentioned heretofore. In DORV, no embryonic arterial switch is performed. A bilateral (subaortic and subpulmonary) conus is another kind of anomaly of normal right-left asymmetry of subarterial conal free wall development.

Double-outlet left ventricle

Rarely, both the subaortic and the subpulmonary parts of the conus can undergo resorption (or may fail to form), resulting in double-outlet left ventricle (DOLV) with aortic-mitral and pulmonary-mitral direct fibrous continuity [9], and the ventricular septum can even be intact [10].

Ventriculo-arterial alignments and connections

Ventriculo-arterial (VA) alignment means what opens into what, i.e., which ventricular sinus (inflow tract) ejects into which great artery or arteries. TGA, DORV, and DOLV are all different anatomic types of VA alignment (or malalignment).

VA connection means what anatomic type of conal connector connects the ventricular sinuses with the great arteries (Fig. 4) [11]: Is it a *subpulmonary conus*, typical of normally related great arteries (Fig. 4) [11]? Or is it a *subaortic conus*, typical of TGA (Fig. 4) [11]? Or is it a *bilateral conus* (subaortic and subpulmonary), typical of

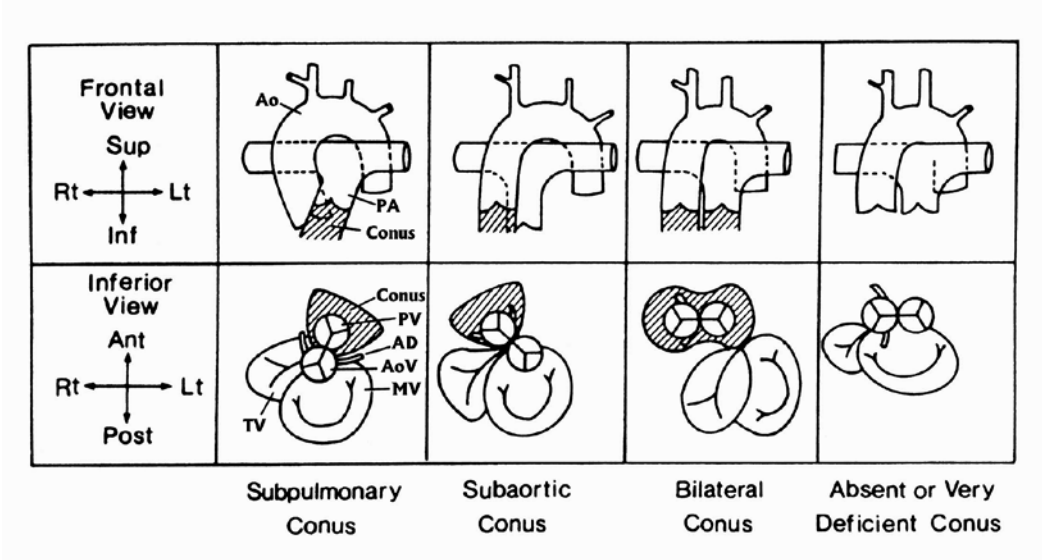

Fig. 4. The four main anatomic types of subarterial conus arteriosus (infundibulum) associated with D-loop ventricles. *Upper row*, frontal view. *Lower row*, inferior view as in a subxiphoid two-dimensional echocardiogram.
(1) Subpulmonary. Solitus (and inversus) normally related great arteries (NRGA) have a subpulmonary conus. The subpulmonary conal free wall normally is left-sided, well developed and well expanded (cross-hatching indicates conal myocardium). The pulmonary valve (PV) is anterior, superior, and to the left of the aortic valve (AoV). Relative to the PV, the AoV is posterior, inferior, and right-sided. The subaortic conal free wall myocardium has undergone normal resorption, permitting direct fibrous continuity between the AoV and the mitral valve (MV), and also permitting tenuous direct fibrous continuity between the AoV and the tricuspid valve (TV) via the pars membranacea septi (membranous septum). The left coronary artery gives rise to the anterior descending (AD) coronary artery. The right coronary artery is diagrammed but not labeled. Thus, solitus NRGA are characterized by total asymmetry of left-right subarterial conal free wall development, the left-sided subpulmonary conal free wall grows and expands, whereas the right-sided subaortic conal free wall undergoes complete resorption. Underdevelopment of the subpulmonary conus is associated with tetralogy of Fallot [26] and with truncus arteriosus [31-33].
(2) Subaortic. Transposition of the great arteries (TGA), both D- and L-, is characterized by right-left subarterial conal free wall development that is the opposite of normal. In typical D-TGA, the right-sided subaortic conal free wall grows and expands (this is the opposite of normal development), and the left-sided subpulmonary conal free wall undergoes resorption (this too is the opposite of normal development). The well developed right-sided subaortic conus elevates the aortic valve superiorly above the right ventricle (RV) and prevents direct fibrous continuity between the aortic valve and the atrioventricular valves. Resorption of the subpulmonary conal free wall facilitates direct fibrous continuity between the pulmonary and the mitral valves. Continuity between the posterior, inferior, and left-sided pulmonary valve and the mitral valve aligns the pulmonary artery with the left ventricle.
(3) Bilateral. When both the left-sided subpulmonary conal free wall and the right-sided subaortic conal free wall grow and expand, i.e., when neither subarterial conal free wall undergoes resorption, then a bilateral (subpulmonary and subaortic) conus results. Both semilunar valves and great arteries are elevated superiorly above the RV, and there is no semilunar-atrioventricular fibrous continuity. A well expanded bilateral conus can result in double-outlet right ventricle (DORV) of the Taussig-Bing type [6, 7]. Or the ventriculo-arterial alignments can be those of D-TGA with a bilateral conus and hence no semilunar-atrioventricular fibrous continuity (Fig. 2, second panel from the left).
(4) Absent or very deficient. Rarely, the subarterial conal free walls can display right-left absence or marked deficiency. The ventriculo-arterial alignments can be those of double-outlet left ventricle (DOLV) [9, 10] or of D-TGA (Fig. 2, leftmost panel).
Note: All of the conotruncal anomalies are associated with malformations in the development of right-left asymmetry of the subarterial conal free walls, as diagrammed above. These anomalies in the development of right-left asymmetry appear to explain the *morphogenesis* of the abnormal ventriculo-arterial alignments. The next challenge appears to be to elucidate the *etiologies* (the basic causes, genetic or other) underlying the abnormal morphogenesis (please see Discussion). Reproduced with permission from Van Praagh [11].

DORV (Fig. 4) [11]? Or is it an *absent or very deficient conus* (neither subaortic nor subpulmonary), that rarely can occur with DOLV (Fig. 4) [11]?

Although the anatomic types of subarterial conal free walls are very important determinants of VA alignments, they are not the only important developmental factors. *Anatomically corrected malposition of the great arteries* exemplifies this fact (Fig. 5, row 6) [12]. In anatomically corrected malposition (ACM), the ventricles loop in one direction (say to the right), and the conotruncus twists in the opposite direction (to the left). The result of these opposite right-left morphogenetic movements is ACM {S,D,L} (Fig. 5, row 6, column 1) [12]. The great arteries are very malpositioned (aortic valve anterior and to the left of the pulmonary valve, i.e., L-malposition of the great arteries). Nonetheless, each malpositioned great artery is located above the morphologically appropriate ventricle. In ACM {S,D,L}, the L-malpositioned aorta (Ao) is above the morphologically left ventricle (LV) and the malpositioned pulmonary artery (PA) is located above the morphologically right ventricle (RV). This is why these anomalies are known as *anatomically corrected malpositions* of the great arteries. Each malpositioned great artery is nonetheless above the

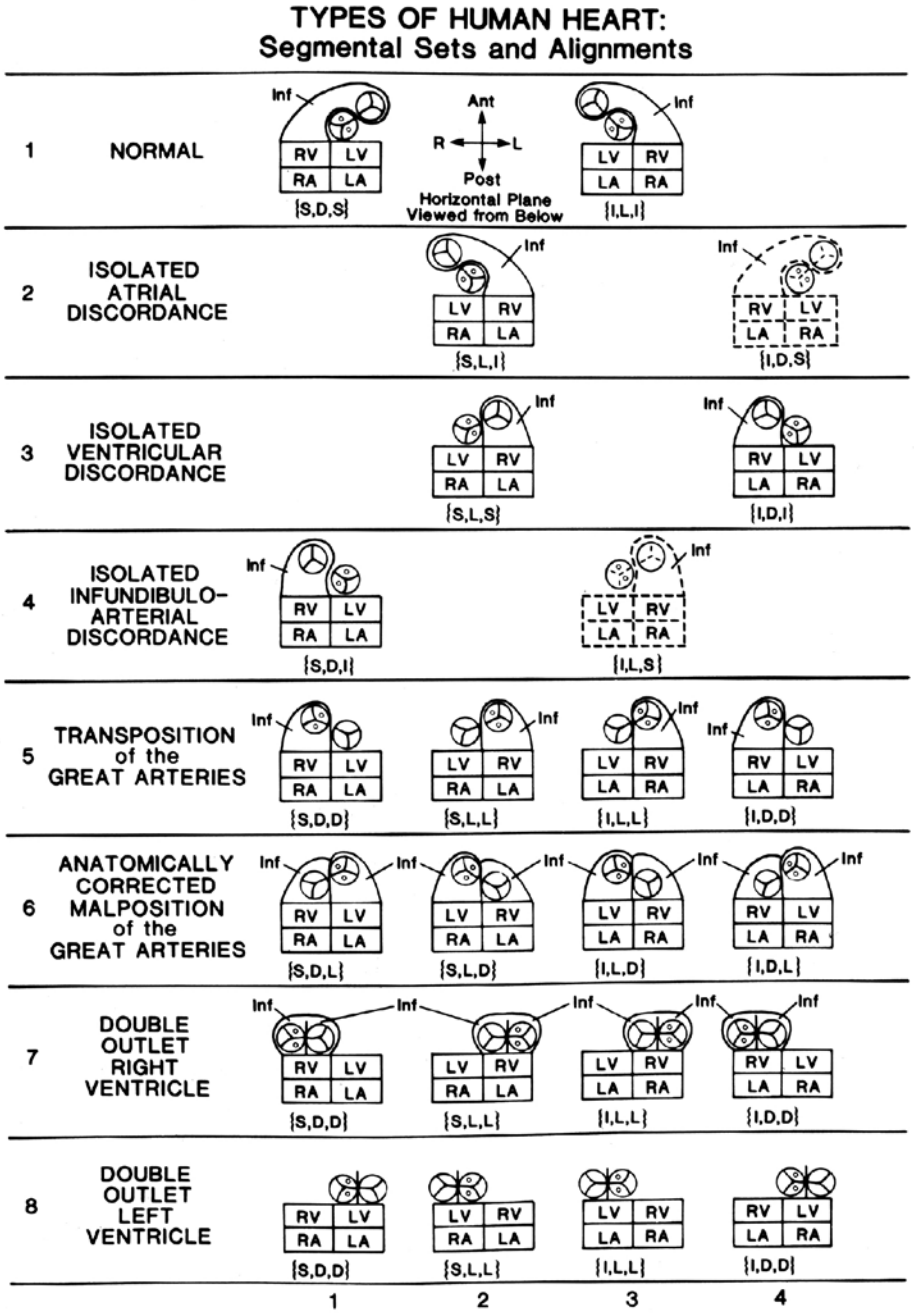

Fig. 5. Types of human heart: segmental sets and alignments. Heart diagrams are viewed from below, similar to a subxiphoid two-dimensional echocardiogram. Hearts depicted in broken lines had not been documented, to our knowledge, when this diagram was made (1988) [12]. The aortic valve is indicated by the presence of coronary ostia, the pulmonary valve by the lack of coronary ostia. Braces {} mean "the set or combination of."

The columns are arranged in terms of atrioventricular (AV) concordance or discordance. *Column 1* has AV concordance with visceroatrial situs solitus {S,-,-} and D-loop ventricles {S,D,-}. *Column 3* has AV concordance in visceroatrial situs inversus {I,-,-} with L-loop ventricles {I,L,-}. *Columns 2 and 4* have AV discordance. *Column 2* has AV discordance in visceroatrial situs solitus {S,-,-} with L-loop ventricles {S,L,-}. *Column 4* has AV discordance in visceroatrial situs inversus {I,-,-} with D-loop ventricles {I,D,-}. Visceroatrial situs ambiguus {A,-,-} with the heterotaxy syndromes is omitted for simplicity.

The rows are organized in terms of the types of ventriculo-arterial (VA) alignment. *Rows 1 to 4* have normal VA alignments, either situs normally related great arteries {-,-,S} or inversus normally related great arteries {-,-,I}. *Row 5* presents some of the anatomic types of transposition of the great arteries (TGA), either D-TGA, i.e., TGA {-,-,D} or L-TGA, i.e., TGA {-,-,L}. A-TGA, i.e., TGA {-,-,A} in which the transposed aortic valve is directly anterior to the transposed pulmonary valve is omitted. Anatomically corrected malposition of the great arteries (ACM) is presented in *row 6*. Some of the anatomic types of double-outlet right ventricle (DORV) are shown in *row 7*. *Row 8* depicts some of the anatomic types of double-outlet left ventricle (DOLV). Ant, anterior; Inf, infundibulum; L, left; LA, morphologically left atrium; LV, morphologically left ventricle; Post, posterior; R, right; RA, morphologically right atrium; RV, morphologically right ventricle. Reproduced with permission from Foran and colleagues [12].

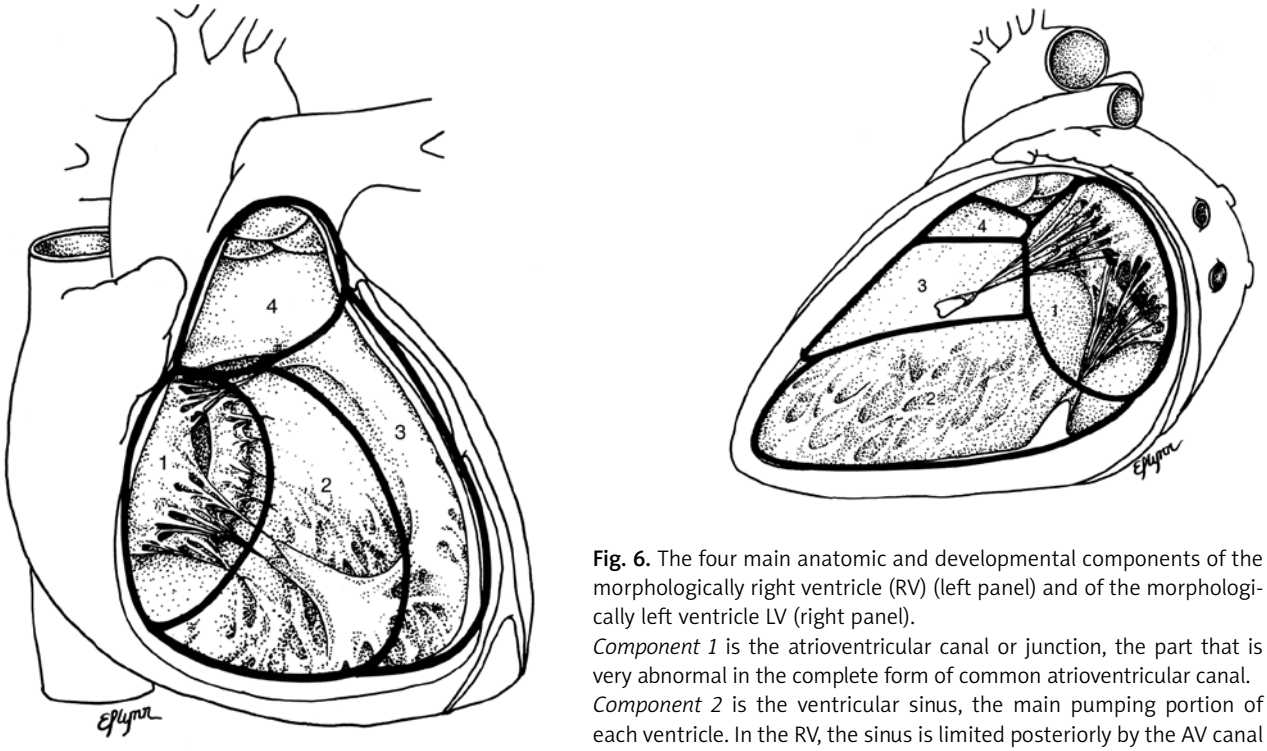

Fig. 6. The four main anatomic and developmental components of the morphologically right ventricle (RV) (left panel) and of the morphologically left ventricle LV (right panel).
Component 1 is the atrioventricular canal or junction, the part that is very abnormal in the complete form of common atrioventricular canal.
Component 2 is the ventricular sinus, the main pumping portion of each ventricle. In the RV, the sinus is limited posteriorly by the AV canal component, and the sinus is limited anteriorly and inferiorly by the septal band (component 3) and the moderator band. The RV sinus is limited superiorly by the inferior rim of the conal (infundibular) septum (*component 4*). The RV sinus is limited laterally and superiorly by the parietal band (not shown).
Component 3 of the RV is the septal band. This is the proximal or apical part of the conus arteriosus, that extends via the moderator band to the anterior papillary muscle of the RV and then on to the RV free wall. The right bundle branch of the atrioventricular conduction system runs down the septal band, close to its inferior margin, and then it crosses on the moderator band to the anterior papillary muscle of the RV and continues on laterally to the RV free wall where the right bundle arborizes, forming the Purkinje network.
In double-chambered RV (or anomalous muscle bundles of the RV), a ring of conal myocardium forms a mid-RV obstruction. A moderator-band-like structure takes off abnormally high from the septal band, usually constituting the main component of the mid RV obstruction. This obstructive conal ring consists of the septal band, the moderator-band-like structure, the inferior rim of the conal septum, and the parietal band. The obstructive conal ring in double-chambered RV clearly demonstrates what is the RV sinus (the upstream RV chamber) and what is the conus (the conal ring and the downstream chamber).
The septal band (*component 3*) is the proximal or apical part of the conus which may be regarded as the "mother" of the RV sinus in the sense that the RV sinus always pouches out or evaginates during normal cardiogenesis just beneath the septal band. The septal band and RV sinus never separate or dissociate.
The distal or subarterial part of the conus is *component 4*.
The RV inflow tract consists of *components 1 and 2*. The RV outflow tract consists of *components 3 and 4*.
In the LV (right panel), note that the left ventricular septal surface of component 2 is finely trabeculated. *Component 3* as seen from within the LV is smooth (nontrabeculated) and often can be seen carrying the left bundle branches of the conduction system. Thus, *component 3* is noteworthy as the bearer of the conduction system bilaterally. *Component 4* – the distal conal septum – is much less prominent from the LV aspect than from the RV aspect.
An understanding of the four main developmental and anatomic components that together make up the definitive RV and LV can be very helpful diagnostically and surgically. **For example, this understanding explains why ventricular septal defects (VSDs) are located where they are.** VSDs occur at the junctions between the various ventricular component parts. Components can also be hypoplastic or absent.
This paper is mostly about the evolution, embryology, and anatomy of the free wall (not the septal) parts of *component 4*, and about the evolution, embryology, and anatomy of the RV sinus that normally occurs immediately beneath *component 3*. *Component 3* is the proximal or apical part of the conus arteriosus. Anatomically, *components 3 and 4* normally make up the outflow tracts of both ventricles.
Ontogenetically, *component 4* normally does the embryonic aortic switch procedure by or before 38 to 45 days of age in utero.
Thus, the conus arteriosus and the RV sinus are responsible for the phylogenesis (evolution) and the ontogenesis (embryology) of the double circulation (systemic and pulmonary) that made possible air-breathing and permanent land-living for craniate vertebrates, including mammals. Reproduced with permission from Van Praagh and colleagues [16].

anatomically correct ventricle; it is in this sense that the malposition of the great arteries is *anatomically* corrected. VA concordance is present: LV to Ao, and RV to PA (Fig. 5, row 6) [12].

Note that ACM may, or may not be *physiologically* corrected. ACM {S,D,L} (Fig. 5, row 6, column 1) is physiologically corrected because there is atrioventricular (AV) concordance and VA concordance. However, ACM {S,L,D}

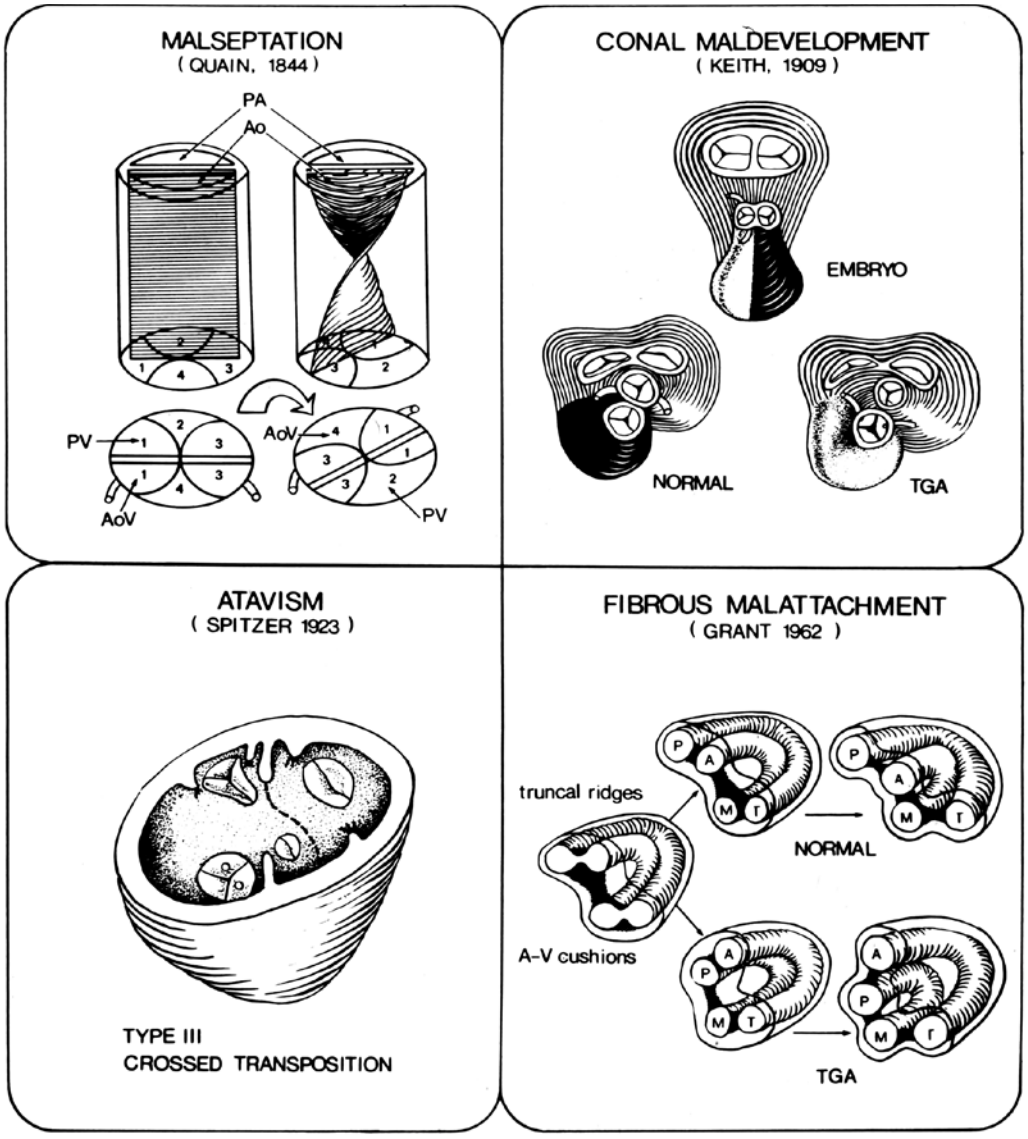

Fig. 7. The four main theories concerning the morphogenesis of transposition of the great arteries:
1. Malseptation of the great arteries. Straight, as opposed to the normally spiral development of the aortopulmonary septum was proposed by Quain [19] in 1844 as the morphogenetic basis of TGA, a concept that was subsequently adopted by many authors. Ao, aorta; AoV, aortic valve; PA, pulmonary artery; and PV, pulmonary valve. The semilunar valve leaflets are designated by conventional numbers, which permit precise leaflet identifications that are independent of spatial relations. There are four septal leaflets that are adjacent to the aortopulmonary septum: aortic and pulmonary leaflets 1, and aortic and pulmonary leaflets 3. There are two nonseptal leaflets that are remote from the aortopulmonary septum: aortic leaflet 4 and pulmonary leaflet 2.
We think that the straight aortopulmonary septum hypothesis is wrong for several reasons:

1. The free walls of the great arteries are just as positionally abnormal as is the aortopulmonary septum, this being indicated by the very abnormal locations of the coronary ostia in TGA. The coronary arteries are the first branches of the aortic free wall, and hence the locations of the coronary ostia are good markers of the development of the aortic free wall, just above the aortic valve.
2. Definite evidence of abnormality of the aortopulmonary septum *per se* is lacking. For example aortopulmonary septal defect (AP window) is vanishingly rare in TGA.
3. The straight aortopulmonary septum hypothesis cannot explain the variations in semilunar valve heights in TGA and other conotruncal anomalies, whereas the conal free wall maldevelopment hypothesis can. Proponents of the straight AP septum hypothesis claim (erroneously) that the conus is part of the RV, but not part of the LV; hence, they say, the transposed aortic valve is high (because the subaortic conus is part of the RV), whereas the transposed pulmonary valve is low (because there is no subpulmonary conus, the conus not being part of the LV). However, in anatomically corrected malposition of the great arteries and in some forms of double-outlet left ventricle (Fig. 5), the conus arteriosus is mostly or entirely above the LV, proving that the conus is not an intrinsic, inseparable part of the RV.
4. There is a valid explanation of why the normal aortopulmonary septum looks spiral, whereas the AP septum in TGA is relatively straight or nonspiral: Normally, following cardiac loop formation to the right, the right-sided subaortic conal free wall resorbs and the left-sided subpulmonary conal free wall grows and expands, performing the normal embryonic aortic switch. Post switch, the pulmo-

nary valve normally is anterior, superior, and to the left relative to the aortic valve that normally is posterior, inferior, and to the right. Distally, at the aortic and pulmonary bifurcation, the aorta (arch 4) is anterior and superior relative to the pulmonary bifurcation (arch 6) which is posterior and inferior. Normally, therefore, the great arteries (AP septum and both great arterial free walls) must *untwist* through approximately 150 degrees in a leftward or clockwise direction as viewed from the front because the AP septum ends distally at the junction between aortic arch 4 and pulmonary arches 6.

In typical TGA, by contrast, the fibroelastic great arteries have much less clockwise untwisting to do as they proceed from the semilunar valves proximally to the fixed aortopulmonary relationship distally – *fixed* because aortic arches 4 are anterior and superior relative to pulmonary arches 6.

In typical TGA, *reversed* right-left asymmetry in subarterial conal free wall development (growth of the right-sided subaortic conal free wall, and resorption of the left-sided subpulmonary free wall) results in an anterior aortic valve and a posterior pulmonary valve. Hence, both proximally at the semilunar valves and distally at the aortic arch 4/pulmonary arch 6 junction, the aorta typically is anterior and the pulmonary artery is posterior. So, in typical TGA, the AP septum has little clockwise untwisting to do, and consequently appears relatively straight, or parallel, or nonspiral.

Consequently, the relatively straight or nonspiral AP septum in typical TGA is regarded as one of the effects of abnormal subarterial conal free wall development, not as the morphogenetic cause of TGA. Many modern developmental investigators still do not understand that the great arteries *per se* are normal in almost all of the conotruncal malformations (except for truncus arteriosus)

2. Conal maldevelopment. Keith [20] proposed in 1909 that TGA results from persistence and development of the subaortic part of the conus (white) and involution of the subpulmonary part of the conus (black). To our knowledge, Keith was the first to understand the morphogenesis of TGA. Note, however, that Keith thought the normal semilunar relationship is the pulmonary valve anterior, superior, and to the *right* of the aortic valve, a frequent preangiocardiographic error.

3. Phylogenetic or atavistic hypothesis. In 1923, Spitzer [21, 22] proposed that TGA results from phylogenetic regression or atavism in our phylum Chordata – reverse evolution back to the stage that is normally found in higher reptiles such as alligators and crocodiles. The hypothesis is that the transposed aorta in human TGA represents the reopened right ventricular aorta of the higher reptiles, plus closure of the normal reptilian and mammalian left ventricular aorta. Spitzer shows the transposed pulmonary artery originating above right ventricular myocardium, i.e., to the right of the anterior part of the true interventricular septum that he says has disappeared (dashed line). He asserts that the apparent anterior portion of the ventricular septum is instead a hugely hypertrophied crista supraventricularis. The flaw in Spitzer's hypothesis is that the myocardium of the anteroseptal part of the left-sided ventricle beneath the transposed pulmonary artery is morphologically *left* ventricular myocardium (not morphologically right ventricular myocardium, as his diagram shows). The problem for any atavistic hypothesis that seeks to explain the morphogenesis of human TGA by regression back to an earlier (pre-mammalian) stage is that there is no animal known in which the pulmonary artery normally arises above the morphologically *left* ventricle, as does occur in human TGA. Thus, Spitzer's hypothesis [21, 22], that mesmerized a generation of English-speaking investigators, is not consistent with the morphologic anatomic findings beneath the transposed human pulmonary artery, and is also not consistent with the anatomic findings in pre-mammalian animals [2, 3].

4. Fibrous malattachment. In 1962, Grant [23] proposed that normally, there is a fibrous tract of low growth potential (in black) between the mitral valve (M) and the aortic valve (A), accounting for the aortic-mitral fibrous continuity of normally related great arteries. In TGA, however, this fibrous tract has shifted to the left (in black), between the mitral valve (M) and the pulmonary valve (P), resulting in pulmonary-mitral fibrous continuity of typical TGA. The semilunar valve that is *not* tethered by this fibrous tract to the mitral valve protrudes anteriorly and arises above the anterior right ventricle. With normally related great arteries and aortic-mitral fibrous continuity, the aorta drains the left ventricle and the pulmonary artery drains the right ventricle. But with TGA and pulmonary-mitral fibrous continuity, the pulmonary artery drains the left ventricle and the aorta drains the right ventricle.

Grant's hypothesis [23] we considered very helpful because it focused attention on the presence or absence of semilunar valve – mitral valve fibrous continuity. This concept is almost the flip side (the opposite) of the conal development hypothesis. We prefer the conal development concept (growth or resorption of the subarterial conal free walls) because TGA can occur *without* pulmonary-mitral fibrous continuity when there is a small, and often obstructive subpulmonary muscular conus. We regard the presence or absence of semilunar (aortic or pulmonary) – mitral fibrous continuity not as a primary morphogenetic mechanism, but rather as a secondary effect of subarterial conal free wall development – which may be growth, or resorption, of variable degrees. The conal free wall development hypothesis can also explain DORV (with a bilateral – subaortic and subpulmonary – conus), and DOLV (that rarely can have a bilaterally absent conus beneath both semilunar valves).

Thus, TGA is a conal malformation, like tetralogy of Fallot, not a conotruncal malformation – because the great arteries *per se* are normal in TGA. The hollow muscular cones immediately beneath the great arteries, the **coni arteriosi**, with developed or resorbed free walls, largely determine the ventriculo-arterial alignments (Fig. 5). Reproduced with permission from Van Praagh [18].

(Fig. 5, row 6, column 2) is physiologically uncorrected because of the presence of one intersegmental discordance: AV discordance (RA to LV and LA to RV) with VA concordance.

ACM is one of the remaining indications for an atrial switch procedure surgically. For example, in ACM {S,L,D}, one would not want to do an arterial switch operation because VA concordance is present, by definition, in ACM.

It is also noteworthy that VA concordance and normally related great arteries are *not* synonymous. With normally related great arteries of all anatomic types (Fig. 5, rows 1 to 4, inclusive), a normal subpulmonary type of conus is present. However, in all anatomic types of ACM (Fig. 5, row 6), an abnormal anatomic type of conal connector is present, either a bilateral conus or a subaortic conus (Fig. 4 and 5).

Accurately speaking, the ventricles (i.e., the ventricular sinuses) do not connect directly (tissue-to-tissue) with the great arteries because of the interposition of the subarterial *conus arteriosus* (arterial cone, Latin) or *infundibulum* (funnel, Latin).

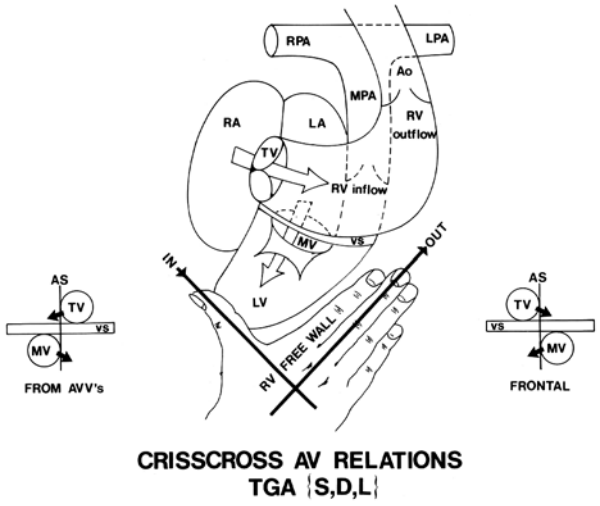

Fig. 8. The D-loop (solitus or noninverted) morphologically right ventricle is right-handed. Figuratively speaking, the thumb of the right hand goes through the tricuspid valve (TV) and indicates the location of the morphologically right ventricular (RV) inflow tract (IN). The fingers of the right hand go into the RV outflow tract (OUT). The palm of only the right hand faces the RV septal surface, and the dorsum of only the right hand is adjacent to the RV free wall surface. Handedness or chirality makes possible the diagnosis of the type of ventricular situs, i.e., D-loop or solitus (noninverted) ventricles versus L-loop or inversus (mirror-image) ventricles when the conventional definitions of noninversion and inversion relative to the sagittal plane break down, as in this case.
The patient illustrated in this diagram had superoinferior ventricles with a superior RV, an inferior morphologically left ventricle (LV), and an approximately horizontal ventricular septum (VS). Crisscross atrioventricular (AV) relations were also present: note the approximately 90-degree angle between the right atrial (RA)-to-RV inflow tract (solid white arrow) and the left atrial (LA)-to-LV inflow tract through the mitral valve (MV) (broken white arrow).
Both ventricles were bilateral – right-sided and left-sided – which is why the conventional definitions of ventricular noninversion and inversion did not apply. The RV began superiorly on the right beneath the TV and then proceeded leftward and was mostly left-sided. The LV began inferiorly on the left beneath the MV and then proceeded rightward and was mostly right-sided.
When viewed from the front in short-axis projection, i.e., from the echocardiographic perspective (FRONTAL), the vertical atrial septum (AS) and the horizontal ventricular septum (VS) were at an angle of approximately 90º to each other, as is characteristic of superoinferior ventricles. The TV was superior and to the *right* relative to the MV that was inferior and to the left. The fact that the RV was right-handed indicates that D-loop (solitus or noninverted) ventricles were present. This diagnosis was confirmed by the presence of concordant AV alignments in association with solitus atria: RA opened through the TV into the RV, and LA opened through the MV into the LV. The diagnosis of D-loop (or solitus) ventricles was also confirmed by the spatial relations of the AV valves: **Whenever the TV is to the** *right* **of the MV, a ventricular** *D*-loop is present. (I am aware of no exception to the latter statement.) The black arrows indicated the crisscross vectors of the AV inflow tracts, blood flow through the TV having gone leftward, and blood flow through the MV having gone rightward. When viewed from the atria, i.e., from the surgeon's perspective (FROM AVVs) (AVVs – AV valves), again the TV was seen to be superior and to the *right* relative to the MV, indicating the presence of *D*-loop (solitus) ventricles.
The aortic valve was anterior, superior, and to the *left* relative to the pulmonary valve that was posterior, inferior, and to the right. There was ventriculo-arterial (VA) alignment discordance: RV to ascending aorta (Ao), and LV to main pulmonary artery (MPA). (LPA, left pulmonary artery; and RPA, right pulmonary artery). Thus, transposition of the great arteries (TGA) was present.
Hence, the segmental anatomic diagnosis was TGA {S,D,L} with AV concordance and VA discordance, with superoinferior ventricles and crisscross AV relations. The presence of L-TGA might suggest erroneously that physiologically corrected TGA was present. But since there was only *one* intersegmental alignment discordance at the VA level (not two), this indicates that physiologically *un*corrected (or "complete") TGA was present.
Why was *L*-TGA present? Because these solitus or noninverted ventricles were very malpositioned. Instead of looping to the right following the establishment of concordant AV alignments, as D-loop ventricles almost always do, instead, these solitus ventricles folded to the *left, i.e., in the wrong direction*. This abnormal leftward folding of D-loop ventricles explains some of the unusual features of the case: why *L*-TGA is present; and why the ventricular septum is horizontal, with superoinferior ventricles.
Why crisscross AV relations? Because the RV sinus (inflow tract) was underdeveloped. This is why there is no RV sinus apex down close to the LV sinus apex. Consequently, the blood flowing through the tricuspid valve went unusually directly toward the transposed aortic valve. Now take this diagram and rotate it 90º counterclockwise so that the ventricular septum is normally vertical. Not only does the condition known as superoinferior ventricles disappear, L-TGA becomes the more familiar *D*-TGA in association with D-loop ventricles. Reproduced with permission from Van Praagh [15].

The infundibulum or conus arteriosus is not a ventricle. For example, in single LV with an infundibular outlet chamber and solitus normally related great arteries (the Holmes heart) [13], the reason that typically there is double-inlet left ventricle is that there is no right ventricle (i.e., RV sinus) for the tricuspid valve to open into. The LV sinus or inflow tract is single (meaning unpaired) because the RV sinus is absent.

The term *conus arteriosus* correctly indicates that the conus or infundibulum is part of the great arteries, not part of the ventricles. The conus arteriosus is how the great arteries connect with the underlying ventricular sinuses (the ventricular pumping chambers) and with the AV canal and the AV valve(s).

Segmental anatomy

There are five diagnostically and surgically important cardiac segments [14, 15].

The three main cardiac segments are: the atria, the ventricles, and the great arteries (Fig. 5).

The two connecting cardiac segments are: the AV canal or junction, and the conus arteriosus or infundibulum.

Comparative anatomy is illuminating concerning the nature of the conus arteriosus. For example, in sharks that are ancient cartilaginous fish (*Chondrichthyes*), the conus arteriosus extends from the heart in a rostral or cephalic direction all the way forward, up to the gill arches. Looking at the heart of the shark, one understands why the comparative anatomists and embryologists have named this structure the *conus arteriosus* – because it coats the ventral aorta in a muscular cone from the heart cephalically to the gill arches (Fig. 1).

In mammals, the conus arteriosus has receded caudally to a subsemilunar valvar position, leaving the great arteries fibroelastic – rather than encased in conus arteriosus musculature. This caudal recession of the conus arteriosus musculature, which leaves the mammalian great arteries fibroelastic, may facilitate the normal *untwisting* of the great arteries as they proceed from the heart cephalically to the aortic arch 4/pulmonary arch 6 junction distally. Here, the aortic arch is ventral and cephalad to the pulmonary artery bifurcation because these are the spatial relations between aortic arch 4 and pulmonary arch 6. In this developmental and evolutionary sense, the conus arteriosus "belongs to" the great arteries, not to the ventricles.

The ventricles and the great arteries *are connected* in various ways by the conus arteriosus (Fig. 5). Note the passive voice of the verb (italicized). It is not anatomically accurate to say that the ventricles *connect* with the great arteries in various ways (note the active voice of the verb) because the conal connector separates the ventricular sinuses from the great arteries – a fact of enormous developmental importance (Fig. 3 to 5) [12].

To summarize these important points, the development of the free walls of the subarterial conal connector largely determines the type of ventriculo-arterial alignment that results (Fig. 2 to 4). There is only one way of doing the embryonic aortic switch right, i.e., only one successful mechanism, with two normal isomers – solitus and inversus (Fig. 5). There are many ways of doing the developmental arterial switch wrong, and they all involve anomalies of right-left asymmetry in the development of the subarterial free walls of the conus arteriosus.

Development of the RV sinus: the lung pump

There are two parts to the conus arteriosus (infundibulum) (Fig. 6) [16]:

1. **The distal or subarterial part of the conus** from the right ventricular viewpoint (Fig. 6 left, component 4) [16] consists of the distal (subarterial) conal septum, the parietal band, and the subpulmonary conal free wall myocardium (in a heart with normally related great arteries).

From the left ventricular viewpoint in a heart with normally related great arteries (Fig. 6 right) [16], a small amount of the distal conal septum can be seen beneath the aortic valve (Fig. 6 right, component 4) [16]. The subaortic conal free wall has undergone resorption, facilitating normal aortic-mitral direct fibrous continuity (Fig. 6 right) [16].

The distal part of the conus is the part that is involved in conotruncal malformations (Fig. 5). More specifically, it is the subarterial conal *free walls* that are abnormal in the conotruncal malformations (Fig. 4).

2. **The proximal or apical part of the conus arteriosus** (*infundibulum*) consists of the septal band and the moderator band (Fig. 6 left, component 3). The right bundle branch of the atrioventricular conduction system runs down the septal band, close to its inferior margin, and then crosses the right ventricular cavity on the moderator band and arborizes on the right ventricular free wall surface as the Purkinje network.

The septal band, well seen from the right ventricular aspect (Fig. 6 left, component 3), is continuous with the smooth (nontrabeculated) portion of the left ventricular septal surface (Fig. 6 right, component 3). The anterior, middle, and posterior radiations of the left bundle branch of the atrioventricular conduction system often can be seen running across this smooth component of the left ventricular septal surface (Fig. 6 right, component 3), even without special stains or histology. Midmuscular ventricular septal defects (VSDs) occur between smooth (nontrabeculated) component 3 above and finely trabeculated component 2 below (Fig. 6 right).

So component 3 is important for the bundle branches of the AV conduction system bilaterally – both in the RV (Fig. 6 left) and in the LV (Fig. 6 right).

The right ventricular sinus evolved beneath the conus arteriosus, i.e., beneath the *conal ring* that consists of the conal septum (component 4, Fig. 6 left), the septal band (component 3, Fig. 6 left), the moderator band, and the parietal band (not shown in Fig. 6, left).

Terminology: The *septal band* (Fig. 6 left, component 3) is called by some the *trabecula septomarginalis*, or the *septomarginal trabeculation*. This was Tandler's term for the moderator band because this trabecula (little beam, Latin) runs from the right ventricular septal surface (*septo*, Latin) at the bottom of the septal band, to the acute margin (or *margo acutis*, Latin) of the right ventricular free wall. Thus, *trabecula septomarginalis* (or *septomarginal trabeculation*, in English) defines both ends of the moderator band: from the septum to the acute margin. The septal band flows into the moderator band (Fig. 6 left); hence these two muscular structures are continuous.

The *parietal band* is the extension of conal musculature into the right ventricular free wall. The parietal band is also known as the *ventriculo-infundibular fold*. This band is infundibular musculature, immediately below which normally lies the right ventricular sinus (or simply, the right ventricle). Thus, in this sense, the parietal band is an infundibulo-ventricular fold.

Evolution and Embryology of the Right Ventricular Sinus: The conus arteriosus or infundibulum is the "mother" of the right ventricular sinus, body, or inflow tract – the lung pump – in the sense that immediately beneath the conus (i.e., the conal ring, mentioned above) is where the right ventricular inflow tract evolved and where it now evaginates or pouches out during normal human embryology.

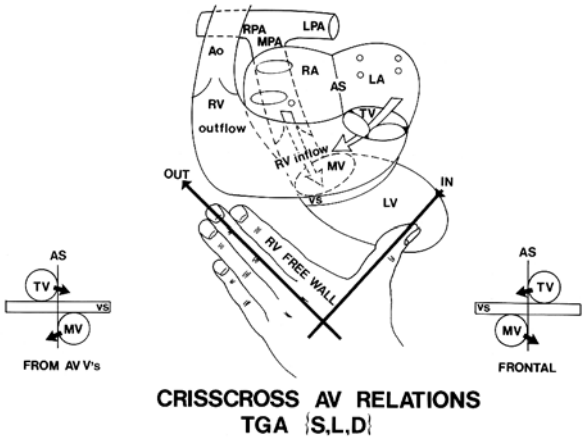

Fig. 9. The L-loop (inverted or mirror-image) morphologically right ventricle (RV) is left-handed. Figuratively speaking, the thumb of the left hand goes through the left-sided tricuspid valve (TV), the thumb representing the right ventricular inflow tract (IN). The fingers of the left hand go into the RV outflow tract (OUT). The palm of only the left hand faces the RV septal surface. The dorsum of only the left hand is adjacent to the RV free wall surface.

This is a case of congenitally physiologically corrected transposition of the great arteries (TGA). The segmental anatomy is {S,L,D}: Viscero-atrial situs solitus {*S*,-,-} is associated with discordant L-loop ventricles {S,*L*,-} and D-TGA {S,L,*D*}. This is a congenitally physiologically corrected TGA because there are *two* intersegmental alignment discordances at both the atrioventricular (AV) and the ventriculoarterial (VA) levels. On the right-hand side, the morphologically right atrium (RA) opens into the morphologically left ventricle (LV); and on the left-hand side, the morphologically left atrium (LA) opens into the morphologically right ventricle (RV). The LV ejects into the main pulmonary artery (MPA), and the RV ejects into the ascending aorta (Ao). Although D-TGA is unusual for physiologically corrected TGA in visceroatrial situs solitus, following the venous blood streams confirms that this is indeed the case: on the left side, LA to RV to Ao; and on the right hand side, RA to LV to MPA.

Superoinferior ventricles is present with RV above, LV below, and ventricular septum (VS) approximately horizontal. The presence of L-loop (inverted or mirror-image) ventricles is indicated by the left-handed RV, by the presence of AV alignment discordance in visceroatrial situs solitus, and by the superior and *left-sided* location of the tricuspid valve (TV) relative to the mitral valve (MV). **Whenever the TV is left-sided relative to the MV, a ventricular L-loop is present.** (I am aware of no well-documented exception to this generalization.)

Crisscross AV relations are also present: Note that the vectors of AV inflow are approximately at right angles to each other. The RV sinus (inflow tract) is underdeveloped; hence there is no RV apex adjacent to the LV apex. Consequently, the pulmonary venous blood stream flows unusually directly from left-sided TV to right-sided aortic valve, creating the crisscross (large angulation) of the ventricular inflow tracts.

After the discordant AV alignments were established, these L-loop ventricles, that usually fold in a leftward direction (i.e., L-loop formation), instead folded to the right – i.e., in the *wrong* direction for an L-loop. This is why the transposed aorta lies to the right of the transposed MPA, i.e., D-TGA is present, instead of the usual L-TGA. This unusual right-left relationship between these transposed great arteries reflects the marked malposition of the ventricles from which the great arteries originate. Superoinferior ventricles also reflects the severe malposition of these L-loop (inverted) ventricles. The RV, which begins on the left beneath the TV, is mostly right-sided. Similarly, the LV that begins on the right-hand side beneath the MV is mostly left-sided. Thus, in TGA {S,L,D} with crisscross AV relations, there is **ventricular bilaterality**, and **atrioventricular contralaterality**. The ventricles lie principally on the side *opposite* to where they are usually located, relative to the solitus atria. The same is true of TGA {S,D,L} (Fig. 8). *Both are examples of severe ventricular malposition, after the AV alignments and connections have been established, in which the ventricles fold in the direction that is the opposite of usual, bearing in mind the type of ventricular situs (loop) that is present: D-loop ventricles folding to the left (Fig. 8); and L-loop ventricles folding to the right (this Fig).* Rotate this diagram 90º clockwise, thereby "correcting" the ventricular malposition. The VS becomes vertical, the RV becomes left-sided, the LV becomes right-sided, and the transposed aortic valve lies to the left of the transposed pulmonary valve – all characteristic of typical physiologically corrected TGA. This simple maneuver reveals the nature of the ventricular malposition that was present in this patient.

Briefly, chirality (handedness) also applies similarly to the morphologically left ventricle: The D-loop LV is left-handed. The L-loop LV is right-handed.

Chirality also applies to the atria: In solitus atria, the RA is right-handed and the LA is left-handed. In inversus atria, the RA is left-handed and the LA is right-handed.

Chirality is a fundamental property of matter displayed by elementary particles in physics. For example, neutrinos are left-handed and antineutrinos are right handed [24]. D-loop and L-loop ventricles are expressions of ventricular *situs*, i.e., the patterns of anatomic organization. D-loop ventricles are the solitus or right-hand *isomer*, and L-loop ventricles are the inversus or left-hand *isomer*. Right-hand and left-hand *topology*, as in a Möbius strip, is not anatomically accurate. For example, draw a right hand on a Möbius strip. Then twist it to the right. The right hand looks normal, as in a D-loop RV. But then twist the strip to the left. The right hand is then left-sided, but it is also *upside down* (with the thumb pointing downward) – *not* like an L-loop or inverted RV. D-loops and L-loops are matters of situs (with two isomers – solitus and inversus), not matters of topology. Ventricular situs is not decided by the direction of looping (D- or L-). Ventricular situs is decided long before loop formation, and is evident even when looping fails to occur, as with superoinferior ventricles (Fig. 8 and 9). Fig. 2 shows only *one* straight tube, with arrows suggesting that it can loop either to the right or to the left forming a D-loop or an L-loop. We now understand that this aspect of Fig. 2 is an oversimplification. There should be *two* straight tubes or preloop hearts shown diagrammatically – one a solitus (or potentially a D-loop) straight heart tube, and the other an inversus (or potentially an L-loop) straight heart tube. Our diagram (Fig. 2) incorrectly suggests that one and the same straight heart tube can become either a ventricular D-loop with a right-handed RV and a left-handed LV, or an L-loop with a left-handed RV and a right-handed LV. Hence, this correction is an important new understanding. Reproduced with permission from Van Praagh [15].

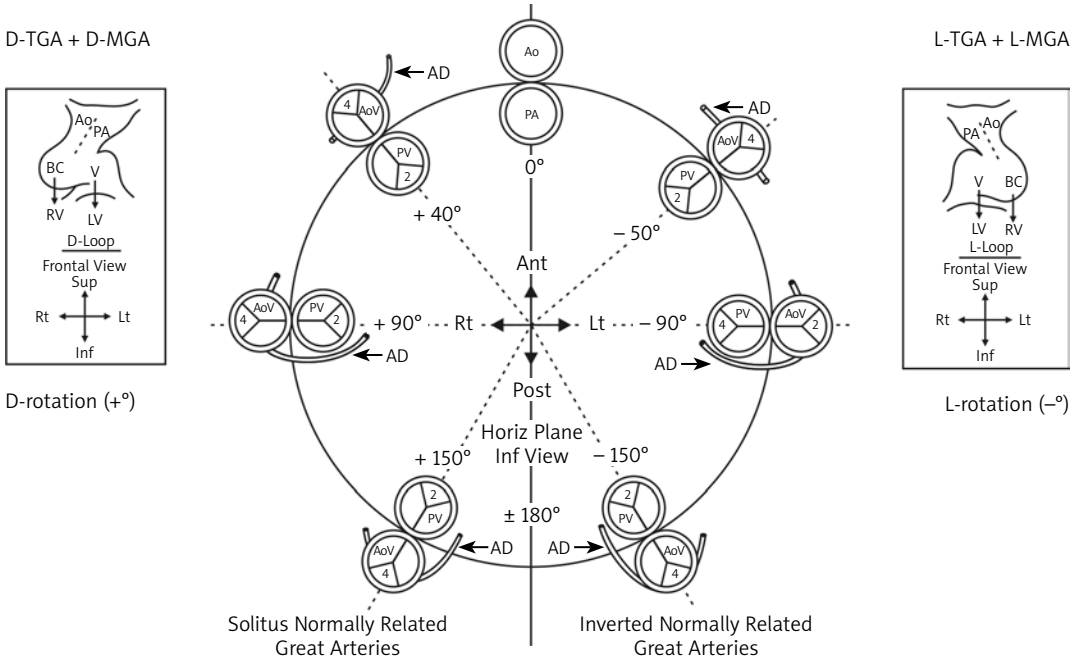

Fig. 10. The untwisting of the great arteries. The great arteries are untwisting as they go from the highly variable semilunar interrelationships proximally to the fixed aortopulmonary relationship distally, where the aortic arch (Ao) is anterior (ventral) and superior (cephalad) relative to the pulmonary artery bifurcation (PA) because these are the fixed relationships between aortic arches 4 and pulmonary arches 6. Relative to the aortic arch (Ao)/pulmonary bifurcation fixed relationship, which may be regarded as having 0° rotation to the right or left, solitus normally related semilunar valves display approximately 150° of rotation to the patient's right side. Dextral rotation or counterclockwise rotation as viewed from the front may be expressed in positive degrees (+150°). Inverted normally related semilunar valves display approximately 150° rotation toward the patient's left side, or clockwise rotation of the semilunar valves as viewed from the front, which may be expressed in negative degrees relative to the fixed distal Ao/PA relationship (–150°). Abnormally related great arteries, such as D- or L-transposition of the great arteries (D-TGA or L-TGA) display a subnormal degree of D-rotation or L-rotation (expressed in absolute degrees, ignoring the + or – sign of the rotation). For example, D-TGA often displays only about 40° of rotation to the right, compared with about 150° of rotation to the right with solitus normally related great arteries. Similarly, L-TGA may display only about 50° rotation to the left; whereas inverted normally related great arteries have about 150° rotation to the left at the semilunar valve level. AoV – aortic valve; PV – pulmonary valve. The 2-4 semilunar diameter passes through the middle of nonseptal pulmonary leaflet 2 and the middle of nonseptal (and normally noncoronary) aortic leaflet 4, at right angles to the aortopulmonary septum. The 2-4 semilunar valvar diameter is helpful in measuring semilunar valvar rotation relative to the sagittal plane. Similarly, D-malpositions of the great arteries (D-MGA) and L-malpositions of the great arteries (L-MGA) such as double-outlet right ventricle (DORV), double-outlet left ventricle (DOLV), and anatomically corrected malposition of the great arteries (ACM) (Fig. 5) also display subnormal semilunar valvar rotations compared with what is normal for the type of ventricular loop that is present. D-TGA and D-MGA typically are associated with ventricular D-loops, while L-TGA and L-MGA usually occur with ventricular L-loops. D-MGA such as DORV typically displays only about 90° of dextro-rotation (compared with a normal of 150° D-rotation). Similarly, L-MGA often has only about 90° L-rotation (compared with a normal of 150° L-rotation with inverted normally related great arteries). Thus, conotruncal malformations such as TGA and various MGAs (DORV, DOLV, and ACM) have much less untwisting to do than do normally related great arteries (solitus or noninverted, and inverted or mirror-image normals). This is why the aortopulmonary septum in TGA usually looks straight or nonspiral when compared with the normal AP septum – which looks spiral because it has much more untwisting to do as it proceeds from the semilunar valve level proximally to the fixed Ao/PA bifurcation relationship distally. Ant – anterior; Ao – ascending aorta; BC – bulbus cordis; Horiz – horizontal; Inf – inferior; Lt – left; LV – morphologically left ventricle; PA – pulmonary artery; Post – posterior; Rt – right; RV – morphologically right ventricle; Sup – superior; V – ventricle. Reproduced with permission from Van Praagh, Layton, and Van Praagh [30].

The septal band and the right ventricular sinus never dissociate or separate. When present, the right ventricular inflow tract is always immediately beneath the septal band, i.e., immediately beneath the proximal or apical part of the conus. By contrast, the conal septum and the parietal band (i.e., the distal or subarterial part of the conus) can and does dissociate from the right ventricle, as in double-outlet left ventricle and as in anatomically corrected malposition of the great arteries {S,D,L} (Fig. 5).

Anatomically, what is the RV sinus versus what is the infundibulum? Double-chambered right ventricle, also known as anomalous muscle bundles of the right ventricle, is a naturally occurring "experiment" that answers this question:

The RV sinus (i.e., the real RV, as opposed to the conus which belongs to the great arteries – as the designation conotruncus indicates) lies proximal or upstream to the "mid-RV" obstruction produced by an obstructive ring of conal musculature. This obstructive conal ring is composed of the septal band, the moderator band, the lower rim of the conal septum, and the parietal band.

More precisely, in double-chambered RV with stenosis or rarely with atresia in the middle of the RV, the muscle bundle that appears to be principally anomalous and obstructive is the *moderator-band-like muscle* that takes off abnormally high from the septal band, too close to the top of the septal band and the muscle of Lancisi (also known as the papillary muscle of the conus), thereby causing obstruction at what is conventionally regarded as the mid-RV.

Indeed, Wong and colleagues [17] were able to predict echocardiographically which patients would develop mid-RV obstruction based on the distance between the pulmonary valve and this moderator-band-like structure. The shorter the pulmonary valve-moderator band distance, i.e., the higher the take off of the "moderator band" from the septal band, the more probable is mid-RV obstruction [17].

This obstructive moderator-band-like structure is not a normal moderator band; hence the quotation marks around "moderator band".

When the RV is viewed with developmental understanding (Fig. 6 left), it is understood that what is conventionally called double-chambered RV is in fact *stenosis or atresia of the proximal os infundibuli (or os coni) pulmonalis.* The septal band and the moderator band are both parts of the *proximal* conus or infundibulum. The conal septum and the parietal band are both parts of the *distal* or *subarterial* part of the conus or infundibulum.

Just as *anomalous muscle bundles of the RV* (or so-called double-chambered RV) is an obstructive anomaly of the proximal conus, *tetralogy of Fallot* (TOF) is an obstructive anomaly of the distal conus – involving the conal septum, the parietal band, and the related subpulmonary conal free wall.

Thus, from a developmental perspective, the designation *double-chambered RV* is a misnomer. The true RV, meaning the RV sinus, is not double-chambered. Instead, there is an obstruction between the RV and the conus, i.e., between the RV inflow tract and the conal outflow tract. Or more precisely, obstruction of the proximal ostium leading into the infundibulum is present typically because of an obstructive moderator-band-like structure.

Thus, one can have *obstruction of the infundibular inlet* (so-called anomalous muscle bundles of the RV, or double-chambered RV) and *obstruction of the infundibular outlet* (tetralogy of Fallot).

So what is the conus arteriosus or infundibulum, as opposed to the right ventricular sinus? As so-called double-chambered RV makes clear, the **conus arteriosus or infundibulum** consists of the conal ring – the septal band, the moderator band, the inferior rim of the conal septum, and the parietal band – and the outflow tract free wall myocardium leading up to the semilunar valve (or valves), normally the pulmonary valve (Fig. 6 left, components 3 and 4).

The right ventricular sinus is the RV inflow tract, i.e., the proximal or upstream chamber in double-chambered RV (Fig. 6 left, components 1 and 2). The RV sinus is the "real" RV – the lung pump. The conus is not a good pump. Typically, double-inlet LV occurs when the RV sinus is missing – *because* the RV sinus is missing.

The functionally right ventricle is much smaller than is generally realized. The conus is there for architectural reasons, not for hemodynamic ones. The subpulmonary conus is there to get the pulmonary valve "out of the way" – away from the interventricular foramen, so that the aortic valve can pass mostly through the interventricular foramen to reach the LV and the mitral valve. So that is what the normally big subpulmonary conus above the RV sinus is doing there: it helps to make possible the normal embryonic aortic switch procedure.

To summarize, the septal band and the moderator band (Fig. 6 left, component 3) serve as the "mother" of the RV sinus (the true RV). The subaortic conal free wall (part of component 4 that undergoes resorption, facilitating aortic-mitral fibrous continuity, Fig. 6 right) also helps to perform the normal developmental aortic switch procedure. Component 4 is also important in septation (VSD avoidance), because it also forms the conal septum.

Evolutionary considerations

Pathology is important because it makes it possible to understand clinical diagnosis and corrective surgery.

Embryology is important because it makes it possible to understand pathology.

Evolution is important because it makes it possible to understand embryology and pathology.

Conotruncal morphogenesis

There have been at least four major and very different hypotheses that have attempted to explain the normal and abnormal morphogenesis of the conotruncus (infundibulum and great arteries) in *Homo sapiens sapiens* (Fig. 7) [18]:

1. **Malseptation** of the truncus and conus was first proposed by Quain [19] in 1844 (Fig. 7, top left).
2. **Conal maldevelopment** was introduced by Keith [20] in 1909 (Fig. 7, top right).
3. **Atavism** or phylogenetic regression was advocated by Spitzer in 1923 [21, 22] (Fig. 7, lower left).
4. **Fibrous malattachment** was proposed by Grant [23] in 1962 (Fig. 7, lower right).

The only hypothesis that is supported by the data is Keith's conal maldevelopment concept. (The deficiencies of the other hypotheses are mentioned briefly in the legend of Fig. 7) [18].

Discussion

As mentioned heretofore, one of the major differences between multicelled plants and animals is that, although both typically have a vascular system, only multicelled animals have a heart, i.e., a *cardio*vascular system.

The cardiovascular system is the first system in man to become functionally active. The heart beat in man is thought to begin during early D-loop formation, i.e., 20-22 days of age in utero.

The two crucial evolutionary cardiovascular adaptations that made possible air-breathing and permanent land-living for mammals, including humans, were:

1. the evolution of an embryonic aortic switch procedure by asymmetrical (opposite) right-left development of the subarterial conal free walls, i.e., by expansile growth of the subpulmonary conal free wall, and by resorption of the subaortic conal free wall that together permit transfer of the aorta to above the LV, while the main pulmonary artery remains aligned with the RV (Fig. 2 to 4); and
2. evolution of the RV sinus (lung pump) beneath the proximal part of the conus, i.e., beneath and upstream to the conal ring (Fig. 6).

These morphogenetic movements of both great arteries and the development of the RV sinus normally are completed by or before 38 to 45 days of age, when the membranous septum typically closes the interventricular foramen.

There is only one way of doing the embryonic aortic switch procedure right (Fig. 3). Or, to say it another way, there are two isomers of one and the same mechanism: a solitus isomer that results in solitus normally related great arteries {S,D,*S*}, and an inversus (or mirror-image) isomer that results in inverted normally related great arteries {I,L,*I*} (Fig. 5, row 1, column 1; and row 1, column 3, respectively).

Please note: we are talking about *isomers* (stereoisomers), *not* about *topology* (as when a Möbius strip can be twisted to the right, or to the left, giving different results). For example, with superoinferior ventricles (RV above, LV below, ventricular septum horizontal), i.e., when looping has not occurred, *chirality or handedness* [24, 25] distinguishes a solitus ventricular anatomic isomer (that normally "should" have been a ventricular D-loop) from an inversus ventricular anatomic isomer (that usually is a ventricular L-loop) (Fig. 8 and 9).

Although there is only one way of doing the embryonic aortic switch procedure right, i.e., one mechanism (Fig. 3), there are many ways of doing the embryonic aortic switch procedure wrong (Fig. 5).

Examples of how the developmental aortic switch can be done wrong include:

1. **Tetralogy of Fallot.** Tetralogy is a "subnormality." The right-sided subaortic conal free wall undergoes resorption normally. But the left-sided subpulmonary conal free wall (in a typical D-loop) undergoes growth and expansion, but to a very subnormal degree. Consequently there is subpulmonary infundibular stenosis or atresia, depending on the degree of hypoplasia of the subpulmonary conus. The pulmonary valve may or may not be stenotic or atretic; the subpulmonary valve is the "back door" of the subpulmonary conus. Because of subnormal growth and expansion of the subpulmonary infundibulum, in TOF the pulmonary valve is not carried as superiorly, nor protruded as anteriorly as normal. Hence, in TOF, the pulmonary valve is abnormally left-sided, posterior, and inferior. Reciprocally, the aortic valve in TOF is abnormally right-sided, anterior, and superior – accounting for the typical aortic overriding, with or without a subnormal degree of aortic-mitral fibrous continuity. Because of the subnormal dextral rotation of the semilunar valves in TOF (because of underdevelopment of the subpulmonary conus), the conal septum (component 4 in Fig. 6) is abnormally anterior, superior, and leftward, resulting in a typically large VSD between the conal septum above (component 4, Fig. 6) and the septal band and ventricular septum below (components 3 and 2, respectively, Fig. 6), i.e., a typically large subaortic malalignment type of conoventricular VSD. Hence, our view is that **the tetralogy of Fallot is really the monology of Stensen**: really just one anomaly and its sequelae [26], i.e., underdevelopment of the subpulmonary conus, not four different and unrelated anomalies. This anatomic type of congenital heart disease was originally described in 1671 by Niels Stensen [27], the Danish anatomist and naturalist of parotid duct fame, not by Etienne-Louis Arthur Fallot, the physician from Marseille, in 1888 [28, 29]. Despite the foregoing, we still make the diagnosis of *tetralogy of Fallot*. We have no desire to change conventional diagnostic and surgical terminology. The monology of Stensen is merely a "hook" to hang this understanding on. (Nicolai Stenonis [27] is Niels Stensen in Latin).
2. **Transposition of the great arteries.** TGA is a malformation of the subarterial conal free walls, an anomaly of right-left asymmetry. With a ventricular D-loop, the right-sided subaortic conal free wall grows and expands (the opposite of normal development) and the left-sided subpulmonary conal free wall undergoes resorption (also the opposite of normal development) (Fig. 2-5). Hence, typical D-TGA (i.e., TGA {S,D,D}, Fig. 5, row 5, column 1) has **inversion or mirror imagery of the subarterial conal free walls**. In typical L-TGA (i.e., TGA {S,L,L}, Fig. 5, row 5, column 2), the same thing happens, but in mirror image. The left-sided subaortic conal free wall grows and expands (the opposite of "normal" development with L-loop ventricles, Fig. 3, right). The right-sided subpulmonary infundibular free wall typically undergoes resorption (also the opposite of "normal" development for L-loop ventricles, Fig. 3, right). Both with D-TGA and L-TGA, the aortic valve is carried superiorly and protruded anteriorly above the anterior (ventral) RV, while the pulmonary valve moves inferiorly and posteriorly, passing through the interventricular foramen and coming into fibrous continuity with the developing mitral valve above the LV. Thus, reversed or opposite right-left development of the subarterial infundibular free walls results in the

performance of the *wrong* embryonic arterial switch procedure. The pulmonary artery is switched into the LV (instead of the aorta).

3. **Double-outlet right ventricle.** When both the subaortic and the subpulmonary conal free walls grow and expand, double-outlet right ventricle (DORV) can result, as in the Taussig-Bing malformation [6, 7] with a bilateral conus and a subpulmonary VSD. The development of a subaortic and a subpulmonary conus prevents semilunar-atrioventricular fibrous continuity, and no embryonic arterial switch is performed – resulting in DORV.

The foregoing are just some of the abnormal ventriculo-arterial alignments (TOF, TGA, and DORV) that can result from abnormal development of the subarterial infundibular free walls; there are others (Fig. 5). There are additional correlations between conal subarterial free wall development and other abnormal ventriculo-arterial alignments (Fig. 5). In the interests of brevity and clarity, I shall try to summarize the unifying basic principles.

The basic principles appear to be as follows:

1. Normal ventriculo-arterial alignments are characterized by complete right-left asymmetry (oppositeness) in the development of the subarterial conal free walls following cardiac loop formation: growth of the subpulmonary conal free wall, and resorption of the subaortic conal free wall.
2. Normal subarterial conal free wall development results in normal morphogenetic movements of the developing pulmonary artery (superior and anterior movement of the pulmonary valve above the RV) and of the ascending aorta (inferior and posterior movement of the aortic valve that passes through the interventricular foramen into fibrous continuity with the developing mitral valve above the LV).
3. All conotruncal malformations have an anomaly of the normal complete right-left asymmetry in the development of their subarterial infundibular free walls (Fig. 2-4).
4. Abnormal right-left development of the subarterial conal free walls leads to abnormal morphogenetic movement of the overlying aortic and pulmonary valves.
5. Abnormal morphogenetic movements of the semilunar valves results in abnormal ventriculo-arterial alignments of many different kinds, only some of which are shown in Fig. 5.
6. Development (growth/resorption) of the subarterial conal free walls is only one of the factors that help to determine the definitive ventriculo-arterial alignments. Other factors that can also play an important role include ventricular loop formation (e.g., anatomically corrected malposition of the great arteries in which the direction of ventricular looping is the opposite of the direction of infundibuloarterial twisting, Fig. 5, row 6), ventricular sinus development, the status of the atrioventricular (AV) canal and the AV valves, and other associated malformations. Thus, subarterial conal right-left development is only one factor, but a very important one, in determining ventriculo-arterial alignments.
7. The morphogenetic movements of the semilunar valves, both normal and abnormal, are very real (Fig. 6 and 7) [29]. This concept is very different from the classical trunco-conal malseptation hypothesis [19] in which normally related great arteries were thought to be due to spiral downgrowth of the trunco-conal septum, whereas transposition of the great arteries was considered to be due to straight downgrowth of the trunco-conal septum (Fig. 7, left upper panel). The outside (free walls) of the truncus arteriosus were thought not to move. All of the movement was thought to be internal: spiral or straight septation.

   Keith [20], who first understood the importance of conal maldevelopment in the conotruncal anomalies in 1909, thought that solitus normally related great arteries have a pulmonary valve that is anterior, superior, and to the *right* of the aortic valve (Fig. 7, top right panel). We now know that with solitus normally related great arteries, the pulmonary valve is anterior, superior, and to the *left* of the aortic valve (Fig. 2-5).

   The comprehension that normal and abnormal morphogenetic movements involve whole great arteries (free walls and septum), and that aorto-pulmonary septation is normal *per se* (except in truncus arteriosus) – this understanding is relatively new [29, 30].
8. It is now understood that normally and abnormally aligned great arteries are *un*twisting as they pass from the semilunar valves proximally to the aortic arch and pulmonary bifurcation distally (Fig. 10) [30]. The latter is the fixed frame of reference distally because the aortic arch (embryonic aortic arch 4) is always anterior (and superior) to the pulmonary bifurcation (embryonic aortic arch 6), as long as both the aortic arch and the pulmonary bifurcation are present. Thus, the aortic arch/pulmonary bifurcation is the *fixed* aorto-pulmonary relationship distally, where the aorta is always anterior to the pulmonary artery because of the embryonic aortic arch 4/pulmonary arch 6 relationship. By contrast, the aorto-pulmonary relationship proximally – at the semilunar valves – is *highly variable*.

   The fibroelastic great arteries must untwist as they proceed from the semilunar valves proximally to the aortic arch/pulmonary bifurcation distally. The untwisting of the great arteries equals (in degrees) the difference between the semilunar valve relationship proximally and the aortic arch/pulmonary bifurcation relationship distally (Fig. 10). In normal cardiac development, approximately 150° of dextrorotation is put into the aortopulmonary relationship at the semilunar valve level by the combination of D-loop formation plus normal conal subarterial free wall development. Consequently, solitus normally related great arteries must untwist through approximately 150° in the other direction (levorotation) as they proceed from the semilunar valves proximally to the aortic arch/pulmonary bifurcation relationship distally (Fig. 10) [30]. In D-TGA, by contrast, because the aortic valve is typically anterior to the pulmonary valve, the great arteries have much less untwisting to do –

often only about 40° (Fig. 10). Consequently in TGA (both D- and L, Fig. 8), the aortopulmonary septum appears relatively straight (nonspiral).

The classical trunco-conal malseptation hypothesis [19] also cannot explain: 1) why the free walls of the great arteries in TGA are just as positionally abnormal as is the aorto-pulmonary septum: the origins of the coronary arteries, which are the first branches from the aortic free wall, are very abnormal in TGA (Fig. 10), indicating that both the aorto-pulmonary septum *and the free walls* are positionally very abnormal in TGA – not just the AP septum only; 2) why there is such variation in semilunar valve heights: why the normally aligned aortic valve is low, but the transposed aortic valve is high – the absence or presence of subsemilunar conus being the explanation; and 3) why there is no definite evidence in TGA of malformation of the aorto-pulmonary septum: if TGA were caused by trunco-conal malseptation, one would expect to find some definite anatomic evidence of AP malseptation such as a high prevalence of aortopulmonary septal defect; however, AP window in patients with TGA is vanishingly rare.

9. Thus, the so-called conotruncal malformations are really conal malformations, like tetralogy of Fallot quite obviously is. So, too, are TGA, DORV, DOLV, and ACM (Fig. 5). The only exception is truncus arteriosus, which also has a great arterial malformation [31-33]. Hence, in almost all of the conotruncal anomalies, the great arteries *per se* are normally formed, but malpositioned because of malformations in the development of the subarterial conal free walls involving anomalies of right-left asymmetry. The free walls (not the septum) of these little, hollow, conical platforms – be they well developed or resorbed – on which the semilunar valves and the great arteries stand – these very important little coni arteriosi (arterial cones) are the keys to understanding normal and abnormal ventriculo-arterial alignments. In other words, the development of the subarterial conal connectors largely determines the definitive ventriculo-arterial alignments.

As was mentioned in the introduction, in our phylum Chordata, the LV is at least 500 million years old, dating from the ancient fish (Fig. 1) of the Ordovician and upper Devonian periods, 500 million to 345 million years ago [34].

Amphibians evolved some 345 million to 325 million years ago. 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.

These primitive amphibians evolved into fully terrestrial animals that did not need to breed in the water. These were the *Amniota*, all animals with an amniotic sac that surrounded a little "mare internum" (internal sea, Latin) of amniotic fluid in which the embryo and later the fetus could float – like our aquatic ancestors.

The terrestrial Amniota then evolved into reptiles, birds (feathered reptiles like *Archaeopteryx*), and mammals (furry or hairy reptiles).

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

Although fish and amphibians do not have an RV, higher reptiles (such as crocodiles and alligators), birds, and mammals do.

The evolution of an RV, and then the necessity of switching the aorta into the LV, were parts of developing a *double circulation* that was both systemic and pulmonary in fully terrestrial vertebrates.

By contrast, aquatic and semi-aquatic vertebrates have a *single circulation* – the systemic – that also supplies the organs of respiration – gills, lungs, and skin. *But why does the evolution of the vertebrate cardiovascular system matter to us? What is its medical and surgical importance?*

Most human congenital heart disease consists of anomalies of the four anatomic and developmental components of the RV (Fig. 6, left), but seldom of the LV (Fig. 6, right). Why?

Perhaps because the RV is a "Johnny Come Lately", a relative newcomer, only about 180 million years old, i.e., only about 36% as old as the LV, which is at least 500 million years old.

The fact that the RV is only slightly more than one-third as old as the LV suggests that we are still having trouble with our comparatively recent major cardiovascular evolutionary adaptations that facilitate air-breathing and permanent land-living. These major cardiovascular evolutionary changes include the development of the RV beneath the proximal part of the conus arteriosus, and the evolution of the embryonic aortic switch procedure performed by the distal or subarterial part of the conus. In contrast, anomalies of the LV are relatively rare. Congenital heart disease is the commonest anomaly in liveborn human babies – almost 1% of all live births (0.8%) [35].

Etiologic considerations

As noted heretofore, solitus normally related great arteries {S,D,S} and inversus normally related great arteries {I,L,I} (Fig. 5, row 1) are achieved by completely asymmetrical right-left development of the subarterial conal free walls: resorption of the right-sided subaortic conal free wall, and growth of the left-sided subpulmonary conal free wall (Fig. 2-7).

Abnormally related great arteries of all anatomic types (Fig. 5, rows 5-8) are characterized by anomalies of this complete right-left asymmetry in the development of their subarterial conal free walls (Fig. 2-5, 7).

These data are reminiscent of the findings in the **heterotaxy syndromes**, that often have congenital asplenia or polysplenia [36-41].

The heterotaxy syndromes are characterized by abnormal visceroatrial right-left *asymmetry*.

This is why the heterotaxy syndromes have often been said to have abnormal *bilateral symmetry,* with the asplenia syndrome being thought to have bilateral right-sidedness with right atrial isomerism, and with the polysplenia syndrome being said to have bilateral left-

sidedness with left atrial isomerism. Superficially, that is often how it looks.

More accurately, however, it is helpful to realize that bilateral morphologically right atria have never been documented with bilateral inferior venae cavae, bilateral superior venae cavae, bilateral coronary sinus ostia, bilateral superior limbic bands of septum secundum, and bilateral broad, triangular right atrial-like atrial appendages [41].

Similarly, bilateral morphologically left atria have never been documented, accurately speaking, with four pulmonary veins bilaterally, with septum primum bilaterally, and with narrow left atrium-like left atrial appendages bilaterally [41].

So, it is now widely agreed that the concepts of right atrial isomerism and left atrial isomerism are not anatomically accurate, superficial appearances to the contrary notwithstanding.

Similarly, it is now widely agreed that the concept of *right or left atrial appendage isomerism* also is not anatomically accurate in the heterotaxy syndromes.

Finally, the notion of *atrial pectinate isomerism* does not apply well in the heterotaxy syndromes. The concept of isomerism (i.e., stereoisomerism or mirror imagery) applies to *whole* structures, *not* just to *parts* of structures. Consider the molecules of D-glucose and L-glucose. They are regarded as isomers because all atoms in each molecule are mirror images of the corresponding atoms in the other molecule. D- and L-glucose would not be regarded as isomers (mirror images) if only a few of the hydrogen atoms, or only some of the hydroxyl groups, or only the carboxyl groups were mirror images – but none of the other atoms was; then D- and L-glucose would *not* be regarded as isomeric molecules. Similarly, atrial pectinate isomerism – that applies to only a part of each atrium – is conceptually erroneous.

The realization that the concept of atrial level isomerism is an inaccurate concept [41] is important for several reasons:

1. This understanding facilitates the diagnosis of the atrial situs in many patients with the heterotaxy syndromes, but not in all such patients [40]. When we are unable to make the diagnosis of the atrial situs in a patient with the heterotaxy syndrome, often with congenital asplenia, we make the diagnosis of visceroatrial *situs ambiguus*, i.e., {A,-,-}, which means that we do not know what the situs is. In this situation, we do not make the diagnosis of any kind of atrial level "isomerism", because we know that this concept is not accurate.

Instead, the concept that is anatomically accurate in patients with the heterotaxy syndromes is that *abnormal visceroatrial right-left asymmetry* is often present.

Why is the hypothesis that *anomalies of right-left asymmetry* may be very important both in the conotruncal anomalies (Fig. 5) and in the heterotaxy syndromes so interesting? Because malformations involving anomalies of right-left asymmetry appear to be basic both to the conotruncal malformations (as mentioned above) and to the heterotaxy syndromes.

Tab. I. The incidence of anatomic types of the transposition of the great arteries (TGA) in newborns of the of the heterotaxy syndrome model mice

	No. of Cases	% of Series
1. TGA {S,D,D} with subaortic conus	6	43
2. TGA {S,D,D} with bilateral conus	1	7
3. TGA {I,D,L} with subaortic conus	1	7
4. TGA {I,L,L} with subaortic conus	6	43
Total	14	100

Tab. II. The incidence of anatomic types of the transposition of the great arteries (TGA) in 14-day-old fetuses of the of the heterotaxy syndrome model mice

	No. of Cases	% of Series
1. TGA {S,D,L} with subaortic conus	1	25
2. TGA {S,L,L} with subaortic conus	1	25
3. TGA {I,L,L} with subaortic conus	2	50
Total	4	100

Tab. III. The incidence of anatomic types of the double-outlet right ventricle (DORV) of the of the heterotaxy syndrome model mice

	No. of Cases	% of Series
Newborn iv/iv mice		
1. DORV {S,D,D} with bilateral conus	6	40
2. DORV {S,D,D} with subpulmonary conus	1	7
3. DORV {I,D,D} with bilateral conus	1	7
4. DORV {A,D,L} with bilateral conus	1	7
5. DORV {I,L,L} with bilateral conus	5	33
14-Day iv/iv mouse fetus		
6. DORV {I,L,L} with bilateral conus	1	7
Total	15	101

For example, Dr. Stella Van Praagh and I have had the pleasure and privilege of working with Dr. William M. Layton concerning the *iv/iv*[1] mouse model [30, 42-44]. The *iv/iv* mouse is really an animal model of the heterotaxy syndromes. I was the mouse "cardiologist" (congenital heart disease diagnostician). Dr. Bill Layton and his wife Mary performed the mating experiments using only mice homozygous for the situs inversus gene (*iv/iv*). Approximately 20 percent of the offspring had congenital heart disease [30].

Of 62 newborn mice with congenital heart disease, **transposition of the great arteries (TGA)** was present in 14 (23%) [30]. Of 18 mouse fetuses of 14 days gestation (full-term gestation is 19 days), TGA was found in 4 (22%) [30].

In the 14 newborn *iv/iv* mice, the anatomic types of TGA are shown in Table I.

[1] iv is the gene symbol for situs inversus.

In the 14-day-old mouse fetuses the anatomic types of TGA are shown (Table II) [30].

Double-outlet right ventricle (DORV) was found in 15 *iv/iv* mice (Table III) [30].

Why am I presenting data concerning the *iv/iv* mouse model and the kinds of congenital heart disease found in this animal model? I am doing so at the urging of Sir Magdi Yacoub, whom I had the pleasure of meeting at the 80th birthday party of Prof. Aldo Castañeda, that was also an outstanding scientific meeting that was held very recently (July 15-18, 2010) in Antigua, Guatemala. In Sir Magdi's talk, he presented what he regards as the very strong possibility that the molecular genetic etiology of the heterotaxy syndromes and anomalies of right-left asymmetry may help to clarify the basic causation of the conotruncal malformations such as D-TGA and DORV. The hypothesis is that the etiologies of the conotruncal anomalies and of the heterotaxy syndromes may be very similar, if not identical.

In my talk, I agreed that this certainly is a hypothesis well worthy of careful evaluation because of my previous experience with the *iv/iv* mouse model, which really is a model of visceral heterotaxy that has high prevalences of both TGA and DORV, as above (Tables 1-3). Sir Magdi Yacoub told me that he was not familiar with the *iv/iv* mouse model of visceral heterotaxy and congenital heart disease, much of which was published some 30 years ago [30] or more. So he urged me to make reference to these highly relevant data in my current and future papers about conotruncal anomalies, for the benefit of current and future molecular genetic research; hence reference is made to some of the experimental heterotaxy *iv/iv* mouse data [30] (Tables I-III).

What was the conal anatomy in these 18 cases of TGA in the *iv/iv* mice [30]? The conus was subaortic (with pulmonary-to-mitral fibrous continuity) in 17 of 18 cases (94%), and was bilateral (subaortic and subpulmonary, with no semilunar-atrioventricular valvar fibrous continuity) in 1 (6%).

The conal anatomy in these 15 cases of DORV in the *iv/iv* mice [30] was bilateral in 14 (93%) and subpulmonary in 1 (7%).

The correlation coefficients in the *iv/iv* mice were as follows: TGA and subaortic conus: r = 0.94 (0.88 to 0.97 being the 95 percent confidence limits). DORV and bilateral (subaortic and subpulmonary) conus: r = 0.88 (0.76-0.94) [30].

In a large companion study of human TGA (n = 221) and DORV (n = 52), the correlation coefficients were similar [30]: TGA and subaortic conus: r = 0.83 (0.79-0.86).

DORV and bilateral conus: r = 0.73 (0.67-0.78).

To summarize, both the conotruncal anomalies and the heterotaxy syndromes have important anomalies of right-left asymmetry. Mammalian models of the heterotaxy syndromes, that also have high prevalences of TGA and DORV, such as the iv/iv mouse [30, 42-44], may help to clarify the etiologies of human conotruncal (infundibuloarterial) anomalies.

As noted above, these so-called *conotruncal* (or *infundibuloarterial*) malformations are really subarterial *conal* or *infundibular* free wall anomalies, period. The great arteries *per se* appear to be intrinsically normally formed in all of these malformations, except for truncus arteriosus.

For at least the last 20 years, there has been intense interest in elucidating the *molecular genetic etiology* of right-left asymmetry, both normal and abnormal [45-47]. DeLuca and colleagues [48] suggested in 2010 that transposition of the great arteries might be considered as a lateralization defect, a view proposed earlier by Digilio et al. [49] in 2001, by Goldmuntz et al. [50] in 2002, by Cipollone et al. [51] in 2006, and by Oliverio et al. [47] in 2010.

The purposes of the present paper are to support the importance of normal and abnormal right-left asymmetry in the development of the subarterial conal free walls in the morphogenesis of normally and abnormally related great arteries. More specifically, this presentation is based on pathologic and embryologic data that appear to strongly support the recent molecular genetic findings.

An understanding of the normal embryonic aortic switch procedure, and the realization that there is only one way to do this procedure right and many ways to do it wrong, makes it readily possible to comprehend how normal and abnormal right-left asymmetry of subarterial conal free wall development works, i.e., the morphogenetic consequences of each (as mentioned heretofore). The present paper seeks to explain what happens at the levels of pathologic anatomy and embryology.

The molecular geneticists are now actively seeking to understand normally and abnormally related great arteries at the level of genes and genetic mutations [45-51]. Marino and his colleagues [47] are proposing that a **mutation in the Nodal signaling cascade** may be responsible for anomalies of right-left asymmetry not only in humans (we are mammals belonging to the group of animals with bilateral symmetry and asymmetry, the Bilateria) but also in snails. Oliverio and colleagues [47] regard the highly conserved Nodal cascade as the most important signaling pathway thus far discovered that plays a critical role not only in right-left axis formation, but also in mesodermal and neural induction, the heart being a mesodermal structure. The elucidation of the molecular genetic causes of normal and abnormal cardiovascular morphogenesis is one of the most important and exciting challenges facing our field in the twenty-first century.

Conclusions

Perhaps the most important insight to emerge from the present study is the following general principle:

Conotruncal (infundibuloarterial) anomalies result from malformations of the normally complete right-left asymmetry (oppositeness) in the development of the subarterial conal free walls. Typically, if the right-sided subaortic conal free wall does not undergo the normal complete resorption, and if the left-sided subpulmonary conal free wall does not undergo the normal growth and expansion, then a conotruncal anomaly results. The anatomic type of conotruncal anomaly (TOF, TGA, DORV, DOLV, etc.) is

largely determined by the type of malformation of right-left asymmetry of the subarterial conal free walls (as detailed above).

A related important insight is the realization that the heterotaxy syndromes, often with asplenia or polysplenia, also are anomalies of visceral right-left asymmetry, not of right-left symmetry as has often been thought [37, 38].

Normal and abnormal right-left visceral asymmetry appears to be under molecular genetic control, in which the Nodal cascade is now thought to be very important (as noted above).

Why is visceral right-left asymmetry important? Because it made possible air-breathing and permanent land-living in vertebrates. How? By the evolution of a double circulation (systemic and pulmonary) in higher reptiles, birds, and mammals from the single (systemic) circulation of our ancient fish ancestors.

Right-left asymmetry is basic to normal human cardiovascular morphogenesis. Examples include not only the normal embryonic aortic switch process with complete right-left asymmetry in the development of the subarterial conal free walls (resorption of the right-sided subaortic, and growth of the left-sided subpulmonary), but also ventricular D-loop formation, and the development of the right-sided RV sinus and of the left-sided LV sinus. The evolution of the double circulation was the major cardiovascular adaptation making possible air-breathing and permanent land-living.

Although the human body, when viewed externally, appears to be characterized by right-left symmetry, internal examination reveals much right-left asymmetry: left-sided heart, right-sided liver, left-sided stomach and spleen, and right-sided appendix, etc.

Now we are beginning to understand why right-left asymmetry is so important in normal human cardiovascular morphogenesis.

References

1. Plant and animal evolution. Harris WH and Levy JS (eds). In: The New Columbia Encyclopedia. New York and London, Columbia Univ Press, 1975; 908.
2. Robb JS. Invertebrate hearts – gross anatomy In: Comparative Basic Cardiology, Grune & Stratton, New York, London 1965; 1.
3. Robb JS. The heart in chordates. In: Comparative Basic Cardiology. Grune & Stratton, New York, London 1965; 41.
4. Van Praagh R. Normally and abnormally related great arteries: what have we learned? World Society For Pediatric And Congenital Heart Surgery 2010; 1: 364.
5. Van Praagh R, Van Praagh S. Isolated ventricular inversion. A consideration of the morphogenesis, definition and diagnosis of nontransposed and transposed great arteries. Am J Cardiol 1966; 17: 395-406.
6. Taussig HB, Bing RJ. Complete transposition of the aorta and a levoposition of the pulmonary artery; clinical, physiological, and pathological findings. Am Heart J 1949; 37: 551-559.
7. Van Praagh R. What is the Taussig-Bing malformation? Circulation 1968; 38: 445-449.
8. Van Praagh R. The importance of segmental situs in the diagnosis of congenital heart disease. Semin Roentgenol 1985; 20: 254-271.
9. Van Praagh R, Weinberg PM, Srebro JP. Double-outlet left ventricle. In: Moss' Heart Disease in Infants, Children, and Adolescents. Adams FH, Emmanouilides GC, Riemenschneider TA (eds). 4th ed. Williams & Wilkins, Baltimore 1989; 461.
10. Paul MH, Muster AJ, Sinha SN, Cole RB, Van Praagh R. Double-outlet left ventricle with an intact ventricular septum. Clinical and autopsy diagnosis and developmental implications. Circulation 1970; 41: 129-139.
11. Van Praagh R. Les malformations conotruncales. Coeur Numéro Spécial 1973; 15.
12. Foran RB, Belcourt C, Nanton MA, Murphy DA, Weinberg AG, Liebman J, Castańeda AR, Van Praagh R. Isolated infundibuloarterial inversion {S,D,I}: a newly recognized form of congenital heart disease. Am Heart J 1988; 116 (5 Pt 1): 1337-1350.
13. Holmes WF. Case of malformation of the heart. Trans Med-Chir Soc Edinburgh 1824; 252.
14. Van Praagh R. The segmental approach to diagnosis in congenital heart disease. In: Birth defects: original article series, viii, no. 5. Bergsma D (ed.). The National Foundation–March of Dimes Baltimore, Md: Williams & Wilkins, 1972; 4-23.
15. Van Praagh R. Segmental anatomy. In: Sabiston & Spencer Surgery Of The Chest. Sellke FW, del Nido PJ, Swanson SJ (eds.). 8th ed. Saunders Elsevier, Philadelphia 2010; 1651.
16. Van Praagh R, Geva T, Kreutzer J. Ventricular septal defects: how shall we describe, name and classify them? J Am Coll Cardiol 1989; 14: 1298-1299.
17. Wong PC, Sanders SP, Jonas RA, Colan SD, Parness IA, Geva T, Van Praagh R, Spevak PJ. Pulmonary valve-moderator band distance and association with development of double-chambered right ventricle. Am J Cardiol 1991; 68: 1681-1686.
18. Van Praagh R. Transposition of the great arteries: history, pathologic anatomy, embryology, etiology, and surgical considerations. Cardiac Surgery: State of the Art Reviews. Hanley & Belfus, Inc. Philadelphia, 1991; 5: 7.
19. Quain R. Cited by Peacock TB. On Malformations, etc of the Human Heart with Original Cases. London, Churchill, 1856, p 116. Birmingham Alabama, The Classics of Medicine Library 1981, Gryphon Editions Limited.
20. Keith A. The Hunterian lectures on malformations of the heart. Lancet August 14, 1909: 433.
21. Spitzer A. Über den Bauplan des normalen und missbildeten Herzens. Versuch einer phylogenetischen Theorie. Virchows Arch f Path Anat 1923; 243: 81.
22. Spitzer A. The Architecture of Normal and Malformed Hearts: A Phylogenetic Theory of their Development, with a Summary and Analysis of the Theory by M Lev and and A Vass. Springfield, IL, Charles C Thomas, 1951.
23. Grant RP. The morphogenesis of transposition of the great vessels. Circulation 1962; 26: 819-840.
24. Van Praagh R, David A, Gordon D, Wright GB, Van Praagh S. Ventricular diagnosis and designation. In: Paediatric Cardiology 1980. Godman M (ed.). Churchill Livingstone, Edinburgh, London 1981; 153.
25. Van Praagh S, LaCorte M, Fellows KE, Bossina K, Busch HJ, Keck EW, Weinberg P, Van Praagh R. Supero-inferior ventricles, anatomic and angiocardiographic findings in 10 postmortem cases. In: Etiology and Morphogenesis of Congenital Heart Disease. Van Praagh R, Takao A (eds). Mt Kisco, Futura Publishing Co New York, 1980; 317.
26. Van Praagh R, Van Praagh S, Nebesar RA, Muster AJ, Sinha SN, Paul MH. Tetralogy of Fallot: underdevelopment of the pulmonary infundibulum and its sequelae. Am J Cardiol 1970; 26: 25-33.
27. Stenonis DN. Embryo monstro affinis Parisii dissectus. In: Acta Medica et Philosophica Hafniensia. Bartholini T (ed.). Petrus Haubold, Copenhagen, 200.
28. Van Praagh R. Etienne-Louis Arthur Fallot and his tetralogy: a new translation of Fallot's summary and a modern reassessment of this anomaly. Eur J Cardiothorac Surg 1989; 3: 381-386.
29. Asami I. Partitioning of the arterial end of the human heart. In: Etiology And Morphogenesis Of Congenital Heart Disease. Van Praagh R, Takao A (eds). Futura Publishing Co, Mt. Kisco, New York 1980; 51.
30. Van Praagh R, Layton WM, Van Praagh S. The morphogenesis of normal and abnormal relationships between the great arteries and the ventricles: pathologic and experimental data. In: Etiology And Morphogenesis Of Congenital Heart Disease. Van Praagh R, Takao A (eds). Futura Publishing Co, Mt. Kisco, New York 1980; 271.
31. Van Praagh R, Van Praagh S. The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases. Am J Cardiol 1965; 16: 406-425.
32. Calder L, Van Praagh R, Van Praagh S, Sears WP, Corwin R, Levy A, Keith JD, Paul MH. Truncus arteriosus communis. Clinical, angiocardiographic, and pathologic findings in 100 patients. Am Heart J 1976; 92: 23-38.
33. Vizcaino A, Campbell J, Litovsky S, Van Praagh R. Single origin of right and left pulmonary artery branches from ascending aorta with nonbranching

main pulmonary artery: relevance to a new understanding of truncus arteriosus. Pediatr Cardiol 2002; 23: 230-234.
34. Van Praagh R. The evolution of the right ventricle and its relation to the surgical management of congenital heart disease. Rev Argentina Cardiol 1995; 63: 417.
35. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. Circulation 1971; 43: 323-332.
36. Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood; an analysis of the heart malformations in the splenic agenesis syndrome, with fourteen new cases. Acta Pediat Scand 1955; 44 (Suppl. 104): 7-110.
37. Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral "left-sidedness". Circulation 1967; 36: 789-799.
38. Van Mierop LH, Wiglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. Lab Invest 1962; 11: 1303-1315.
39. Van Praagh S, Kakou-Guikahue M, Kim HS, Van Praagh R. Atrial situs in patients with visceral heterotaxy and congenital heart disease. Conclusions based on findings in 104 postmortem cases. Coeur 1988; 19: 484-502.
40. Van Praagh S, Kreutzer J, Alday L, Van Praagh R. Systemic and pulmonary venous connections in visceral heterotaxy, with emphasis on the diagnosis of the atrial situs: a study of 109 postmortem cases. In: Developmental Cardiology, Morphogenesis and Function. Clark EB, Takao A (eds). Futura Publish Co, Mt. Kisco, New York 1990; 671.
41. Van Praagh R, Van Praagh S. Atrial isomerism in the heterotaxy syndromes with asplenia, or polysplenia, or normally formed spleen: an erroneous concept. Am J Cardiol 1990; 66: 1504-1506.
42. Layton WM Jr. Random determination of a developmental process. Reversal of normal visceral asymmetry in the mouse. J Hered 1976; 67: 336-338.
43. Layton WM Jr. Heart malformations in mice homozygous for a gene causing situs inversus. In: Morphogenesis and Malformation of the Cardiovascular System. Rosenquist G, Bergsma D (eds,). Alan R Liss for the National Foundation March of Dimes, New York 1980; 14: 277.
44. Layton WM, Manasek FJ. Cardiac looping in early iv/iv mouse embryos. In: Etiology And Morphogenesis Of Congenital Heart Disease. Van Praagh R, Takao A (eds). Futura Publishing Co, Mt. Kisco, New York 1980; 109.
45. Yost HJ. Establishing cardiac left-right asymmetry. In: Heart Development. Harvey RP, Rosenthal N (eds). Academic Press, San Diego, London 1999; 373.
46. Majumder K, Overbeek PA. Left-right asymmetry and cardiac looping. In: Heart Development. Harvey RP, Rosenthal N (eds). Academic Press, San Diego, London 1999; 391.
47. Oliverio M, Digilio MC, Versacci P, Dallapiccola B, Marino B. Shells and heart: are human laterality and chirality of snails controlled by the same maternal genes? Am J Med Genet A 2010; 152A: 2419-2425.
48. De Luca A, Sarkozy A, Consoli F, Ferese R, Guida V, Dentici ML, Mingarelli R, Bellacchio E, Tuo G, Limongelli G, Digilio MC, Marino B, Dallapiccola B. Familial transposition of the great arteries caused by multiple mutations in laterality genes. Heart 2010; 96: 673-677.
49. Digilio MC, Casey B, Toscano A, Calabrò R, Pacileo G, Marasini M, Banaudi E, Giannotti A, Dallapiccola B, Marino B. Complete transposition of the great arteries: patterns of congenital heart disease in familial precurrence. Circulation 2001; 104: 2809-2814.
50. Goldmuntz E, Bamford R, Karkera JD, dela Cruz J, Roessler E, Muenke M. CFC1 mutations in patients with transposition of the great arteries and double-outlet right ventricle. Am J Hum Genet 2002; 70: 776-780.
51. Cipollone D, Amati F, Carsetti R, Placidi S, Biancolella M, D'Amati G, Novelli G, Siracusa G, Marino B. A multiple retinoic acid antagonist induces conotruncal anomalies, including transposition of the great arteries, in mice. Cardiovasc Pathol 2006; 15: 194-202.