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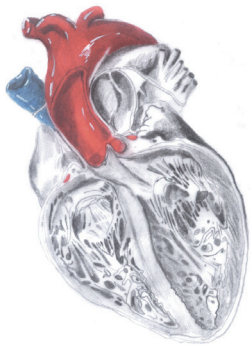
# 3 The Algebra and Geometry of Normally and Abnormally Related Great Arteries



## 3.1. Basic Principles

1. When the situs (or pattern of anatomic organization) of the subarterial infundibulum and the situs of the great arteries are the same (concordant), the great arteries are normally related.
2. When the situs of the subarterial infundibulum and the situs of the great arteries are different (discordant), the great arteries are abnormally related.

**The degree of development of the subarterial infundibulum** may be graded as follows:

- **grade 0** = absence;
- **grade 1** = very severe hypoplasia, with outflow tract atresia;
- **grade 2** = severe hypoplasia, with severe outflow tract stenosis;
- **grade 3** = mild to moderate hypoplasia, with mild to moderate outflow tract stenosis; and
- **grade 4** = normal development, with no outflow tract stenosis.

## 3.2. Functions of the Infundibulum

A well developed (grade 4) subarterial infundibulum blocks or prevents such a great artery from undergoing an embryonic great arterial switch from above the developing right ventricle (RV) to above the developing left ventricle (LV).

Absence of a subarterial muscular infundibulum (grade 0) beneath a great artery permits or facilitates an embryonic great arterial switch, normally during the fifth week of life in the human embryo.

**Infundibulo-arterial situs equations1** facilitate infundibulo-arterial situs analysis, which in turn reveals the many different kinds of infundibulo-arterial situs differences (or discordances) that result in different kinds of abnormally related great arteries.

**1. Solitus normally related great arteries:**

**SNRGA {S,D,S} = OR + 4L**

In words, this equation says: solitus normally related great arteries with the segmental situs set of solitus atria,

D-loop (or solitus) ventricles, and solitus normally related great arteries equals absence of the right-sided subaortic infundibular free wall plus a well developed left-sided subpulmonary infundibular free wall. {} braces mean "the set of". In solitus normally related great arteries, the right--sided great artery is the aorta and the left-sided great artery is the pulmonary artery (Fig. 3.1, third column from the right).

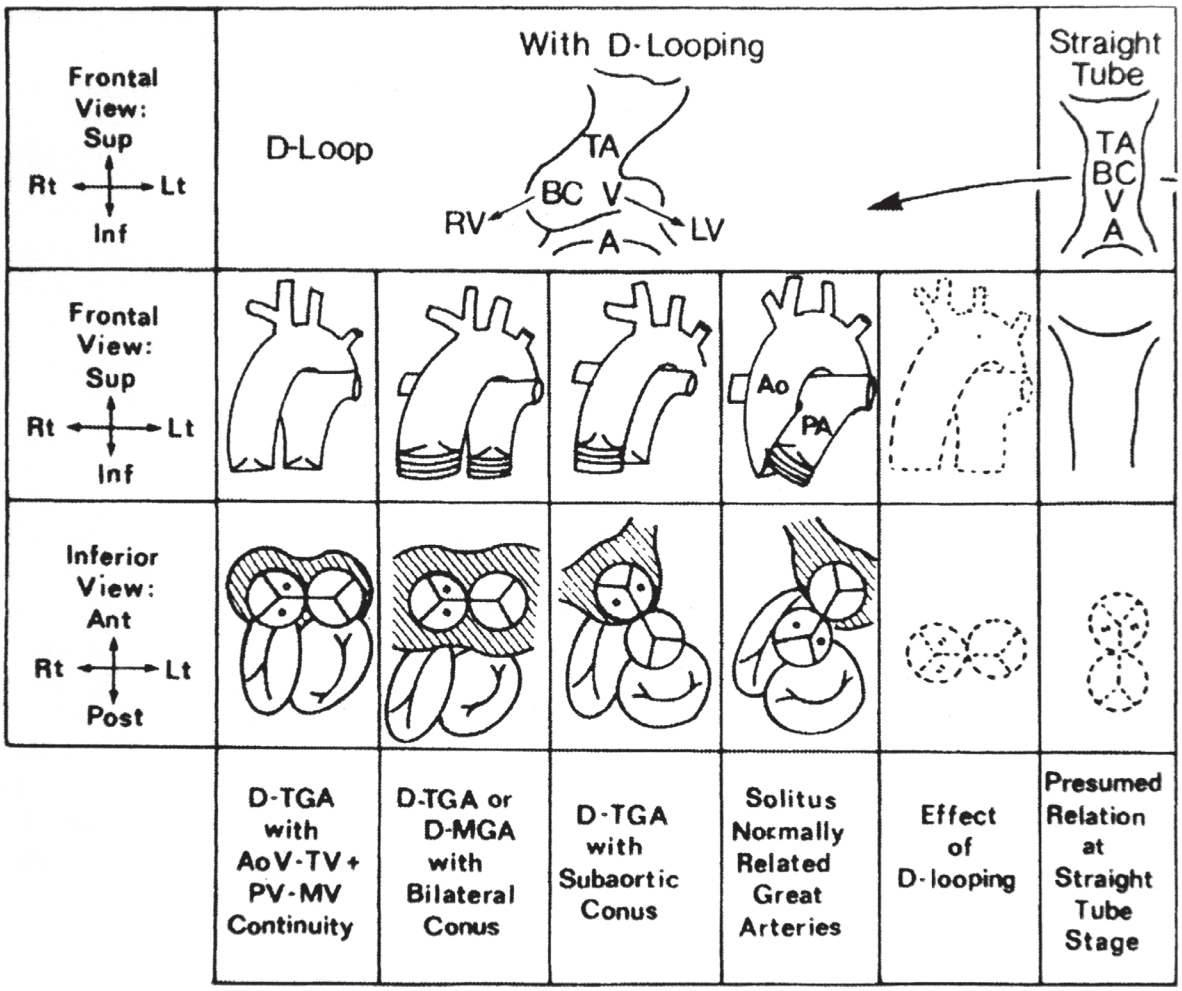



**FIGURE 3.1.**

Normal and abnormal anatomy and development of the solitus (noninverted) human heart, presented diagrammatically.

*Rightmost column:* Straight tube stage. TA, truncus arteriosus, where the great arteries will develop. BC, bulbus cordis, where the infundibulum (or conus arteriosus) will develop beneath the great arteries, and where the morphologically right ventricular sinus (inflow tract) normally will develop beneath the infundibulum. V, the ventricle of the bulboventricular straight tube and of the D-bulboventricular loop, where the morphologically left ventricle (LV) normally will develop. The semilunar valves are depicted in broken lines to indicate that these valves are not really separate at this early stage, as they are shown here for comprehensibility. The developing aortic valve, indicated by coronary ostia, is thought to be directly anterior to the developing pulmonary valve at this early stage. The long axis of the semilunar valves may be defined as a straight line from the midpoint of the noncoronary sinus of Valsalva of the aortic valve to the midpoint of the pulmonary nonseptal sinus of Valsalva. The long axis of the developing aortic and pulmonary valves is parallel to the sagittal (or anteroposterior) plane. At the straight tube stage, there is no rotation of the long axis of the semilunar valves relative to the sagittal plane.

*Second column from the right:* D-loop formation, i.e., looping of the straight heart tube convexly to the right forming a dextro- or D-bulboventricular loop results in about 90° dextrorotation of the semilunar valves, with the aortic valve to the right of the pulmonary valve. The semilunar valves are viewed from below, as in a subxiphoid 2-dimensional echocardiogram. At this stage, both great arteries are above the RV, as they are at the straight tube stage.

*Third column from right:* Solitus normally related great arteries. *Solitus* means usual, ordinary, customary (Latin). In anatomy, solitus often means the usual, noninverted form, not the inverted or mirror-images form. So, how are solitus normally related great arteries achieved? The subaortic and the subpulmonary infundibular free walls display complete right-left asymmetry.[27] The right-sided subaortic infundibular free wall normally undergoes involution. It disappears, it is thought, because of apoptosis, i.e., genetically programmed cell death. The aortic valve then sinks inferiorly, posteriorly, and leftward and passes through the interventricular foramen to arise above the LV. The aortic valve then comes into direct fibrous continuity with the mitral valve via an intervalvar fibrosa. This process is known as the normal embryonic aortic switch from above the RV to above the LV. Simultaneously, the subpulmonary infundibular free wall is behaving in a completely opposite way. The subpulmonary infundibular free wall is growing strongly. The pulmonary valve is being carried anteriorly, superiorly, and rightward – away from the interventricular foramen, to aid the aortic switch. The presence of a well developed subarterial infundibulum typically prevents an arterial switch, keeping the main pulmonary artery above the RV.[27]

*Fourth column from the right:* D-transposition of the great arteries (D-TGA) with a well developed subaortic infundibular (conal) free wall and absence of the subpulmonary infundibular free wall. What is typical D-TGA really? Infundibular inversion and its sequelae. The development of a right-sided subaortic infundibular free wall prevents a normal embryonic aortic switch, so the aorta remains above the RV. Apoptosis destroys the subpulmonary infundibular free wall. So the pulmonary artery gets switched. Voilà D-TGA.

*Fifth column from the right:* A bilateral infundibulum – subaortic and subpulmonary – is perhaps most typically seen in double-outlet right ventricle (DORV) of the Taussig-Bing type.[21,22] This may represent absence of apoptosis.

*Leftmost column:* D-TGA with pulmonary-mitral and aortic-tricuspid fibrous continuity. A rare case. When this diagram was made, we had not yet seen the Paul type of double-outlet left ventricle.[23]

**Infundibulo-Arterial Situs Equations:**

SNRGA {S,D,S} = OR + 4L (Solitus normal)

TGA {S,D,D} = 4R + OL (D-TGA)

DORV {S,D,D} = 4R + 4L (Taussig-Bing)[21,22]

*Abbreviations:* Ant, anterior; Inf, inferior; Lt, left; Post, posterior; Rt, right; Sup, superior.

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An equation is a symbolic sentence. The verb is the equals sign (=), meaning "is" or "are". The subject of the sentence lies to the left of the equals sign. The predicate lies to the right of the equals sign. Being an equation, this sentence is true bidirectionally. Read from left to right, this equation is a definition of the solitus normal heart. But read "backwards" – from right to left – this equation tells how the solitus normal heart is made. The situs formula or "recipe" of the all-important infundibulum lies to the right of the equals sign, in the "predicate."

The infundibular situs formula to make a normal solitus (noninverted) human heart is **OR + 4L**. The right-sided subaortic infundibular free wall is absent, it is now thought, because of apoptosis, i.e., genetically programmed cell death. The left-sided subpulmonary infundibular free wall is well developed.

How do you know this is the formula for producing a normal solitus heart? It's all in equation 1. The important parts are bolded: **SNRGA** {S,D,**S**} = **OR + 4L**

**OR + 4L** is the recipe for producing a solitus normal heart. There is only one way of doing it right: equation 1 and its mirror-image or inverted isomer:

**2. INRGA {I,L,I} = 4R + OL**

The inverted normal heart is presented diagrammatically in Figure 3.2, third column from the left. As we shall soon see, there are many different ways of producing abnormally related great arteries.

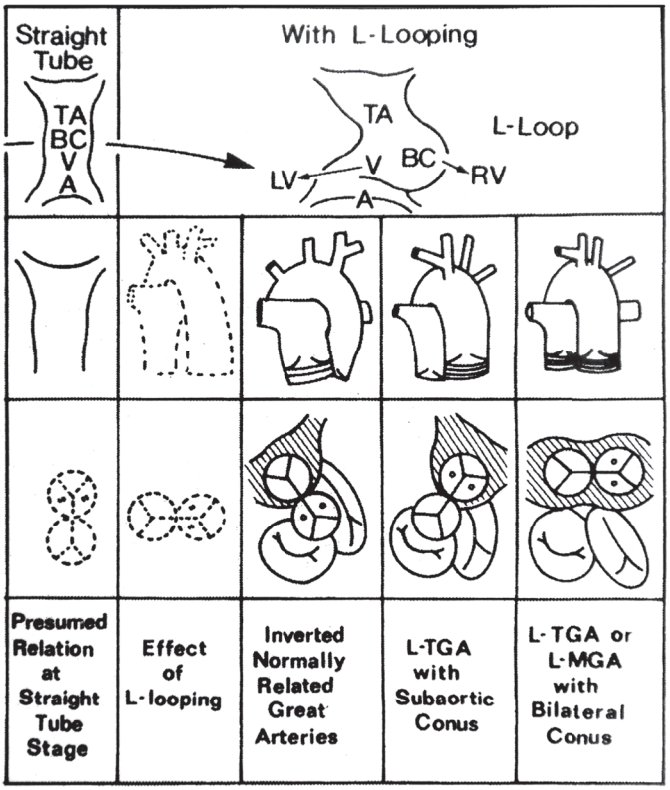


**FIGURE 3.2.**

The anatomy and development of the inverted heart. This figure is a mirror-image of Figure 3.1. L-loop formation is associated with 90° L-rotation at the level of the semiluncar valves. The heart with inverted normally related great arteries is a mirror-image of the heart with solitus normally related great arteries in Fig. 1. Similarly, the heart with L-TGA is a mirror-image of the heart with D-TGA in Figure 3.1.

**Infundibulo-Arterial Situs Equations**

INRGA {I,L,I} = 4R + OL (Inverted Normal)

TGA {I,L,L} = OR + 4L (L-TGA)

TGA {I,L,L} = 4R + 4L (L-TGA)

The atrioventricular valves, the subarterial infundibulum, and the semilunar valves are diagrammed as viewed from below. Columns 4 and 5 from the left both show L-TGA. Column 4 has a subaortic infundibulum and no subpulmonary infundibulum, whereas column 5 depicts a case of L-TGA with a bilaterally well developed infundibulum. These are just *some* of the diagrams and *some* of the equations that could be presented, but by no means all.

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**Returning to the solitus normal infundibulum, OR + 4L, the numerals are very important.** Zero (0) means that there is no subaortic infundibular free wall. **Absence of a subaortic infundibular free wall permits or facilitates a switch of the aorta from above the RV to above the LV.** The aortic valve passes through the interventricular foramen and comes into direct fibrous continuity with the mitral valve via the intervalvar fibrosa.

- **The presence of a well developed subpulmonary infundibulum in a normal solitus infundibulum (OR + 4L) prevents a great arterial switch of the pulmonary artery**, which therefore remains above the RV in solitus normally related great arteries.

The morphogenetic movements of the great arteries are reciprocals (opposites). As the aortic valve moves inferiorly, posteriorly and leftward, the pulmonary artery moves superiorly, anteriorly, and rightward. This gets the pulmonary valve "out of the way" – away from the interventricular foramen, facilitating the embryonic aortic switch into the LV.

**Thus, the infundibulum is the "switch master":**
**(1) no subarterial infundibulum typically permits an embryonic great arterial switch; and**
**(2) a well developed subarterial infundibulum typically prevents an embryonic great arterial switch.**

**This will become more and more obvious in the equations that follow.**

## 3.3. The tetralogy of Fallot

**The tetralogy of Fallot is really the monology of Stensen.** The malformation now known as the tetralogy of Fallot was first described in 1671 by Niels Stensen[2], the Dane of parotid duct fame. In 1888, Arthur Fallot of Marseille

published his papers concerning what he called the blue disease *(la maladie bleue)*. He wrote with charm, anatomic accuracy, and clinicopathologic relevance. Fallot unhesitatingly acknowledge the prior work of others.

In 1924, Abbott and Dawson[4] coined the term *tetralogy of Fallot*. They thought it would be more brief and convenient than having to repeat all four anomalies every time one encountered such a case.

In 1970, Van Praagh and colleagues[5] proposed that *the tetralogy of Fallot is basically a "monology", just one malformation, i.e., underdevelopment of the subpulmonary infundibulum, and its sequelae.* The classical tetrad of anomalies all appear to be secondary to hypoplasia of the subpulmonary infundibulum:
(1) pulmonary outflow tract stenosis or atresia;
(2) ventricular septal defect;
(3) aortic overriding; and
(4) right ventricular hypertrophy.

Morphometric study by Lev and colleagues[6] has shown that right ventricular hypertrophy is not present at birth in tetralogy of Fallot, but instead is a postnatally acquired sequel. This means that the "tetralogy" of Fallot is really a trilogy, not a tetralogy, even if counted conventionally – without developmental understanding.

**We published a detailed study of the monology of Stensen (MOS) in 2009, including a statistically controlled morphometric study of neonatal heart specimens of this anomaly.** The salient findings were as follows:
(1) the infundibular cross-sectional area in neonatal MOS was statistically significantly smaller than normal controls ($p < 0.01$);
(2) the pulmonary valve area in neonatal MOS was statistically significantly smaller than in normal neonatal controls ($p < 0.01$);
(3) the main pulmonary artery area in neonatal MOS was statistically significantly smaller than neonatal age-matched normal controls ($p < 0.01$); and
(4) the subpulmonary infundibular volume in neonatal MOS was statistically significantly smaller than in age-matched neonatal controls ($p < 0.01$).

**So this is what the neonatal monology of Stensen ("T" OF) really is: a statistically significantly low-volume subpulmonary infundibulum compared with age-matched controls ($p < 0.01$).**

Now let us return to the infundibulo-arterial situs equations:
**3.TOF {S,D,S} = OR + 1L** (TOF – atresia)
**4.TOF {S,D,S} = OR + 2L** (TOF, severe PS)
**5.TOF {S,D,S} = OR + 3L** (TOF with mild/moderate PS)

Equations 3, 4, and 5 concern TOF. I am using TOF (instead of MOS) in deference to common usage. Each equation has the set of solitus atria, solitus or D-loop ventricles, and solitus normally related great arteries.

But to the right of the equals signs, each equation is different, i.e., the degree of the left-sided PS is different. In equation 3, the expression **1L** indicates that the left-sided subpulmonary infundibulum is extremely hypoplastic, **grade 1**, and therefore maximally obstructive hemodynamically, i.e., **atretic.**

In equation 4, the degree of subpulmonary infundibular hypoplasia is **grade 2**, i.e., severe, resulting hemodynamically in **severe stenosis** of the pulmonary outflow tract.

In equation 5, the degree of subpulmonary infundibular hypoplasia is **grade 3**, i.e., mild to moderate, resulting in **mild to moderate pulmonary outflow tract stenosis.**

Regarding infundibulo-arterial situs analysis in TOF, the infundibular situs recipes or formulas lie to the right of the equal signs in equations 3 – 5: OR + 1L, OR + 2L, and OR + 3L. These infundibular formulas in TOF closely resemble the normal situs solitus infundibular formula in equation 1: OR + 4L. The only differences in the formulas of TOF are those that are necessary to indicate the variable hypoplasia of the subpulmonary infundibulum – which is what TOF is.

Thus, the leftward infundibular expressions in the TOF equations 3 – 5, that govern the status of the pulmonary outflow tract, belong in the family of solitus equations (equation 1).

The aorta in TOF also fits into the solitus normal family of equations (as in equation 1).

**Thus, the infundibulo-arterial situs analysis in TOF (equations 3 – 5) is solitus-solitus.**

Geometrically, however, in TOF the great arteries appear to be *almost* normally related: (1) Aortic overriding indicates that the aortic valve is not as fully levoposed as normal. Aortic-mitral fibrous continuity is present, but it is often somewhat tenuous. In fully normally related great arteries, the noncoronary-left coronary commissure of the aortic valve is located above the middle of the anterior mitral leaflet. Consequently, in fully normally related great arteries, the aortic-mitral fibrous continuity is between the noncoronary leaflet and the left coronary leaflet of the aortic valve and the deep anterior leaflet of the mitral valve.

But in many cases of TOF, the aortic-mitral fibrous continuity is between only the left coronary leaflet of the aortic valve and the anterior mitral leaflet, because the aortic valve is too far to the right for the noncoronary aortic leaflet to be in fibrous continuity with the normally located mitral valve.

- In other words, in TOF, the aortic valve is a little bit too right-sided, a little bit too superior, and a little bit

too anterior compared with a fully normally located aortic valve. This is why the aortic valve in TOF is said to be "overriding".

- But there's more. In TOF, the pulmonary valve is a little bit too left-sided, too posterior, and too inferior. But we don't talk about that much because the pulmonary artery is nonetheless arising above the right ventricle.

In TOF, what is really going on?

The locations, and the morphogenetic movements of the aortic and the pulmonary valves are reciprocals (or opposites):

(1) The aortic valve is a little too right-sided, superior, and anterior.

(2) The pulmonary valve is a bit too left-sided, inferior, and posterior.

Why is that?

Because in TOF, the great arteries are incompletely dextrorotated.

Again, why is that?

Because of the hypoplasia of the subpulmonary infundibulum, which is what TOF basically is.[2]

Normally (Fig. 3.3), D-loop formation is associated with about 90° of D-rotation at the semilunar valves relative to the sagittal plane. Normal development of the solitus infundibulum (OR + 4L, equation 1) is associated with another 60° of D-rotation at the semilunar valves (Fig. 3.3).

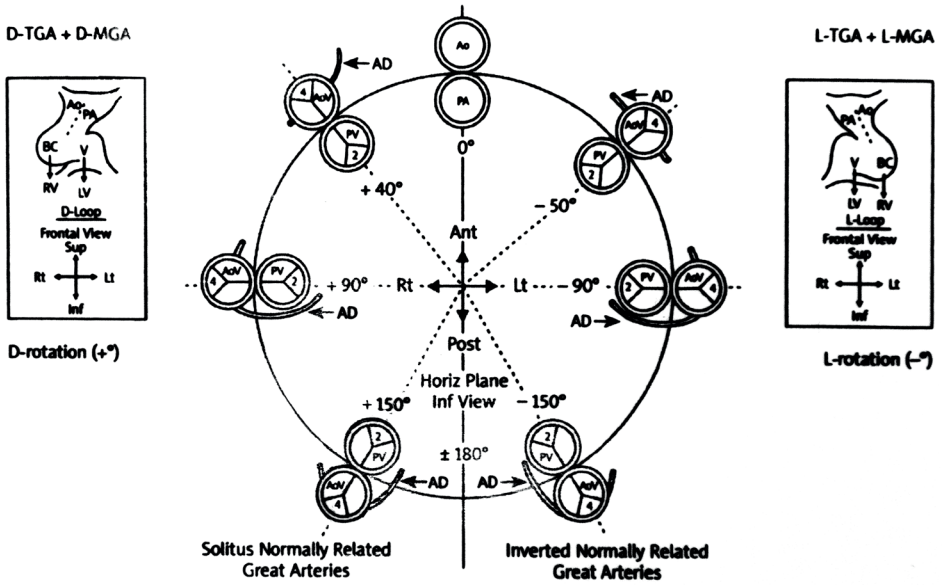


**FIGURE 3.3.**

Normal and abnormal morphogenetic movements of the great arteries in solitus and inverted hearts. *In solitus or D-loop hearts*, D-loop formation is associated with approximately 90° dextrorotation at the semilunar valves. The aortic valve (AoV) and the pulmonary valve (PV) are viewed from below, as in a subxiphoid 2 D-echocardiogram. The AoV is to the right and the PV is to the left. The development of the normal solitus infundibulum is associated with an additional 60° of D-rotation at the semilunar valves, bringing the total normal dextrorotation of solitus semilunar valves to approximately 150°, relative to the sagittal plane. The two "engines" of normal semilunar dextrorotation (D-loop formation, and solitus infundibular development) are bolded in the solitus normal infundibulo-arterial situs equation: SNRGA {S,**D**,S} = **OR + 4L**.

In inverted or L-loop hearts, L-loop formation is associated with approximately 90° of levorotation (or −90° L-rotation). Development of the "normal" inverted infundibulum is associated with an additional 60° of L-rotation, bringing the "normal" total L-rotation at the semilunar valves to about −150° L-rotation. The two "engines" of L-rotation at the semilunar valve in "normal" inverted hearts are bolded in its equation: INRGA {I,**L**,I = **4R + OL**

In TGA, why is the aorta (Ao) typically anterior to the pulmonary artery (PA)? The brief answer is **synergy,** which means combined or cooperative action or force: *syn*, together + *ergon*, work (Greek). D-TGA is isolated infundibular inversion: TGA {S,D,D} = **4R + OL**. The expression to the right of the equals sign is the formula of the infundibulum, which determines the relationship between

the great arteries. This infundibular formula of D-TGA is the same as the infundibular formula for the inverted normal heart: INRGA {I,L,I} = **4R + OL**. This means that D-TGA has isolated infundibular inversion. We know that infundibular inversion is associated with 60º of L-rotation (from −90º to −150º). This means that a heart with typical D-TGA has 90º of dextrorotation (associated with D-loop formation) and 60º of levorotation (associated with infundibular inversion). The normal solitus heart has **positive synergy**: 90º + 60º = 150º. Both forces are working in the same healthy direction. But a patient with D-TGA has **negative synergy** – two forces working in opposite directions: 90º D-rotation (D-looping) and 60º L-rotation (inverted infundibulum). The same applies to L-TGA, but in mirror image. **So, why does TGA typically have an anterior aorta? A more precise answer. Negative synergy.** What is "complete" transposition of the great arteries in situs inversus totalis? Its infundibular situs equation is: TGA {I,L,L} = **OR + 4L**.

The infundibular situs formula for physiologically uncorrected TGA in situs inversus totalis (OR + 4L) is the same as that for solitus normally related great arteries: SNRGA {S,D,S} = **OR + 4L**. So, solitus (D-) TGA in situs solitus totalis has isolated infundibular inversion, all other cardiovascular segments being noninverted. Inverted (L-) TGA in situs inversus totalis has isolated infundibular noninversion, all other cardiovascular segments being inverted. The infundibular formula for solitus or D-TGA (4R + OL) and for inverted or L-TGA (OR + 4L) are mirror-images that may be expressed verbally, diagrammatically, or algebraically. These primarily infundibular anomalies may also be grouped by the arterial switch process: (1) aortic switch: normally related great arteries, and tetralogy of Fallot; (2) pulmonary arterial switch: transposition of the great arteries; (3) no switch: double-outlet right ventricle; (4) double switch: double-outlet left ventricle. Anatomically corrected malposition of the great arteries (ACM) is not included because it is a different kind of anomaly: the infundibulum and great arteries twist in a direction opposite to that of the bulboventricular loop. ACM not only has subarterial infundibular anomalies. ACM also has major ventricular looping anomalies. The usual D-loop or L-loop is chaped like a capital C, convex to the right (D-loop), or like a reversed capital C, convex to the left, i.e., Ↄ as in an L-loop. But ACM has a cardiac loop that is shaped like a capital S, as in ACM {S,L,D} or like a reversed capital S, i.e., Ƨ, as in ACM {S,D,L}. Thus, ACM is more than infundibulo-arterial situs discordance. ACM also has a unique reversing malformation of the cardiac loop. Truncus arteriosus communis is also omitted because we now realize that it is erroneous; please see the text.

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In TOF, although D-loop formation typically is normal (90º D-rotation, Fig. 3.3), subpulmonary infundibular development is subnormal (< 60º D-rotation, Fig. 3.3).

This is why in TOF, D-rotation at the semilunar valve level typically is mildly subnormal, resulting in aortic "overriding", subnormal aortic-mitral fibrous continuity, and abnormally leftward, posterior, and inferior pulmonary valve. As a pediatric cardiologist, I was privileged to spend one year of post-graduate training in the Cardiac Catheterization Laboratory of the Mayo Clinic. In the left lateral angiocardiograms of patients with TOF, we often saw the pulmonary artery arising in the *middle* of the large aortic shadow, not anterior to the aorta. In TOF, the great arteries are more side-by-side than normal. Deficient D-rotation at the semilunar valve level, because of subpulmonary infundibular hypoplasia, explains why (Fig. 3.3).

## Conclusions Concerning TOF

1. TOF typically is characterized by infundibulo-arterial situs sameness (concordance): situs-solitus.
2. However, the semilunar relationship in TOF is subnormal because of characteristic aortic "overriding", often subnormal aortic-mitral fibrous continuity, and abnormally leftward, posterior, and inferior pulmonary valve. These abnormalities are related to subnormal dextrorotation of the great arteries at the semilunar valvar, which in turn is caused by subnormal expansible growth and development of the subpulmonary infundibulum.
3. Despite the foregoing abnormalities, TOF is still regarded as a form of normally related great arteries because of origin of the aorta from the left ventricle, with aortic--mitral fibrous continuity (albeit tenuous), and origin of the pulmonary artery from the right ventricle.

## Segmental Anatomy of TOF

Is it always normal, i.e., **TOF {S,D,S}?**

The answer is, "No, not always, but almost always." In a detailed study of 100 postmortem cases of TOF, it was found that 97 cases (97%) had the usual segmental anatomy, i.e., **TOF {S,D,S}**[7].

But prior to this study that was published in 2009,[7] Foran and colleagues[8] in 1988 had reported a case of TOF with isolated infundibulo-arterial inversion, i.e., **TOF = {S,D,I}.** The infundibulum and the great arteries were inverted normally related and afflicted with tetralogy of Fallot, i.e., **TOF {-,-,I}**, but the atria and the ventricles were noninverted or solitus, i.e., **- {S,D,-}.**

Why does TOF {S,D,I} matter? With the usual TOF {S,D,S} segmental anatomy, the obstructed pulmonary outflow tract lies to the left and the unobstructed aortic outflow tract lies to the right (Fig. 3.4). However, with isolated infundibulo-arterial inversion, i.e., TOF {S,D,**I**}, the obstructed pulmonary outflow tract lies to the *right,* and the nonobstructed aortic outflow tract lies to the *left* (Fig. 3.5). In order for the right coronary artery to reach

the right atrioventricular groove, the right coronary artery "must" run across the right-sided pulmonary outflow tract. Thus, from a surgical standpoint, the right coronary artery is always "in the way". Traveling left-to-right from its origin from the left-sided aorta, the right coronary artery "must" pass right across the obstructive right-sided pulmonary outflow tract to reach the right atrioventricular groove. This is precisely where the surgeon would like to place an infundibulotomy to open up the patient's obstructive infundibulum.

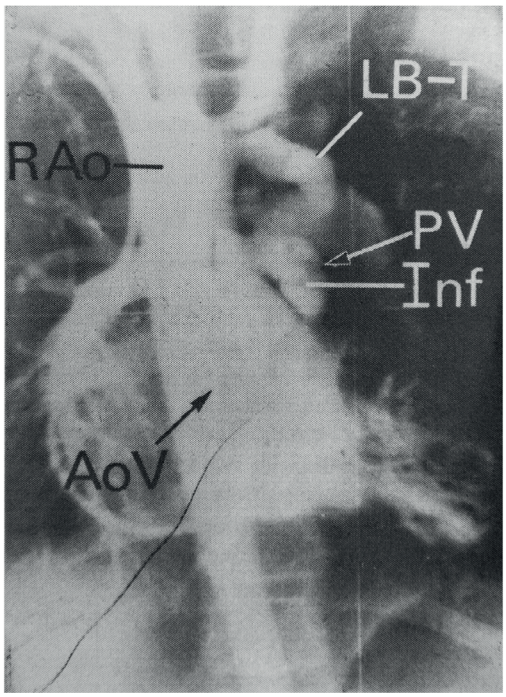


**FIGURE 3.4.**

Tetralogy of Fallot {S,D,S}, i.e., TOF with the usual solitus (noninverted) infundibulum and great arteries. Selective right ventricular injection, posteroanterior projection. The small volume infundibulum (Inf), the small pulmonary valve (PV), and the small main pulmonary artery are well seen. The aortic valve (AoV) is low, typical of a normally located AoV. There is a right aortic arch (R Ao) with mirror-image branching of the brachiocephalic arteries. A classical left Blalock-Taussig anastomosis (LB-T) has been placed on the side opposite to that of the aortic arch. A left subclavian artery has been turned down to perform this B-T shunt. Note that the normal or solitus semilunar right-left relationship is: AoV is right-sided, relative to the PV which is left-sided. This normal R-L semilunar relationship is initially counter-intuitive, but factually important. The pulmonary outflow tract that needs to be enlarged lies to the *left* of the ascending aorta.

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From the surgical view point, in order to avoid injury to the right coronary artery, a conduit can be used to create a nonobstructive right ventricular outflow tract; or the same objective may be achieved by myocardial resection within the right ventricular outflow tract beneath the crossing right coronary artery, as Santini and colleagues[9] did successfully and reported in 1995.

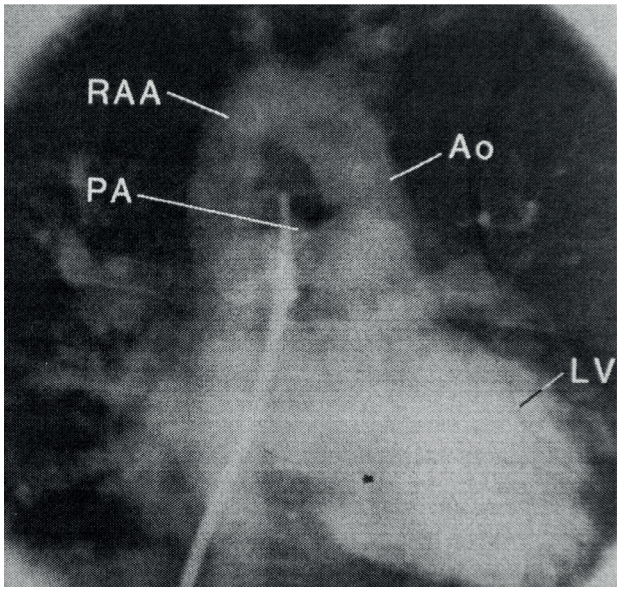


**FIGURE 3.5.**

Angiocardiography in tetralogy of Fallot {S,D,I}, postero--anterior projection. The catheter is in the stenotic main pulmonary artery (PA), which lies to the *right* of the ascending aorta (Ao). The left ventricle (LV) and a right aortic arch (RAA) are also seen. These findings indicate that the right coronary artery almost certainly will run from the left-sided aorta in a rightward direction across the stenotic subpulmonary infundibulum in order to reach the right atrioventricular groove. In other words, the right coronary artery is "in the way". It will be running right across the subpulmonary infundibulum that the surgeon may well want to incise in order to open up the right ventricular outflow tract. What to do? Either a right ventricular outflow tract conduit to "jump" over the right coronary artery; or myocardial excision beneath the right coronary artery to unobstruct the right ventricular outflow tract. Fortunately, Drs. Santini and Jonas[9] were able to avoid a conduit by myocardial resection.

(Reproduced with permission from Santini and colleagues.[9])

It should be added that if there are any skeptics regarding the above-mentioned surgically important course of the right coronary artery in isolated infundibuloarterial

inversion in TOF {S,D,I}, the right coronary artery can be visualized angiocardiographically running immediately anterior to the obstructive subpulmonary infundibulum (Fig 6).

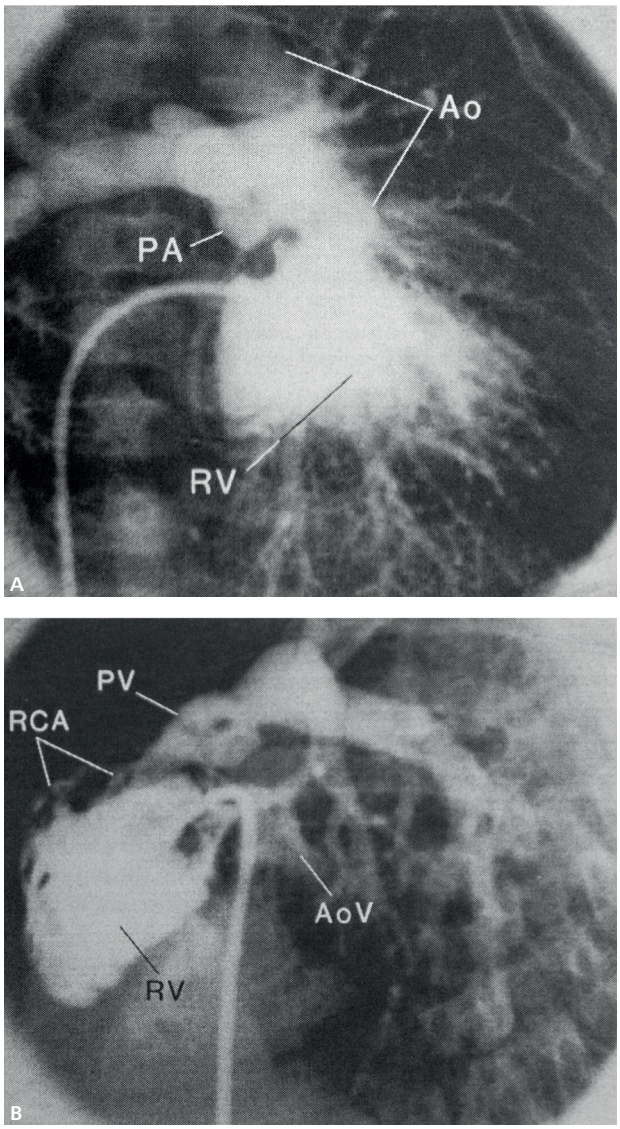


**FIGURE 3.6.**

Angiocardiography in TOF {S,D,I}, selective right ventricular injection, posteroanterior projection (left), left lateral projection (right). Selective RV injection shows not only the RV, the aortic valve (AoV), and the pulmonary valve (PV), but also the right coronary artery (RCA) running anteriorly across the subpulmonary infundibulum.

(Reproduced with permission from Santini and colleagues.[9])

**Does TOF occur in visceroatrial situs inversus?** The answer is "yes".

In our study of 100 unrelated cases of TOF,[7] there was 1 patient with **TOF {I,L,I}.** (1%). The segmental anatomy indicates that the patient had tetralogy of Fallot (TOF) with the segmental situs set of situs inversus of the viscera and atria TOF {I,-,-}, inverted ventricles –L-loop ventricles – {-,L,-}, and inverted normally related great arteries – {-,-,I}.

Surgically, inverted TOF patients need an inverted or mirror-image TOF repair.

**TOF {I,D,S}** was present in 2 of our 100 cases (2%).

**TOF only occurs to patients with normally related great arteries, solitus or inversus.**

These two rare patients had isolated noninverted ventricles and great arteries, with visceroatrial situs inversus and atrioventricular discordance. Most cardiologists and surgeons find the segmental anatomy clearer and easier to understand: TOF {I,D,S}. Both the words and the anatomic symbols strive to describe the same situation:

The viscera and atria are inverted. The ventricles are noninverted or D-loop. Consequently there is one intersegmental alignment discordance at the atrioventricular (AV) junction. One intersegmental alignment discordance physiologically uncorrects the systemic venous and the pulmonary venous circulations because the right atrium and the aorta are ipsilateral (both left-sided), and the left atrium and the pulmonary artery are both ipsilateral (both right-sided).

Because of the physiological uncorrection of the circulations, a right-left switch procedure needs to be done: a mirror-image Senning or Mustard procedure at the atrial level. A solitus or noninverted TOF repair also needs to be done.

**How common is tetralogy of Fallot?**

In our cardiac pathology database, TOF is the fifth commonest anatomic type of congenital heart disease: 407 cases, 14% (Table 3.1).[7]

**TABLE 3.1.**

Autopsied Cases of Congenital Heart Disease: Top 15 Anatomic Types (n = 2965)

| Anatomic Types | No. | % |
|---|---|---|
| 1. Ventricular septal defect | 1077 | 36 |
| 2. Atrial septal defect, secundum | 745 | 25 |
| 3. Patent ductus arteriosus ( > 2 weeks) | 557 | 19 |
| 4. Transposition of the great arteries | 442 | 15 |
| 5. Tetralogy of Fallot | 407 | 14 |
| 6. Aortic stenosis | 358 | 12 |
| 7. Coarctation of the aorta | 356 | 12 |
| 8. Persistent left superior vena cava | 345 | 12 |
| 9. Completely common atrioventricular canal | 343 | 12 |
| 10. Pulmonary stenosis | 304 | 10 |
| 11. Bicuspid aortic valve | 240 | 8 |
| 12. Bicuspid pulmonary valve | 238 | 8 |
| 13. Double-outlet right ventricle | 233 | 8 |
| 14. Anomalous pulmonary venous return | 223 | 8 |
| 15. Aortic atresia, valvar | 207 | 7 |

**Table 3.1. Percentages are all rounded off to the nearest whole number. This table summarizes the findings in 2,965 patients who had 5,852 congenital heart malformations. Many patients had more than one cardiac malformation.**

## Associated Malformations With TOF

Patients with TOF often have clinically and surgically important associated malformations that are summarized in Table 3.2.

**TABLE 3.2.**

Associated Malformations In Patients With Tetralogy of Fallot n = 100 postmortem cases

| Associated Anomalies | No. & % |
|---|---|
| Pulmonary atresia | 37 |
| Secundum atrial septal defect with common atrium in 5 | 35 |
| Multiple congenital anomalies | 29 |
| Right aortic arch | 28 |
| Aortopulmonary collateral arteries | 26 |
| Persistent left or right superior vena cava: LSVC 15, RSVC 1 | 16 |
| Patent ductus arteriosus | 13 |
| Absent ductus arteriosus | 12 |
| Completely common atrioventricular canal: type C, 6; type A, 1; not specified, 2 | 9 |
| Zespół Downa | 8 |
| Down's syndrome familial, 2 | 2 |
| Aberrant right or left subclavian artery | 8 |

**TABLE 3.2, CONTINUED**

| | |
|---|---|
| Anomalous muscle bundles of the right ventricle | 8 |
| Absent pulmonary valve leaflets syndrome | 6 |
| Restrictive ventricular septal defect | 5 |
| Additional muscular ventricular septal defects | 5 |
| Ectopia cordis: complete thoracic, 1; thoracoabdominal, 3 | 4 |
| Familial congenital heart disease | 4 |
| Myxomatous aortic valve | 4 |
| Aortic valvar regurgitation | 4 |
| Bicuspid aortic valve | 3 |
| Coronary sinus septal defect | 3 |
| Single left coronary artery | 3 |
| Trisomy 18 | 2 |
| Parachute mitral valve | 2 |
| Superior vena cava to left atrium because of unroofed coronary sinus | 2 |
| Chromosomal anomalies | 2 |
| Twins | 2 |
| Conjoined twin | 1 |
| Aortic stenosis, valvar | 1 |
| Partially anomalous pulmonary venous connection | 1 |
| Turner's syndrome | 1 |
| Kleinfelter's syndrome | 1 |
| Thick-walled and small-chambered right ventricle with restrictive ventricular septal defect | 1 |
| Sinusoids between right ventricle and right coronary artery with restrictive ventricular septal defect | 1 |
| Small anterolateral papillary muscle group of left ventricle | 1 |
| Dextrocardia | 1 |
| Mesocardia | 1 |
| Heterotaxy with polysplenia syndrome | 1 |
| Quadricuspid aortic valve | 1 |
| Vascular ring: right aortic arch, aberrant left subclavian artery, and left-sided patent ductus arteriosus | 1 |
| Congenital mitral stenosis | 1 |
| Intussusception of left atrial appendage, inside-out appendage producing supramitral stenosis | 1 |
| Absence of infundibular septum | 1 |
| Hypertrophy of infundibular septum | 1 |
| Viscero-atrial situs discordance: {IS,D,S}, situs inversus of abdominal viscera, with situs solitus of the atria, and with appropriate veno-atrial connections | 1 |
| Absence of main pulmonary artery, left pulmonary artery, right pulmonary artery, and of both ductus arteriosi | 1 |

## Language Note

*Ductus* is an important fourth declension, masculine Latin noun. The plural of *ductus* is *ductus (or ductūs)*, not *ducti* – as it would be if *ductus* were a second declension noun like *Romanus*. So the correct plural of *ductus arteriosus* is *ductus arteriosi.*

*Situs* is another important fourth declension masculine Latin noun. The plural of *situs* is *situs* (not *siti*).

### Infundibulo-Arterial Situs Equations for TOF

3. TOF {S,D,S} = OR + **1**L
4. TOF {S,D,S} = OR + **2**L
5. TOF {S,D,S} = OR + **3**L

TOF is characterized by variable hypoplasia of the left--sided subpulmonary infundibulum. In TOF, the left-sided infundibular hypoplasia can be mild to moderate (grade 3, equation 5), or severe (grade 2, equation 4), or extreme (grade 1, equation 3).

This progressively more severe left-sided infundibular hypoplasia suggests the question: **Is it possible for the left-sided, subpulmonary infundibular hypoplasia to be absent? If so, what happens then?**

As we will see in a moment, the answer to this question is fascinating.

But first, the tetralogy equations also show that the right-sided subaortic infundibular free wall muscle appears to have undergone normal involution or resorption due to apoptosis, permitting or facilitating an embryonic aortic switch from RV to LV and achieving aortic-mitral fibrous continuity.

The subpulmonary left-sided infundibulum, however hypoplastic, appears also to have prevented an embryonic pulmonary arterial switch. Hence, the pulmonary artery in TOF remains unswitched, above the RV.

## 3.4. Absence of the Infundibulum

Yes, it is possible for the subarterial infundibulum to be absent, a finding that we noted[10] in 1965 in a study of the pathologic anatomy of truncus arteriosus communis that Dr. Maurice Lev had asked me to do.

In 1927, Abbott introduced the concept of a persistent common aortopulmonary trunk. The title of her publication was "absence or rudimentary development of aortic septum". Other distinguished authors then described and classified persistent truncus arteriosus.[12–16] In 1976, Calder and colleagues[17] described the clinical, angiocardiographic, and pathologic findings in 100 patients with truncus arteriosus communis, 79 of whom were autopsied cases.

**Our classification of truncus arteriosus communis** is presented diagrammatically in Figure 3.7.

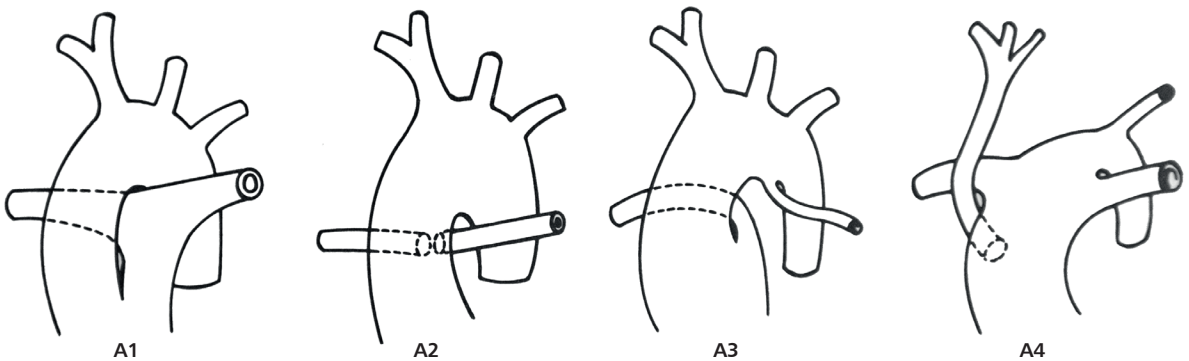


**FIGURE 3.7.**

Anatomic classification of "truncus arteriosus communis." *Type A* indicates that a ventricular septal defect is present. *Type A1* indicates that a remnant of the aortopulmonary (AP) septum is present. Type A2 indicates that no remnant of the AP septum is present. Type A3 is like type A2, except that a pulmonary artery branch is also absent. Type A4 has a small or absent aortic arch 4 and a large aortic arch 6 or ductus arteriosus. Types A1, A2, and A3 have a large aortic arch 4 and a small or absent pulmonary arch 6.

In 1927, Abbott[11] introduced the concept of truncus arteriosus communis persistens for cases that she thought had absence of the aortopulmonary septum, and consequently had a truncus arteriosus that was persistently in common or unseparated. In our cases[10] of type A1, the aortopulmonary septum was often quite well developed and the AP septal defect was small and low, not large. But type A2 seemed like the kind of cases that Abbot[11] had in mind. The AP septum seemed to be absent. But then I recalled Congdon's[18] embryologic study in 1922 in which he found that the pulmonary artery branches both originated from the aortic sac and that only the main pulmonary artery originated from the truncus arteriosus. The right pulmonary artery (RPA) and the left pulmonary artery (LPA) both migrate on the 6th aortic arches to join with the main pulmonary artery (MPA). This means

that the pulmonary arterial system has two different components: (1) the RPA and the LPA branches from the aortic sac, and (2) the MPA from the truncus arteriosus. [The 6th aortic arches on which the RPA and the LPA migrate could be included as an essential third component in the pulmonary artery system.]

In type A2, the MPA is absent. The RPA and the LPA could no longer be used to hypothesize that the MPA must be present, even though we can't see it, because the RPA and LPA branches are present. So the MPA **must** be present. That argument no longer works, because now we know that the RPA and LPA branches, and the MPA are derived from different components.
So now we have to accept the data-based fact that in type A2, the MPA is absent, and that the *unmigrated* RPA and LPA support the conclusion that the MPA is absent. The RPA and the LPA are unmigrated because they have nowhere to migrate to, because the MPA is absent. In type A2, the great artery is a solitary aorta, not a common aortopulmonary trunk. Because the MPA is absent, it is not possible to have a common aortopulmonary trunk. Consequently it is proposed that the diagnosis of common aortopulmonary trunk be discontinued when it is anatomically inaccurate.

(Reproduced with permission from Calder and colleagues.[17])

**In about 2001, I realized that the classical concept of truncus arteriosus communis is incorrect.** Dr. Alfredo Vizcaino from Mexico City, Mexico brough us a fascinating consultation (Fig. 3.8). The right and left pulmonary artery branches originated from the dorsal surface of the ascending aorta via a short common pulmonary artery called the aortic sac. The main pulmonary artery was well formed, but it had no branches.

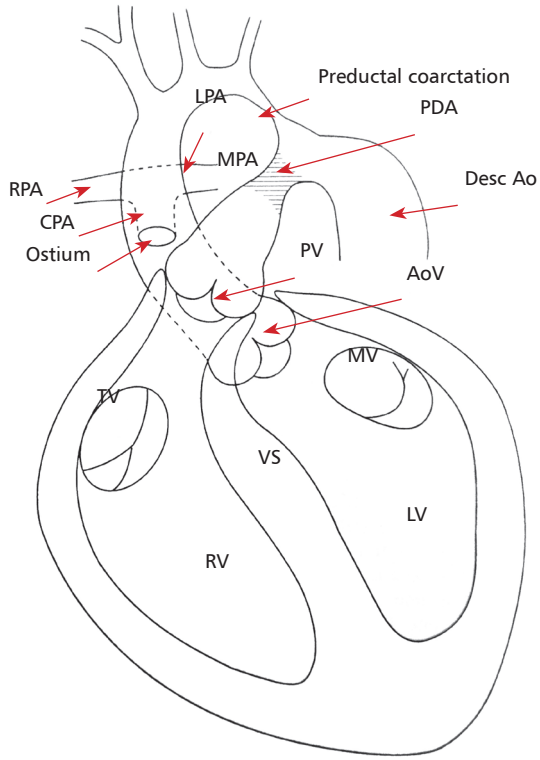


**FIGURE 3.8.**

Unmigrated right pulmonary artery (RPA) and left pulmonary artery (LPA) arising from the aortic sac that we called the common pulmonary artery (CPA). [We prefer Congdon's term[10] "aortic sac", in his honor]. Also noteworthy is the branchless main pulmonary artery. Normally, the RPA and the LPA migrate on the 6 aortic arches to fuse with the MPA. In this patient with multiple congenital anomalies, this migration of the RPA and LPA did not happen. Hence, the first diagnosis in this case probably should be: Apparent absence or dysfunction of the sixth aortic arches, resulting in nonmigration of the RPA and LPA, and in a main pulmonary artery without branches. Other noteworthy findings include preductal coarctation of the aorta (Preductal Coarc) and a narrowing patent ductus arteriosus (PDA). Perhaps one of the most important aspect of Viscaino's case[28] and others like it[19,20] is that it confirms Congdon's[18] embryologic findings in 1922 that the pulmonary arterial branches (RPA and LPA) and the main pulmonary artery (MPA) have different developmental origins. Hence, concerning truncus arteriosus communis, the presence of unmigrated pulmonary artery branches do not suggest that the MPA must be present – even though we can't see it. On the contrary, the findings in so-called truncus arteriosus communis strongly support the opposite conclusion: The MPA is absent. That is also why the pulmonary branches have not migrated from their starting position in the aortic sac. The pulmonary artery branches have nowhere to migrate to, *because* the MPA is absent. Also a common aortopulmonary trunk cannot be present when the MPA is absent. What we are looking at in "truncus" type A2 is a solitary aorta with unmigrated pulmonary branches that have been widely misunderstood.

(Reproduced with permission from Vizcaino and colleagues.[28])

I had worked in 1966 in the Department of Embryology of the Carnegie Institution of Washington, and fortunately I remembered the work of Congdon[18] that had been published in 1922. Congdon found that at the 4 mm stage, at 24 to 26 days of age in the human embryo, before the 6th aortic arches have been completely formed, the pulmonary artery branches both arise from the aortic sac. Completion of both 6th arches can occur as early as the 5-mm stage (26–28 days after fertilization), and usually occurs by the 6-mm stage (28–30 days of age).

As soon as both sixth aortic arches have been completely formed, they enlarge considerably, and both pulmonary artery branches migrate on the sixth arches to reach the main pulmonary artery.

So the pulmonary artery system has three component parts:

(1) the right and left pulmonary artery branches that arise initially from the aortic sac;
(2) the right and left sixth aortic arches on which the pulmonary artery branches migrate to fuse with the main pulmonary artery; and
(3) the main pulmonary artery.

We think that the diagnosis in Vizcaino's case (Fig. 3.8) is: bilateral absence (or other failure) of both sixth aortic arches, resulting in unmigrated pulmonary artery branches and in a branchless main pulmonary artery.

Absence of both sixth aortic arches is rare. To our knowledge, there are only two other published cases.[19,20]

Occasionally only one pulmonary artery branch arises from the ascending aorta. This is so-called **hemitruncus**, which really is functional failure (effective absence) of one sixth aortic arch, resulting in nonmigration of one pulmonary artery branch.

**What does this case of unmigrated pulmonary artery branches (Fig. 3.8) have to do with truncus arteriosus communis?**

In truncus arteriosus communis type A2 (Fig. 3.7 and 3.9)[10], the right pulmonary artery (RPA) and the left pulmonary artery (LPA) are unmigrated pulmonary artery branches that arise from the aortic sac. There is no remnant of the aortopulmonary septum (Fig. 3.9).

How should these findings be interpreted? Our old interpretation was as follows. There is no remnant of the aortopulmonary septum. But the main pulmonary artery must be present because both pulmonary artery branches are present. This conclusion was based on the assumption that the main pulmonary and its branches are one structure. The presence of one part (the branches) was thought to indicate the presence of the other part (the main pulmonary artery), even if one could not see the latter.

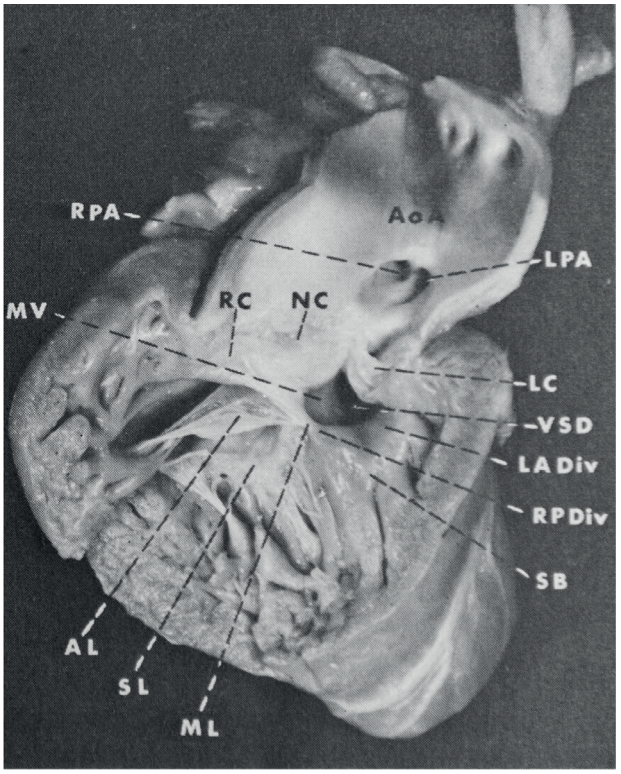


**FIGURE 3.9.**

So-called truncus arteriosus communis type A2.[10,17] The left-sided subpulmonary infundibulum is absent, septum and free wall. The pulmonary valve is absent. The main pulmonary artery is absent. The unmigrated right pulmonary artery (RPA) and left pulmonary artery (LPA) are arising from the aortic sac, their starting point. So, what is this malformation really? As already stated, this is absence of the left-sided subpulmonary infundibulum (septum and free wall), absence of the pulmonary valve, and absence of the main pulmonary artery (MPA) – but with lungs. This is reminiscent of the normal situation in amphibia (e.g., frogs): they have lungs, but no right ventricle (RV). Those two pulmonary artery branches (the RPA and the LPA) are physiologically like bilateral Blalock-Taussig anastomoses. Arising from the aortic sac, the RPA and the LPA get blood to the lungs via aortic branches, with no MPA.
*Abbreviations:* AL, anterior leaflet of tricuspid valve; AoA, aortic arch, LAD, left anterior division of septal band; LC, left coronary leaflet of aortic valve; ML, muscle of Lancisi, or Lushka; MV, mitral valve; NC, noncoronary leaflet of aortic valve; RC, right coronary leaflet of aortic valve; RPD, right posterior division of the septal band; SB, septal band; SL, septal leaflet of the tricuspid valve; VSD, ventricular septal defect.

(Reproduced with permission from Van Praagha nd Van Praagh.[10])

Our present interpretation is different. Now we know that the pulmonary arterial system consists of two separate components. Vizcaino's case (Fig. 3.8), and others like it,[19,20] prove that. Congdon's[18] embryologic research has been confirmed.

So now when we look at Figure 3.9, we see unmigrated right and left pulmonary artery branches arising from the aortic sac. We accept that the subarterial infundibulum is absent. The pulmonary valve is absent. The main pulmonary artery is absent; that is thought to be why the pulmonary artery branches remained unmigrated. The pulmonary artery branches had nowhere to migrate to – because the main pulmonary artery really is absent.

This also supports the view that in Figure 3.9, we are looking at a solitary aorta, not at a common aortopulmonary trunk.

**One cannot have a common aortopulmonary trunk if the main pulmonary artery is absent.**

**Truncus arteriosus communis, as classically conceived,[11–16] may not exist.**

However, **huge aortopulmonary septal defects** rarely do exist, in which the aortopulmonary septum is virtually absent (Fig. 3.10). But the aortic and pulmonary valves are normally formed, and there is no ventricular septal defect.

**In conclusion**, the classical concept of truncus arteriosus communis persistens – with the great arteries, the semilunar valves, and the infundibular septum all undivided or in common[11–16] -- is now considered to be an erroneous concept that should be abandoned. Consequently, equations concerning common aortopulmonary trunk are not presented. **The realization that truncus arteriosus communis types A2 and A3 have no main pulmonary artery component, and that type A4 (Fig. 3.7) may well have no ascending aorta component have forced us to recommend abandoning the diagnosis of truncus arteriosus communis because of its anatomic inaccuracy.**

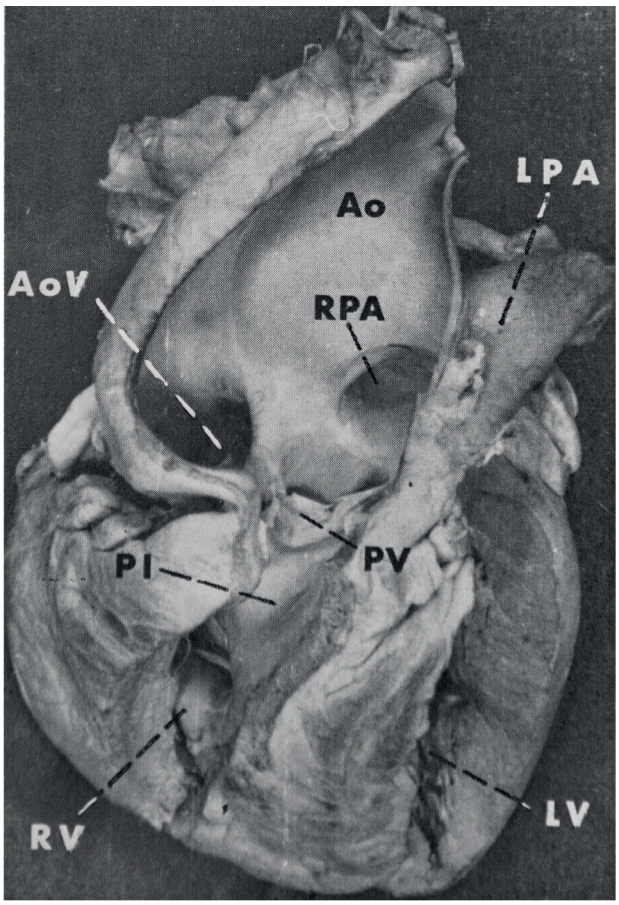


**FIGURE 3.10.**

Absence of the aortopulmonary septum, but with separate and normally formed pulmonary valve (PV) and aortic valve (AoV), and with an intact ventricular septum (no VSD). We used to favor the diagnosis of common aortopulmonary trunk for this type of case.[10] However, others thought that the classical concept of truncus arteriosus communis also included the concepts of a common (undivided) semilunar valve and a subarterial VSD; i.e., the classical concept essentially was a common (undivided) *cono*truncus arteriosus. Hence, in the interest of clarity and also because we think that the diagnosis of truncus arteriosus should be discontinued, we are happy to make the diagnosis of **absence of the AP septum** in this type of rare case. In the early 1960's, this photograph was kindly sent to us by Prof. J. W. A. Duckworth, Professor of Anatomy, University of Toronto, Canada. This is the heart of a 42-year-old white woman who died of undiagnosed pulmonary tuberculosis. The heart specimen is from the Department of Anatomy, University of Edinburgh, Scotland. *Abbreviations*: Ao, aortic; AoV, aortic valve; LPA, left pulmonary artery; LV, left ventricle; PI, pulmonary infundibulum; PV, pulmonary valve; RPA, right pulmonary artery, RV right ventricle.

(Reproduced with permission from Van Praagh.[10])

## 3.5. Transposition of the Great Arteries

Physiologically uncorrected D-TGA typically has the following infundibulo-arterial situs equation:

**6. TGA {S,D,D} = 4R + OL**

Diagrammatically, typical D-TGA is presented in Figure 3.1, 4th column from the right. In words, equation 6 says: transposition of the great arteries with the set of solitus atria, solitus or D-loop ventricles, and solitus or D-transposition of the great arteries is a well developed right-sided subaortic infundibular free wall plus absence of the left--sided subpulmonary infundibular free wall.

The presence of a well developed, right-sided subaortic infundibulum is associated with absence of an embryonic switch of the aorta from above the RV to above the LV.

So the wrong great artery did not get switched – the aorta. And the wrong great artery did get switched – the pulmonary artery.

Why did that happen?

Because the infundibulum is inverted: 4R + OL (equation 6). The infundibulum in equation 6 is the same as that in equation 2 of situs inversus totalis: 4R + OL.

**That is what typical D-TGA really is: isolated infundibular inversion. The great arteries, *per se*, are normal. The problem in D-TGA is immediately below the semilunar valves, at the level of the muscular infundibulum or the membranous semilunar-atrioventricular fibrosa.**

Typical D-TGA has an inverted infundibulum with noninverted great arteries. Hence, **infundibulo-arterial situs comparison** is inverted – noninverted, i.e., discordant or abnormal, i.e., D-TGA.

**7. TGA {S,L,L} = OR + 4L**

This is the infundibulo-arterial situs equation for typical congenitally physiologically corrected transposition of the great arteries. In words, equation 7 says: Transposition of the great arteries with the set of solitus atria, inverted or L-loop ventricles, and inverted or L-transposition of the great arteries is absence of the right-sided subpulmonary infundibulum plus a well developed left-sided subaortic infundibulum. Typical physiologically corrected L-TGA is presented diagrammatically in Figure 3.2, 4th column from the left.

**Basically, what is physiologically corrected L-TGA? It is isolated infundibular noninversion ((OR + 4L – the same as in equation 1 of the solitus normal heart). The rest of the bulboventricular loop is inverted: The great arteries are L-TGA, which is inverted TGA, i.e., TGA with R-L reversal. The ventricles are inverted, L-loop.**

**The infundibulo-arterial situs comparison** is solitus-inversus, respectively, i.e., discordant, or abnormal. Hence, the great arteries are abnormally related, i.e., L-TGA.

The infundibulo-arterial situs equation of physiologically corrected L-TGA indicates the embryological switch status of each great artery: TGA {S,L,L} = **O**R + **4**L. So, too, does the diagram: Figure 3.2, 4th column from the left. The presence of a well developed infundibulum beneath the left--sided L-transposed aorta typically prevents an embryonic switch of the aorta from above the left-sided RV to above the right sided LV. By contrast, the absence of an infundibulum beneath the pulmonary artery permits an embryonic switch of the pulmonary artery from above the left-sided RV to above the right-sided LV. Thus, infundibulo-arterial situs discordance results in TGA because the wrong great artery gets switched (the PA), and the wrong great artery does not get switched (the Ao).

The hemodynamic effects in TGA {S,D,D} and in TGA {S,L,L} typically are as follow (Fig. 3.11, row 5, columns 1 and 2):

(1) **In TGA {S,D,D}**, there is atrioventricular (AV) alignment concordance (Fig. 3.11, row 5, column 1), RA opens into RV and LA opens into LV. But at the ventriculo-arterial (VA) junction, there is VA alignment discordance: the RV ejects into the Ao, and the LV ejects into the PA.

**One intersegmental alignment discordance physiologically uncorrects the circulations.** The RA and the Ao are ipsilateral, both right-sided. The LA and the PA are ipsilateral, both left-sided. Hence, the unoxygenated systemic venous blood flows into the aorta, producing cyanosis. The oxygenated pulmonary venous blood flows into the pulmonary artery and back to the lungs. Postnatal life depends on shunting of blood (left-to-right and right--to-left) at atrial and/or ventricular and/or great arterial levels.

In TGA {S,L,L} (Fig. 3.11, row 5, column 2), there are two intersegmental alignment discordances at both the AV and the VA junctions. The right-sided systemic venous blood stream flows from the RA to the LV to the PA; and the left-sided pulmonary venous blood stream flows from the LA, into the RV, and into the aorta.

In physiologically corrected L-TGA, two intersegmental alignment discordances may cancel each other, resulting in physiologically corrected circulations, if the absence of associated malformations permits. In other words, associated malformations such as pulmonary stenosis or atresia with a ventricular septal defect frequently vitiate the potential physiologic correction of the circulations associated with a double intersegmental alignment discordance.

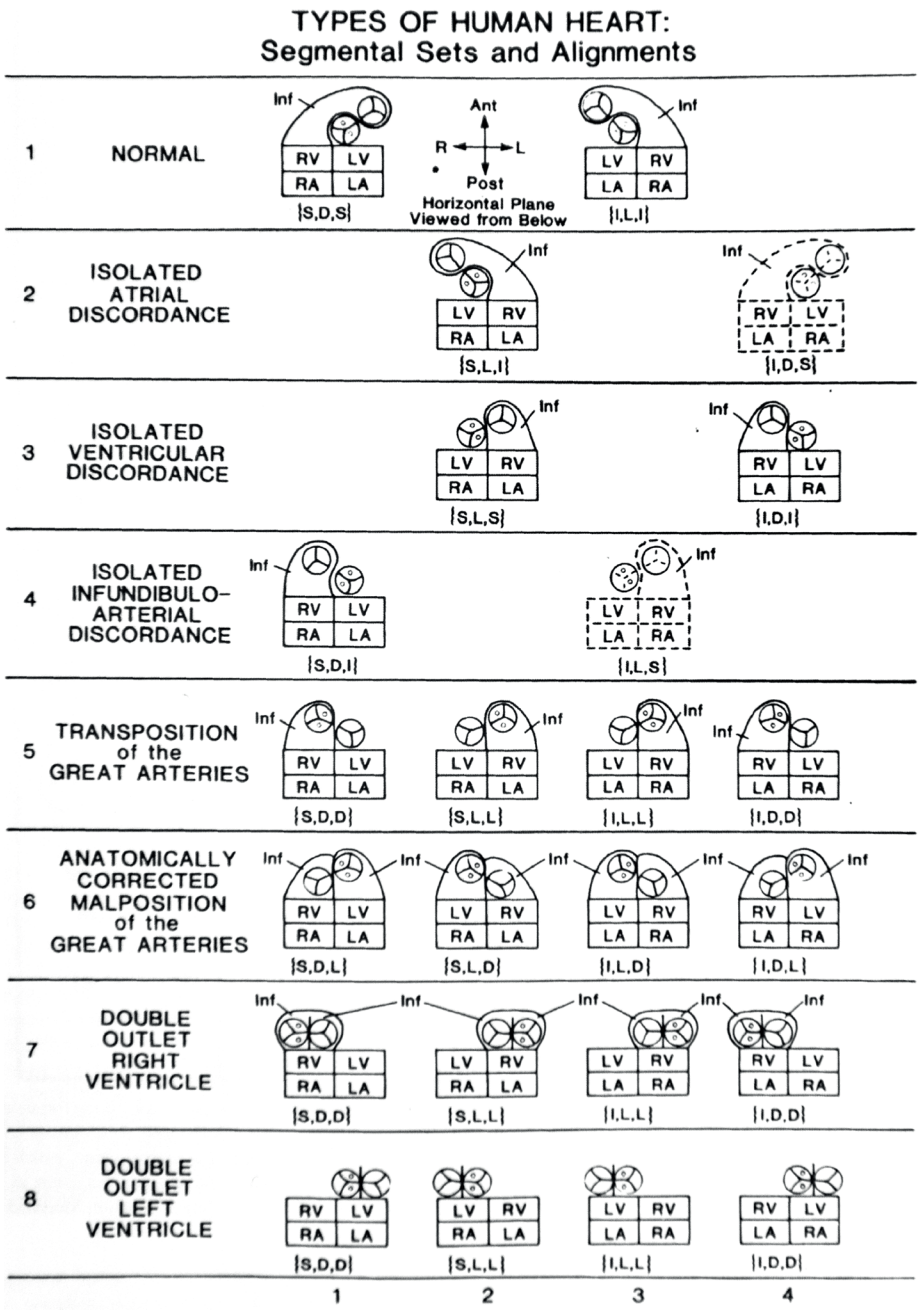


**FIGURE 3.11.**

Types of human hearts in terms of segmental anatomy. The three main cardiac segments are {atria, ventricles, great arteries}. Braces {} mean "the set of." There are two connecting cardiac segments: the atrioventricular (AV) canal or junction, and infundibulum or conus arteriosus. The AV canal is a dependent variable. Its situs usually is the same as that of the ventricles of entry, not that of the atria of exit. The infundibulum is an independent variable. The atria and the ventricles are named morphologically, not positionally. The aortic valve is indicated by coronary ostia. The pulmonary valve is indicated by no coronary ostia. The infundibulum is labelled Inf.

Column 1 has atrioventricular alignment concordance: {S,D,-}. Column 2 has AV alignment discordance: {S,L,-}. Column 3 has AV alignment concordance in visceroatrial situs inversus: {I,L,-}. Column 4 has AV alignment discordance in visceroatrial situs inversus: {I,D,-}. Rows 1 to 4 present various types of normal ventriculoarterial (VA) alignments. Rows 5 to 8 present various types of abnormal VA alignments: transposition of the great arteries (TGA), row 5; anatomically corrected malposition of the great arteries (ACM), row 6; double-outlet right ventricle (DORV), row 7; and double--outlet left ventricle (DOLV), row 8.

(Reproduced with permission from Van Praagh.[1])

**In TGA, why is the aorta usually anterior to the pulmonary artery? The brief answer to this question is synergy. When more than one force is at work, the result obtained may depend on whether the forces are working *with* each other, or *against* each other.**

To achieve solitus normally related great arteries, two forces are working with (in support of) each other (Fig. 3.3):

(1) Solitus D-loop formation results in approximately 90° dextrorotation at the semilunar valves relative to the sagittal (or anteroposterior) plane (Fig. 3.3, to 90°).

(2) Solitus infundibular formation (OR + 4L, equation 1) results in approximately another 60° dextrorotation at the semilunar valves, giving a normal total semilunar dextrorotation of approximately + 150° (Fig. 3.3).

Thus, both solitus D-loop ventricular formation, and solitus infundibular formation are associated with semilunar dextrorotation. Both of these forces are working together with (or in support of) each other, making it possible to achieve the normal ≈ 150° of semilunar dextrorotation relative to the sagittal plane.

*Synergy* means to work together: *synergia*, joint work, from *syn*, together + *ergon*, work (Greek).

**Inverted normally related great arteries** also require synergy (Fig. 3.3). For convenient brevity, D-rotation may be recorded in positive degrees (e.g., 90°) and L-rotation in negative degrees (e.g., −90°):

(1) Ventricular L-loop formation is associated with approximately −90° L-rotation (Fig. 3.3).
(2) Inverted "normal" infundibular formation (4R + OL, equation 2) is associated with an additional −60° L-rotation (Fig. 3.3).

When two forces are operating in the same direction or are supporting each other, this may be regarded as **positive synergy.**

When two forces are not operating in the same direction or are not supporting each other to produce a normal outcome, this may be regarded as **negative synergy.**

Thus, solitus (or noninverted) ventriculo-infundibular development is associated with D-rotation at the semilunar valves (Fig. 3.3); whereas inverted (or mirror-image) ventriculo-infundibular development is associated with L-rotation at the semilunar valves (Fig. 3.3).

**Typical D-TGA and typical L-TGA both have negative synergy.**

(1) In TGA {S,D,D} = 4R + OL (equation 6), the infundibular situs formula is inverted (the same as in equation 2), but the situs formulas of the ventricles and of the great arteries both are solitus (noninverted).

Consequently, the rotational result at the semilunar valve level equals approximately 90° + (−60°) = 30° (Fig. 3.3). This is why, in typical D-TGA, the aortic valve usually is anterior or ventral to the pulmonary valve. **The brief reason: negative synergy.** Ventricular D-loop formation results in about 90° D-rotation at the semilunar valves. But the inverted infundibulum results in about 60° in the wrong direction – to the left. Hence, the final rotation at the semilunar valve level is only about 30° to the right, much less than normal (150°, Fig. 3.3).

A mirror-image pertains in **typical L-TGA.** In equation 7, TGA {S,L,L} = OR + 4D, the infundibulum is noninverted (solitus, the same as in equation 1 of the solitus normal heart), but the ventricles and the great arteries are inverted. So, as far as the bulboventricular loop is concerned, **typical L-TGA has isolated infundibular noninversion** (OR + 4L, the same as in equation 1).

Typical D-TGA has isolated infundibular inversions: TGA {S,D,D} = 4R + OL.

**So, TGA (both D-and L-) has isolated infundibular situs discordance (relative to the ventricles and great arteries).**

Typical L-TGA also has negative synergy: −90° + 60° ≈ −30°. The −90° is associated with the inverted ventricular L-loop. The + 60° is associated with the solitus (nonnverted) infundibulum. The resulting final rotation at the semilunar valve level (approximately −30°) is much different than with inverted normally related great arteries −150° (L-rotation). Hence, the L-transposed aorta typically is anterior to the transposed pulmonary artery (Fig. 3.3).

**Positive and negative synergy** are important concepts for the understanding of normally and abnormally related great arteries.

## 3.6. Double-Outlet Right Ventricle, Taussig-Bing Type[21,22]

The Taussig-Bing type of double-outlet right ventricle (DORV) may be represented by the following infundibulo--arterial situs equation:

**8. DORV {S,D,D} = 4R + 4L**

In words, equation 8 says: Double-outlet right ventricle with the set of solitus atria, solitus (D-loop) ventricles, and solitus (D-) malposition of the great arteries equals a well developed right-sided subaortic infundibular free wall, a well developed left-sided subpulmonary infundibular free wall, and a subpulmonary ventricular septal defect.

**The original Taussig-Bing heart** of a 5 ½ year old white girl is presented in Figure 3.12.[21,22] External inspection strongly suggests DORV. Both great arteries arise side-by--side, anterior to the plane of the anterior descending coronary artery that suggests the location of the ventricular septum and hence the presence of DORV.

The opened right ventricle (**b** and **c**) reveals a large subpulmonary VSD (14 x 11 mm). The pulmonary valve is dilated (56 mm in circumference). The infundibular (or conal) septum is 20 mm in length. The subpulmonary infundibular

free wall measures 9 mm in height from the pulmonary valve above to the mitral valve below. The height (or length) of the subaortic infundibular free wall, from the aortic valve above to the tricuspid valve below, is 8 mm long.

Hence, a bilateral infundibulum, both right-sided subaortic and left-sided subpulmonary, is present. Neither subarterial infundibular free wall has undergone involution or resorption. In other words, neither the subaortic infundibular free wall, nor the subpulmonary infundibular free wall has undergone **apoptosis** (genetically programmed cell death).

**The presence of a well developed infundibulum beneath both great arteries prevents both great arteries from undergoing an embryonic great arterial switch from RV to LV. Hence, DORV is the result.**

Figure 3.12d shows the opened LV. The only outlet from the LV is the large VSD.

Figure 3.12e is a **geometric diagram** of the original Taussig-Bing heart. Relative to the anteroposterior plane (or Z axis), the plane of the atrial septum 30° to the left; the plane of the ventricular septum is 70° to the left; the plane of the infundibular (conal) septum is 0° on the right side and 5° left on the left side; and the rotation of the semilunar valves is 90° to the right. The valve circumferences and the mural thicknesses are measured in centimeters.

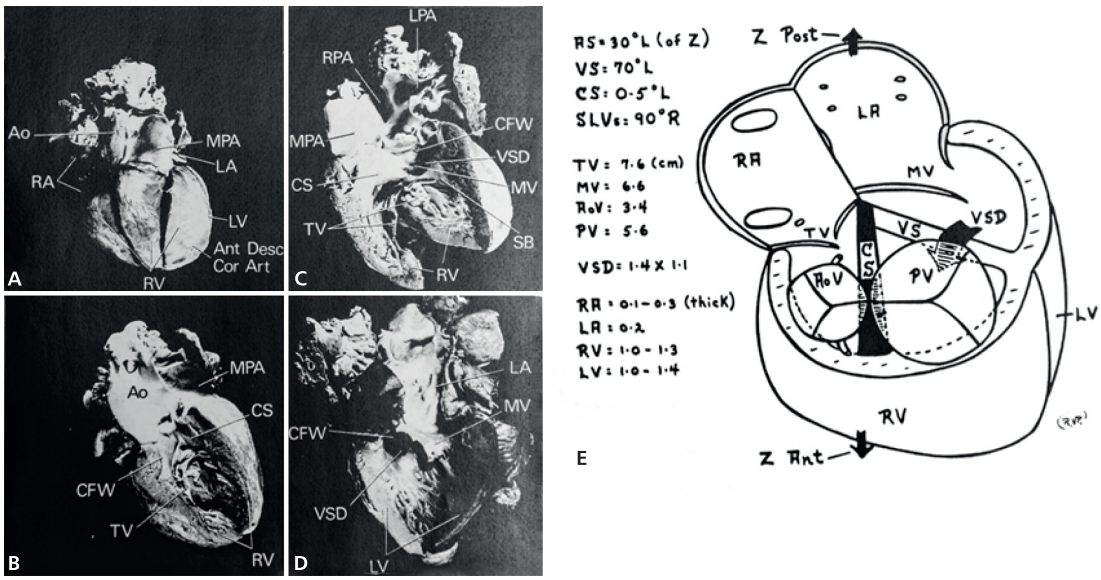


**FIGURE 3.12.**

The original Taussig-Bing heart.[21,22] a. Exterior frontal view. b. Opened right ventricle and pulmonary artery. c. Opened right ventricle and ascending aorta. d. Opened left atrium, mitral valve, and left ventricle; and e. geometric horizontal plane diagram. The Taussig-Bing malformation is DORV {S,D,D} with a bilateral infundibulum and a subpulmonary VSD. The subaortic infundibular free wall measures 8 mm in height from the aortic valve above to the tricuspid valve below, (a).

The subpulmonary infundibular free wall measures 9 mm in height from the pulmonary valve above to the mitral valve below (b). The pulmonary valve overrides the ventricular septum, but does not override the left ventricular cavity at all. Thus, the Taussig-Bing malformation is a type of DORV, not a TGA with an overriding pulmonary artery. The only outlet from the LV is the VSD. The infundibulo-arterial situs equation for the Taussig-Bing malformation is: DORV {S,D,**D**} = **4R + 4L**. The infundibular situs (4R + 4L) is ambiguus i.e. different from situs solitus (OR + 4L) and different from situs inversus (4R + OL). Thus, infundibulo-arterial situs comparison is **ambiguus – solitus,** i.e., discordant or abnormal. The Taussig-Bing type of DORV also illustrates that a well developed infundibular free wall beneath both great arteries prevents both great arteries from getting switched in utero, resulting in DORV.

*Abbreviations*: Ant, anterior; Ant Desc Cor Art, anterior descending coronary artery; Ao, aorta; AS, atrial septum; AoV, aortic valve; CFW, conal (infundibular) free wall; CS, distal conal septum, crista supraventricularis, or parietal band; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; MPA, main pulmonary artery; MV, mitral valve; Post, posterior; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SB, septal band or proximal conal septum; SLVs, semilunar valves; TV, tricuspid valve; VS, ventricular septum; VSD, ventricular septal defect.

(Reproduced with permission from Van Praagh.[22])

## 3.7. Double-Outlet Left Ventricle

The infundibulo-arterial situs equation for DOLV of the Paul type is:[23]

**9.DOLV {S,D,D} = OR + OL**

In words, equation 9 says: Double-outlet left ventricle with the set of solitus atria, solitus (D-loop) ventricles, and solitus (D-) malposition of the great arteries equals absence of right-sided subaortic infundibular muscle and absence of left-sided subpulmonary infundibular muscle.

**Both the subaortic and the subpulmonary connections of the great arteries are membranous or fibrous. There is aortic-mitral and pulmonary-mitral direct fibrous continuity, and the ventricular septum is intact (Fig. 3.13). The right ventricle (RV) was small-chambered and thick-walled, with endocardial fibro-elastosis (EFE). The only outlet from the RV was via an apical fistula that connected with the anterior descending branch of a single right coronary artery.**

**There is right ventricular infundibular atresia, even though both great arteries are left ventricular. Thus, there is infundibulo-arterial separation – a predominantly right ventricular infundibulum, and left ventricular great arteries. The ventricular septum could not be intact if the normally subarterial infundibulum were absent.**

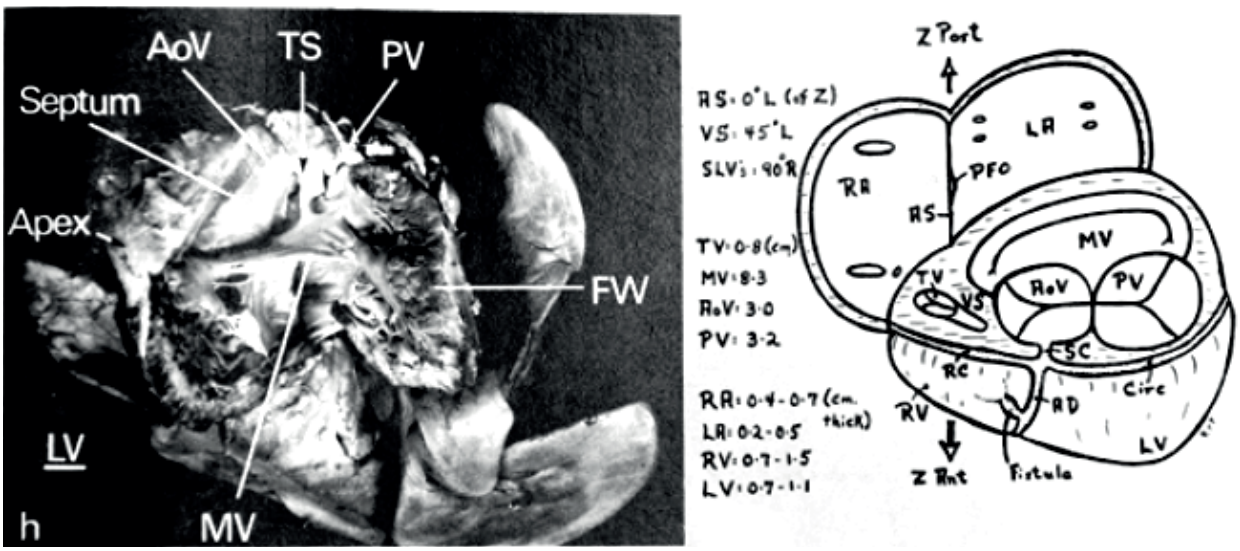


**FIGURE 3.13.**

Double-outlet left ventricle of the Paul type.[23] Opened left ventricle. Looking upward from the left ventricular apex, note the aortic valve (AoV) to the right, the pulmonary valve PV to the left, the aortopulmonary (or truncal) septum (TS) between the semilunar valves, the anterior leaflet of the mitral valve, the direct fibrous continuity between the AoV and the MV, the direct fibrous continuity between the PV and the MV, the absence of subsemilunar infundibular muscle (septum or free wall), and the intact ventricular septum (no VSD). In the geometric horizontal plane diagram, note how small the tricuspid valve (TV) and right ventricular cavity (RV) are. The outflow tract of the small-chambered and thick-walled RV with endocardial fibroelastosis (EFE) is atretic. There is a fistula between the RV apex and the anterior descending coronary artery. There is a single right coronary artery, i.e., absence of the left coronary ostium. The infundibulo-arterial situs equation is: DOLV {S,D,**D**} = **OR + OL**. The infundibulo--arterial situs combination is ambiguus-solitus, which is discordant (abnormal). The infundibular situs (to the right of the equals sign in the situs equation) indicates no infundibular free-wall muscle beneath either the right-sided aorta or beneath the left-sided pulmonary artery:

**O**R + **O**L. This is a very rare situation. The fact that the RV outflow tract is atretic, and that the ventricular septum is intact suggests the possibility that some infundibular muscle may have become displaced, perhaps explaining (1) the RV outflow tract atresia, (2) the absence of a VSD, and (3) the bilateral absence of subarterial infundibular muscle. Again we see that absence of infundibular muscle beneath either or both great arteries is associated with a great arterial switch in utero. A well developed subarterial infundibulum is associated with a great arterial embryonic nonswitch. Why? **How does this work? Hypothesis: Switch**

**involves a movement of the great artery that is inferior and posterior and leftward – heading towards the interventricular foramen. Subvalvar infundibular muscle may prevent this morphogenetic movement inferiorly, posteriorly and leftward (in a D-loop).**

*Abbreviations:* AD, anterior descending coronary artery; AoV, aortic valve; AS, atrial septum; circ, circumflex branch of single right coronary artery; FW, free wall of left ventricle; MV, mitral valve; PFO, patent foramen ovale; PV, pulmonary valve; RA, right atrium; RC, right coronary branch of single right coronary artery; SC, single (right) coronary artery; SLVs, semilunary valves (rotation at); TS, truncal (or aortopulmonary) septum; TV, tricuspid valve; VS, ventricular septum; Z Ant, Z axis (anteroposterior axis), pointing anteriorly (or ventrally); Z Post, Z axis pointing posteriorly (or dorsally). Z axis is useful for measuring atrial septal angles, ventricular septal angles, and rotations at semilunar valves.

(Reproduced with permission from Paul and colleagues.[23])

## 3.8. Anatomically Corrected Malposition of the Great Arteries

Anatomically corrected malposition of the great arteries (ACMOTGA) is defined as a malposition in which both great arteries nonetheless arise from the morphologically appropriate ventricles – aorta (Ao) from the morphologically left ventricle (LV), and pulmonary artery (PA) from the morphologically right ventricle (RV).

I know that ACMOTGA sounds like a developmental impossibility. [Let me call it ACM for short.] But, ACM does indeed exist.[24] ACM may be physiologically corrected or physiologically uncorrected:

**10. ACM {S,D,L} = OR + 4L24**

In words, this equation says: Anatomically corrected malposition of the great arteries with the set of solitus atria, solitus (D-loop) ventricles, and inverted (L-) malposition of the great arteries equals absence of a right-sided subpulmonary infundibulum plus a well developed left-sided subaortic infundibulum.

This anatomic type of ACM, i.e., ACM {**S**,D,**L**}, is physiologically corrected because the RA and the PA are ipsilateral (both right-sided), and the LA and the Ao are ipsilateral (both left-sided).

**11. ACM {S,L,D} = 4R + 4L**

In words, equation 11 says: Anatomically corrected malposition of the great arteries with the set of solitus atria, inverted (L-loop) ventricles, and solitus (D-) malposition of the great arteries equals a well developed right-sided subaortic infundibulum plus a well developed left-sided subpulmonary infundibulum.

This anatomic type of ACM is physiologically uncorrected – ACM {**S**,L,**D**} – because the RA and Ao are ipsilateral (both right-sided), and the LA and the PAare ipsilateral (both left-sided).

**All well documented cases of ACM have one feature in common: the ventricles loop in one direction, say to the right, and the infundibulum and great arteries twist in the opposite direction, to the left, as in equation 10; or vice versa, as in equation 11.**

## 3.9. The Evolution of the Human Heart[25]

Our phylum Chordata goes back to ancient **fish** of the Ordovician and upper Devonian periods, 500 million to 345 million years ago. Our aquatic ancestors had a single ventricle, from which our morphologically left ventricle (LV) is derived.

**Amphibia** evolved 345 million to 325 million years ago during the Carboniferous period. Then our ancestors had lungs and so could breathe air, but they had no right ventricle.

Some amphibia evolved into fully terrestrial animals that did not have to return to the water to breed. These animals, the **Amniota**, had an amniotic sac filled with amniotic fluid in which the embryo and fetus could float, like our fish ancestors. The Amniota became land animals – by bringing the water ashore with them.

Some Amniotes evolved into **reptiles**. Others evolved into **birds**, which are feathered reptiles like *archaeopteryx* (ancient wing, Greek). Still others evolved into **mammals**, which are furry or hairy reptiles.

Mammals evolved during the Jurassic period, about 180 million years ago.

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

The RV is comparatively recently evolved compared with the LV. Phylogenetically, the RV is only about 36% as old

as the LV: 180 million versus at least 500 million years old, respectively.

Most of human congenital heart disease consists of anomalies of one or more of the four components that make up the more recently evolved RV (Fig. 3.14). Malformations of the much older LV are comparatively infrequent.

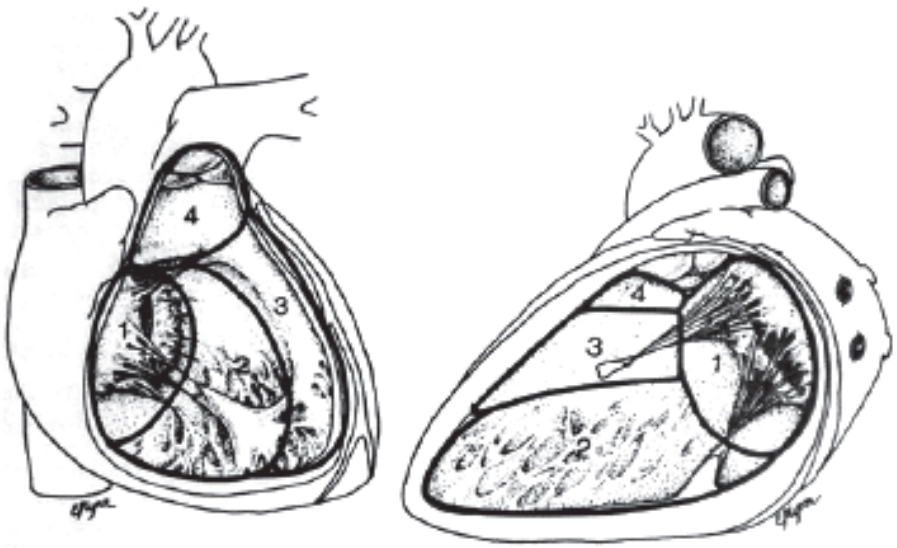


**FIGURE 3.14.**

The four components of the morphologically right ventricle (**A**) and of the morphologically left ventricle (**B**). *Component 1* is the atrioventricular (AV) canal or junction. *Component 2* is the sinus (body, or inflow tract) of the right ventricle (RV) and of the left ventricle (LV). *Component 3* in the RV is the septal band, the proximal or apical part of the infundibulum. Component 3 of the RV is continuous with component 3 of the LV – the smooth nontrabeculated upper part of the left ventricular septal surface. Component 4 is the subarterial infundibulum, better seen in the RV (Figure 3.15) than in the LV. Component 4 is the switch master – what this chapter is all about.

(1) When the situs of the subarterial infundibulum (component 4) and the situs of the great arteries are the same (concordant), then the great arteries are normally related: (a) solitus normally related (16 a); or (b) inversus normally related; or (c) tetralogy of Fallot – almost normally related (Figure 3.16 b).

(1) SNRGA {S,D,S} = OR + 4L
The infundibular situs is solitus, OR + 4L, and the great arterial situs is also solitus: {-,-,S}.

(2) INRGA {I,L,I} = 4R + OL
The infundibular situs is inversus, 4R + OL, and so is the great arterial situs: {-,-,I}.

(3) TOF {S,D,S} = OR + 1L
OR + 2L
OR + 3L

The infundibular situs in TOF is of the solitus type, but with variable hypoplasia of the subpulmonary infundibulum: grades 1, 2, or 3 (but not grade 4 which is normal).
All other malformations of the infundibulum and great arteries have infundibulo-arterial situs discordance (not concordance) and hence have abnormally related great arteries. For example:

(4) TGA {S,D,D} = 4R + OL
Infundibulum inverted, as in equation 2. Great arteries are not inverted. Typical D-TGA is isolated infundibular inversion.

(5) TGA {I,L,L} = OR + 4L
Physiologically uncorrected TGA in visceroatrial situs inversus is isolated infundibular noninversion. The situs of the infundibulum is the same as the situs of the infundibulum for solitus normally related great arteries (equation 1).

(6) DORV of the Taussig-Bing type[21,22]: DORV {S,D,D} = 4R + 4L
The infundibular situs (4R + 4L) is in situs ambiguus (uncertain or unknown) because it is different from that of the solitus normal infundibulum (equation 1) and different from the inversus normal infundibulum (equation 2). The presence of a well developed infundibulum beneath both great arteries prevents both potential great arterial switches, resulting in DORV.

(7) Double-outlet left ventricle of the Paul type[23]: DOLV {S,D,D} = OR + OL
Infundibular situs: ambiguus. Great arterial situs: solitus. The infundibulo-arterial situs comparison is ambiguus-solitus, i.e., discordant, therefore abnormal. Bilateral absence of subarterial infundibulum facilitates a double embryonic great arterial switch, resulting in DOLV.

(8) ACM {S,D,L} = OR + 4L
Anatomically corrected malposition of the great arteries in this patient had: infundibular situs: solitus normal (as in equation 1), and great arterial inversion: {-,-,L}.

Infundibulo-arterial situs combination is solitus-inversus, respectively, i.e., discordant and therefore abnormal. This conclusion is correct, even though both great arteries arise, by definition, above the morphologically appropriate ventricles.

Thus, ventriculo-arterial alignment concordance can mean: (1) normally related great arteries, solitus or inversus; or (2) anatomically corrected malposition of the great arteries.

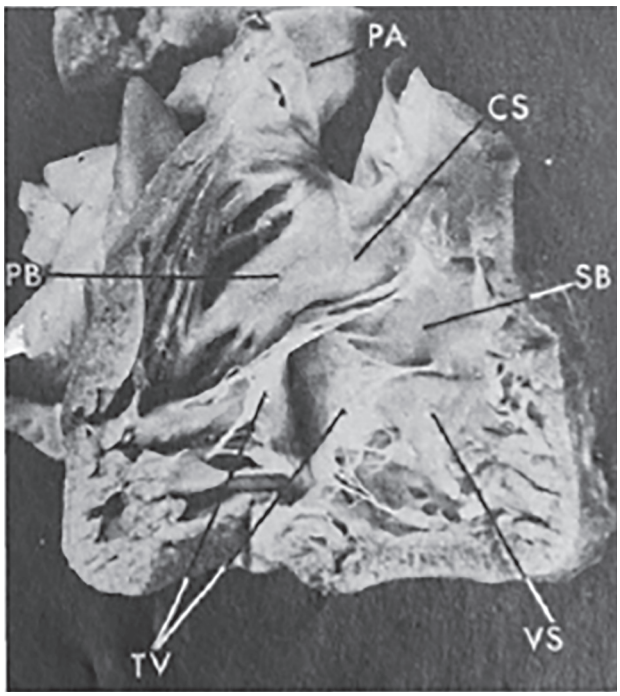


**FIGURE 3.15.**

Normal morphologically right ventricle showing the subarterial infundibulum i.e., the conal or infundibular septum (CS) and the parietal band (PB). SB, septal band; TV, tricuspid valve; VS, ventricular septum.

(Reproduce with permission from Van Praagh and colleagues[5])

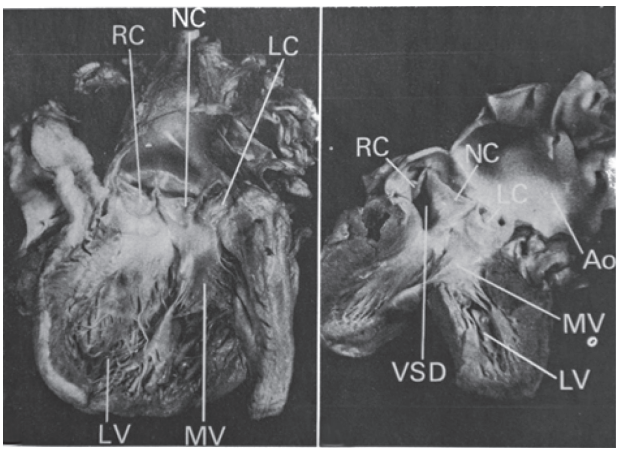


**FIGURE 3.16.**

Figure 3.16a shows an opened normal morphologically left ventricle, LV). Note that the non-coronary (NC) – (LC) commissure is normally above the middle of the anterior mitral leaflet (MV). In tetralogy of Fallot (b) the NC-LC commissure is further to the right, above the ventricular septum. Thus the great arteries in tetralogy of Fallot are almost normally related but not entirely normally related as aortic valvar overriding indicates in tetralogy of Fallot (Figure 3.16 b).

(Reproduced with permission from Van Praagh and colleagues[5]).

**It is proposed that we should diagnose the situs of the subarterial infundibulum and the situs of the great arteries. Comparison of these two situs diagnoses increase one's understanding of normally and abnormally related great arteries. The algebraic and geometric approach is also a step in a quantitative direction. For example, positive and negative embryonic synergies help to explain the geometric anatomy of normally and abnormally related great arteries.**

Congenital heart disease is the commonest anomaly in live-born infants (0.8%).

Congenital heart disease also accounts for more than 20% of all spontaneous abortions.

Congenital heart disease is responsible for 10% of all still-births.

Thus, we humans are still having significant trouble with our cardiovascular evolutionary adaptations to permit air--breathing and permanents land-living. These adaptations include:

(1) development of the RV sinus (inflow tract), the lung pump;
(2) the embryonic aortic switch procedure,; and
(3) septation to separate the systemic and pulmonary circulations.

Molecular genetic data suggest that mutations in the Nodal cascade may well be of great importance in anomalies of right-left asymmetry – such as the embryonic aortic switch, and the heterotaxy syndromes of asplenia and polysplenia. However, much remains to be learned in cardiovascular molecular genetics. More time and investigation are needed.

**Apoptosis**, genetically programmed cell death, appears to be very important in the great arterial switch and non-switch processes, as have been noted previously.

The embryonic **first heart field** gives rise to most of the myocardium of the cardiogenic crescent and the early heart tube. The embryonic first heart field contributes only to the embryonic LV. The embryonic **second heart field** contributes to the more recently evolved RV.

The embryonic **anterior heart field** (a subdomain of the second heart field) contributes to the development of the subarterial infundibular free walls that are important in the formation of normally and abnormally related great arteries (the equations).

Speaking of **evolution**, it should be noted that the first person to undersand the concepts of evolution, natural selection, and survival of the fittest – and to attribute evolution to chance – was **Empedocles**, an ancient Greek physicist in the fifth century BC.

Charles Darwin and Alfred Russell Wallace rediscovered these concepts (evolution, natural selection, and survival of the fittest) in the mid 19th century (1858, London). The primacy of Empedocles is proved by the surviving work of Aristotle (384–322 BC). Aristotle cited Empedocles at length in order to show what he (Aristotle) disagreed with.[25,26] So now there is no doubt that Empedocles understood and promoted the concept of evolution, natural selection, and survival of the fittest in the 5th century BC. Dr. Stella Van Praagh, my wife who was a Greek from the island of Crete and who also was an expert in Ancient Greek (the language of Aristotle), retranslated Aristotle's disapproving citation of Empedocles [Aristotle, The Physics, Vol 4, Books 1–4], to make sure that the English translation is accurate. It is.[26]

Darwin's classics translator thought he was translating Aristotle. He was. But the translator did not understand that Aristotle was citing or quoting Empedocles. So Empedocles got lost in translation. This may help to explain why Empedocles has not received the credit he deserves for the discovery of the concept of evolution, attributed to chance, in the fifth century BC.[25,26]

## 3.10. Conclusions

1. *Situs* is very important in the understanding of congenital heart disease. In anatomy, *situs* means the pattern of anatomic organization.
2. There are two anatomic types of situs: (1) *situs solitus*, the usual, noninverted pattern of anatomic organization; and (2) *situs inversus*, the mirror-image pattern of anatomic organization.
3. When the situs of the subarterial infundibulum and the situs of the great arteries are the same (concordant), then the great arteries are normally related – solitus normally related, or inverted normally related.
4. Solitus normally related great arteries may be represented by the following infundibulo-arterial situs equation: SNRGA {S,D,S} = OR + 4L
5. Inverted normally related great arteries INRGA {I,L,I} = 4R + OL
6. Tetralogy of Fallot, or more accurately "monology" of Stensen:[2]
   - TOF {S,D,S = OR + 1L (TOF with PAt)
   - TOF {S,D,S} = OR + 2L (TOF, severe PS)
   - TOF {S,D,S} = OR + 3L (TOF, mild/moderate PS)

7. Truncus arteriosus communis, as classically conceived, may not exist, i.e., with absence of the aortopulmonary septum, a common (undivided) semilunar valve, and an infundibular septal defect.
8. Transposition of the great arteries
   - Physiologically uncorrected D-TGA:
     TGA {S,D,D} = 4R + OL
   - Congenitally physiologically corrected L-TGA:
     TGA {S,L,L} = OR + 4L
9. Double-outlet right ventricle, Taussig-Bing type:[21,22]
   DORV {S,D,D} = 4R + 4L
10. Double-outlet left ventricle, Paul type:[23]
    DOLV {S,D,D} = OR + OL
11. Anatomically corrected malposition of the great arteries, physiologically corrected:[24]
    ACM {S,D,L} = OR + 4L
    ACM, physiologically uncorrected:
    ACM {S,L,D} = 4R + 4L
12. The subarterial infundibulum is the embryonic switch master.
    **(a)** When a well developed (grade 4) subarterial infundibulum is present beneath a great artery, this subarterial infundibulum prevents an embryonic switch of this great artery from above the developing RV to above the developing LV and into fibrous continuity with the mitral valve.
    **(b)** When there is little or no subarterial infundibulum beneath a great artery, this marked paucity or absence of subarterial infundibulum is associated with permitting or facilitating an embryonic great arterial switch from above the RV to above the LV and into fibrous continuity with the mitral valve.
    The foregoing equations illustrate these two patterns:
    (a) the great arterial non-switch; and
    (b) the great arterial switch.
13. The only exception to the subarterial infundibulum serving as the embryonic great arterial switch master is anatomically corrected malposition of the great arteries (ACM). In ACM, the ventricles loop in one direction, and the infundibulum and the great arteries twist in the opposite direction. Hence, ACM is a cardiac looping anomaly that is different from the other infundibulo-arterial malformations. In ACM, the anatomically corrected ventriculo-arterial alignments are related to the reversed twisting of the infundibulum and great arteries relative to the ventricles.
14. The above-mentioned equations are a contribution to the algebra of congenital heart disease.
15. This chapter is also a contribution to the geometry of congenital heart disease. The positive and negative synergy of D-rotation and L-rotation at the semilunar valve level helps to explain the differences between normally and abnormally related great arteries, respectively. For example, synergy reveals why the aorta typically is anterior to the pulmonary artery in transposition of the great arteries.

## 3.11. Apoptosis

Normally and abnormally related great arteries result from normally and abnormally located apoptosis, which means "a falling off", from **apo** off, + ptosis, fall (Greek).

Apoptosis is a morphologic pattern of cell death affecting single cells. It is characterized by cell shrinkage, condensation of chromatin, cytoplasmic blobs, fragmentation into membrane-bound apoptosis bodies that are eliminated by phagocytosis.

Often called **programmed cell death**, apoptosis is normal or physiologic cell death – as opposed to abnormal or pathologic cell death which is not part of the normal developmental program.

**The location of apoptosis determines whether the great arteries are related normally or abnormally.**

In the equation, O = the site of apoptosis and the site of great arterial switching. For example:

1. In SNRGA (equation 1), the aorta is switch into the LV.

In INRGA (equation 2), the inverted Ao is switched into the inverted LV.

The PA is held above the RV by the subpulmonary infundibulum and by the absence of apoptosis in both equations 1 and 2.

**Thus, the "switch master" is the presence of apoptosis and the absence of a subarterial infundibulum.**

2. Apoptosis beneath the left-sided PA results in the PA being switched into the LV and the Ao not being switched into the LV, i.e., TGA.
3. No apoptosis, right-sided or left-sided results in no switch of the right-sided Ao and no switch of the left-sided PA, i.e., DORV – of the Taussig-Bing type.
4. Bilateral apoptosis, right-sided subaortic and left--sided subpulmonary, rarely can be associated with a double great arterial switch, i.e., DOLV of the Paul type.

Thus, apoptosis determines subarterial infundibular morphology, normal and abnormal, that in turn determines great arterial morphology, i.e., normally and abnormally related great arteries.

But what determines whether subarterial infundibular apoptosis is normal or abnormal?

To the best of my knowledge, that remains to be determined.

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