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Original Article

Abnormal Rotation of the Primary Heart Tube. Linking Embryogenesys to Malformed Cardiac Phenotypes: Future Perspectives

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Abstract

We observed the Trabecula Septomarginalis anatomy in malformed cardiac phenotypes reviewing the related literature and the current concepts on cardiac embryogenesis.

The embryological and anatomical insights in formed cardiac phenotypes support the hypothesis that the ventriculo arterial cardiac connections in any pathological settings recapitulate an abnormal counterclockwise rotation on the ventricular base-apex axis of the primary cardiac tube in the first month of life at the Carnegie stages XIV-XVII.

The Trabecula rotates and follows the development of the Right ventricle in every specific pathological formed phenotype: a teratological continuum encompassing single phenotypes.

The Trabecula's rotation at bulbar level (embryologic conus) on the septal aspect of the right ventricle links embryology to anatomy and finally to new investigations during pregnancy possibly leading up to less severe or even normal cardiac phenotypes what we refer to as Molecular Cardiac Surgery.

It is beyond the scope of this paper to enter into embryological dissertations or to appraise the hitherto postulated morphogenesis of specific phenotypes.

The purpose of this paper is to provide further evidence of the sequential Trabecula Septomarginalis rotation in formed phenotypes with embryological traits related to the development during the first month of life.

We are currently investigating the contribution of external forces on the interventricular septum rotational process during looping in the chick heart and we are organizing a biologists network to realize a research protocol based on exosomes for early detection of Congenital Heart Disease.

ABBREVIATIONS

CHD: Congenital Heart Disease; TSM: Trabecula Septomarginalis; VS: Ventricular Septum; AL: Anterior Limb; PL: Posterior Limb; VIF: Ventriculo Infundibular Fold; RV: Right Ventricle; CSV: Crista Supraventricularis; OS: Outlet Septum; VSD: Ventricular Septal Defect; TF: Tetralogy of Fallot; TGA: Transposition of Great Arteries; DORV: Double Outlet Right Ventricle; DOLV: Double Outlet Left Ventricle; UH: Univentricular Heart; CS: Carnegie Stages*; Horizon**: Cushion/Swelling/Ridge

*Carnegie stages are named after the Institute which first classifyied embryos in the early 1900's. Stages are based on the external and/or internal development and are not directly dependent on age or size. The embryonic period is divided into 23 Carnegie stages covering the first 8 weeks post-ovulation. Criteria beyond morphological features include age in days, number of somites, and crown rump length.

The developmental term "Horizon"defines 23 stages in human embryos from fertilization to the first two months from Streeter G.L. **[1,2] and O'Railly R.**[3]**.

INTRODUCTION

For the terminology and classification of CHD refer to Van Praagh R. 1972 **[4]** ; Shinebourne E.A., Macarteney F.J., Anderson R.H. 1976 **[5]**; Anderson R.H., Becker A.E., Van Mierop L.H.S. 1977 **[6]**; Anderson R.H.,Tynan M. 1984 **[7]**; International Paediatric and Congenital Cardiac Code (IPCCC) and European Paediatric Cardiac Code (EPCC) : http://www.IPCCC.net **[8].**

We refer to the Trabecula Septomarginalis (TSM) definition introduced by Tandler in 1913 [9] and described by Brandt 1953 **[10]**, Grant 1961 **[11-12]**, Wenink 1977 **[13]**, Anderson 1977 **[7]**.

In formed phenotypes the TSM is an extensive compaction

of the septal trabeculations on the right septal surface of the ventricular septum. It is composed of two limbs, the Anterior Limb and the Posterior Limb. The AL is committed to the Outlet Septum and the PL to the Ventriculoinfundibular Fold. Capuani et al **[14-17]**. The moderator band, first observed by Leonardo da Vinci **[18],** is the continuation of the TSM towards the apico-lateral side of the right ventricle**.**

In our vision the ideal plane passing through the two limbs rotates clockwise on the apex-base axis of the septum during the development of the Right Ventricle determining the formed cardiac phenotypes.

Any pathological deviation from this pre-established architectural design in cardiac embryogenesis carries abnormal phenotypes. The cardiac morphogenesis is a continuous very complex process which involves rotation, looping and partitioning of the primary straight cardiac tube at different levels and stages aligning finally the aorta and the pulmonary artery with the left and right ventricle respectively.

MATERIALS AND METHODS

We refer to the Visible Embryo Project **[21,22]**, the Virtual Human Embryo Project **[23]**; the embryos and phenotypes data from the collection of Carnegie Institution Washington Baltimore and from the following centers and researchers in alphabetical order: Anderson RH et al. **[24-31]**; Asami I. **[32]**; Bersch W. **[33]**; Bostrom MPG, Hutchins GM. **[34]** Capuani A et al. **[14]**; Chuaqui B, Bersh W. [35,36]; Castellanos LM, Vasquez MA, Kuri MJ. **[37-39]**; Conte G, Grieco M, Arrigoni P.**[19,20]**; Davis CL. **[40]**; De La Cruz MV et al. **[41,42-51]**; De Vries PA, Saunders JB de CM. **[52]**; Doerr W. **[53-56]**; Goor DA et al. **[57,58-62]**; Grant RP et al. **[11,12,63,64]**; Kramer TC. **[65]**; Lomonico MP et al. **[66,67]**; Manasek FJ, Monroe RG. **[68]**; Manner J, Monroe RG, Seidl W, Steding G. **[69-73]**; Markwald RR, Trusk T, Moreno-Rodriguez R. **[74]**; Meredith MA, Hutchins GM, Moore GW. **[75]**; McBride RE, Moore GW, Hutchins GM. **[76]**; 0'Rahilly R. **[3]**; Orts-Llorca F, Puerta-Fonolla J, Sobrado J. **[77]**; Pexieder T. **[78-80]**; Spitzer A. **[81,82]**; Streeter GL. **[1,2]**; Thiene G et al. **[83]**; Van Mierop LHS et al. **[84-89]**; Van Praagh R et al. **[90-96]**; Wenink ACG. **[13,97]**; Zavaleta D et al. **[98]**. Other Authors are cited under specific topics.

We drew **Schemes 1-2** illustrating the heart rotational process and we have reproduced the morphology of specific phenotypes to underline the ideal TSM rotation during the first month of life (Figures 6-16).

We discuss the presented concepts on embryogenesis and morphology while linking the embryogenetic process to formed phenotypes. On the base of our vision we comment on new potential treatments of CHD.

RESULTS

From Dextroposition of Aorta to Tetralogy of Fallot (TF), Single Outlets, Double Outlets Right Ventricles (DORV), Transposition of Great Arteries (TGA), and towards Double Outlets Left Ventricles (DOLV), the CSV, the OS and the VS progressively divorces with partial or complete loss of the outflow spiraling flow and development of pulmonary mitral continuity **(Scheme 1,2).**

Morphology of formed phenotypes

DISCUSSION

The Doerr's Vectorial Bulbus Rotation Hypothesis [53-56]from Chuaqui B. and Bersch W. 1973, 1979 [35,36] according to the photograms by Asami I. 1969 [32].

Schwalbe in 1906 introduced in biology the concept of Teratological Series as developmental anomalies with a similar pathogenetic disturbance **[120]**. These entities represent distinct manifestations of a similar process occurring at different sequential times and are morphogenetically linked. On the one extreme the least deviation from normal and on the other the most severe malformation.

Spitzer in 1923, 1928 **[81,82]** in a new phylogenetic hypothesis for the Transposition of Great Arteries (the general organs develop in series from fishes to birds and mammals in response to forces of varying conditions) applied the Schwalbe concept arguing that an incomplete torsion of the primitive cardiac tube is the causation of cardiac defects.

He postulated that in transpositions of great vessels there is a torsion of the bulboventricular septum recapitulating phylogenetically an earlier form: the reptilian left Aorta which becomes obliterated while the right Aorta regains patency.

Doerr in 1938 **[53-56]** introduced the Spitzer concept to the "Vectorial Bulbus Rotation Hypothesis" in the morphogenesis of cardiac malformations from the Eisenmenger Complex to Tetralogy of Fallot, Taussig Bing and Transposition of Great Arteries.

The morphogenetic disturbance involved is an arrest, to a varying extent, of the Vectorial Bulbus Rotation.

Basically the rotation process of the primary cardiac tube consists in **(Figures 1-3)**:

A. displacement of the bulbus to the left and clockwise rotation of 45°on the long axis at the level of the metaampullar orifice so called Ostium Bulbi* (anticlockwise rotation seen from the heart base) from XV through XVI Streeter stages;

B. counterclockwise torsion of 150°on the orizontal plane at the level of the Bulbotruncal Orifice in the direction of blood flow. The bulbus septation does not start until stage XVII.

As stated by Chuaqui and Bersch 1973, 1979 **[35-36]** the results abtained by De Vries and Saunders 1962 **[52]** and Asami 1969 **[32]** on development of the ventricles may be considered as a verification of the Vectorial Bulbus Rotation Hypothesis.

In our vision any spatial relationships between Truncus, Conus (Infundibulum) and Ventricles have to be linked to the embryological TSM's rotation (anterior and posterior crest of the primary interventricular foramen) during the ventricular septation process **(Figure 4).**

The anatomical spectrum of the embryological cardiac rotation extend from TF **[99,100]**, to Double Outlet Ventricles **[100-103]**, classic TGA **[90,107-110,111-115]**, TGA with

left aorta **[121]**, Truncus Arteriosus **[105,106]**, Corrected TGA **[116-118,91]**, anatomically corrected TGA **[92-93]** and DOLV **[94,122].** In concordant and discordant atrioventricular connections**,** univentricular **[119,95,96]** and biventricular hearts.

According to Chuaqui B, Bersch W. 1973,1979 **[35,36]**, the Vectorial Bulbus Rotation hypothesis explain the position of great arteries while other hypothesis are inadequately supported by known facts (straight bulbotruncal septum De La Cruz 1951 **[53] [42],** abnormal heart skeleton Grant 1962 **[108],** conal inversion Van Praagh 1966 **[90]**.

From Embryology to Formed Phenothypes. The Looping Process

Excellent morphogenetic studies describe the development of the cardiac chambers and the embryogenesis of the outflow tract. Many of these works are coupled with molecular aspects 0,84,85,86,87,88,89,97,1,2,41,52,3,33,19,20,14,3,33,19,20,14,24-31,32,35,36,37-39,42-51,53-56,58-62,63,64,66,67,68,69-73,74,75,76,77,78-80,81,82,123-150].

Despite this, the cardiac embryogenetic process is still controversial. As stated by Kramer in 1942 **[65]"** the region of the heart in which the partitioning process is most difficult to interpret is where the atrioventricular cushions, the bulbar ridges and the crest of the interventricular septum meet ".

In this study we link the malformed cardiac phenotypes to the rotation of the primitive cardiac tube underlining the importance of the primary interventricular foramen crest, future TSM, during the first month of life. This concept open to new diagnostic and therapeutic perspectives.

The primary heart tube remains a straight symmetrical structure during stage IX (Embryo:1,5-2,5 mm, around 20 days) when right and left interventricular sulcus appear. At stage X-XI the primary tube bends (loops) medially and dorsally: the segments (atrial, ventricular, outflow) are defined by the right atrioventricular sulcus and the left interventricular sulcus. The disappearance of the right sulcus produces the initial lateral asymmetry of the primary tube **[57,33,75]**.

The symmetry breaking process is followed by the Looping and transformation of the straight embryonic heart tube in Helical Wound Loop. Rotation**,** septation and spiralling of the outflow tract ridges are independent closely related consequences of the looping process **[68-74,150,151-156]**.

By stage XIV (Embryo 5-7 mm, around 32 days) the left interventricular forms a spiral whose ventral limb passes caudally to the crest of the anterior interventricular groove (Septal Band TSM) and cranially towards the dorsal atrioventricular forming the Crista Supraventricularis.

At stages XIV-XV Grant in 1962 **[12]**and Wenink in 1977 **[13,97]** described a non trabeculated ridge on the interventricular septal surface emerging over the interventricular foramen and evolving into the Tandler's Trabecula Septomarginalis which separates the right bulbar musculature from the ventricular trabecular in origin. This has to be underlined in this work.

The 180° elicoidal rotation of the aortic and pulmonary truncoconal septum at the Streeter Horizons XIV-XVIII (the primary interventricular foramen closes at Horizon XIX) ends up to the normal twisted relationships.

If the spiral process is not complete the aorta remains overriding the Primary Interventricular Foramen and there will be DORV morphology in a fully developed heart.

Since the 6th pulmonary arch develops posteriorly to the 4th aortic arch, we assume that the pulmonary conus is dorsal (posterior) to the aortic conus. Following D-Looping **[4,90,60-62]** the presumptive aortic conus is right sided and the presumptive pulmonary conus is left sided. The converse applies in L-Looping. To understand the process of bulboventricular rotation it is important to focus that the embryological extra cardiac segments (the atria and the aortic sac) are anatomically fixed and the elongation of the tube, mainly due to the growth of the bulbus cordis, is forced to bend. The anterior protrusion of the pulmonary conus twists the developing great arteries because they are fixed distally.

In our vision the TSM sequential malrotation (Septal Band) from stage XIV to XVI is the "anatomical teratological continuum" (Schwalbe 1906) **[157]** of the Doerr's Vectorial Bulbus Rotation Hypothesis **[53-56]**. We definitely agree with Pexieder 1992 **[78-80]**, who stated that in Transposition of Great Arteries the primary impact is situated in the Looping process and not in the conotruncal development.

Conus and Truncus

The basic concept emerging from the presented embryological and anatomical observations is that the Conus (Infundibulum) and the Truncus (Great Arteries) are independent structures.

The conotruncus may be twisted in one direction and the ventricular loop in the opposite direction. Why this occurrence, as documented originally by Van Praagh 1964,1965,1966,1975,1977,1998 **[91-93,119,96]** is nowdays still inexplicable.

The Conus is not an inseparable part of the morphological right ventricle because it may be located predominantly above the left ventricle and may bear any relationships with the ventricle.

In the normal heart the proximal end of the spiral conotruncal septum is coincident with that of the muscular portion of the interventricular septum stemming from the TSM **(Figure 1-2)**.

Any spatial relationships between Truncus, Conus (Infundibulum) and Ventricles is related to the embryological TSM (anterior and posterior crest of the interventricular foramen) rotation during the septation process and the transition from DORV to Transpositions Phenothypes.

If the spiral process is not complete the aorta remains overriding. If the interventricular Foramen remains open with overriding aorta there is a DORV morphology in a fully developed heart.

The stage XV is a transitory normal stage present in all embryos before the closure of the ventral part of the Interventricular Foramen (the interventricular septum develops towards the

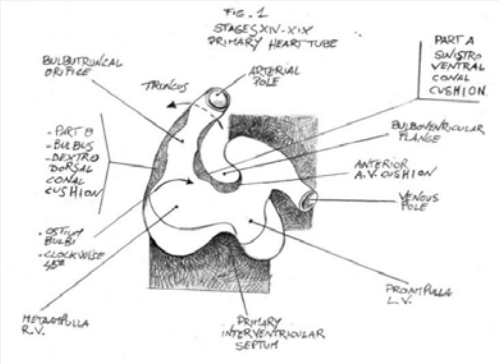


Figure 1 In german literature the ascending limb of the primary heart tube at the level of the developing right ventricle is named Metampulla. Distally, at the Ostium Bulbi level, it continues with the Bulbus* (embryologic conus). The term Proampulla is applied to the trabeculated areas. The outflow tract of the right ventricle contains both metaampulla and bulbus [57].

*Bulbus, Conus, Infundibulum: Davis 1927 in 1927 [40] introduced the term Bulbus (embryologic conus: the region between the growing RV and the truncus arteriosus in the primary straight heart tube) to designate a region of the primary straight tube that gives origin to the right ventricle. Kramer in 1942 [65] recommended to substitute the Bulbus term with Conus.

The conus or infundibulum has two parts: one proximal, septal band and moderator band always part of the morphological right ventricle and one distal, parietal band (CSV) which is not inseparable part of the right ventricle because it may be located predominantly above the left ventricle [90]. The actual right-left translocation of the primordia is unknown. The precise origin of the free-standing infundibulum is still unexplained.

In the present paper we distinguish: 1- the bulbar ridge A which starts proximally on the anterior wall of the conoventricular junction and spirals through the left wall of the conus to the right wall of the truncus; 2- the bulbar ridge B which starts on the back wall of the conoventricular junction and spirals to the left wall of the truncus Goor DA 1975 [57].

The Part A corresponds to the proximal sinistroventral (inferior) conal cushion of Van Mierop and the Part B to the proximal right dextrodorsal (posterior) conal cushion [84-89].

Normally the anterior endocardial crest of the Interventricular Septum (septal band, Tandler's TSM) is committed to the sinistroventral conal swelling A and spirals right-left. The enlargement of the AV canal brings the dextrodorsal conal swelling B (where the Crista Supraventricularis originates Wenink 1981) [97] close to the superior AV endocardial cushion with which blends.

This right ventricular remodeling and the formation of the spiral conotruncal septum align the pulmonary artery (6th aortic arch) with the right ventricle and the aorta (4th aortic arch) with the left ventricle.

At this stage we can figure out the malrotation of the TSM (inter ventricular primary foramen endocardial crest) resulting in twisted cephalic interventricular septum in formed phenotypes (in discussion).

During the normal ventricular remodeling the anterior endocardial crista free edge (developing TSM) of the embryonic primary interventricular foramen stems from the sinistroventral conal swelling (part A), spirals in the developing right ventricle right-left.

The posterior free edge connects to the dextrodorsal conal swelling (part B) via a ridge that crosses the fusion of the endocardial AV cushions and continues to the aortic arch placing the CSV in the normal position.

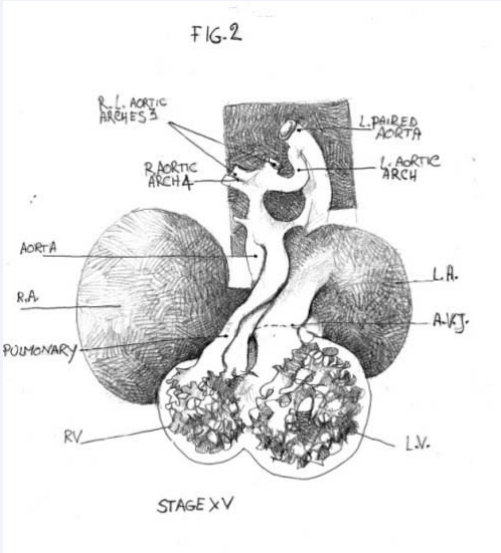


Figure 2 From Streeter G.L. [1,2] as reported by De la Cruz M.V, Miller B.L. [41]. The flow path wax models were made from embryo 836 of the Carnegie collection by Mr. Heard and drawn from De Vries P.A. and Saunders J.B. de C.M. illustrations [52] as reported by Grant R.P. [10]. The embryo 836 is the prototype of the Visible Embryo Project NIH founded to comunicate life (http://embryo.asu.edu/about/network.php) [21-23].

bulbar septum and not vice versa). Conte et al 1967,1984 **[19,20]** (**Figure 3)**

DORV may result not only from an abnormal development of the embryonic Conotruncus but also from an abnormal connection between the muscular Ventricular Septum and the Conus septum.

Normally the torsion of the bulbotruncal orifice at the truncus level produces the spiral course of the already formed truncal septum and at the bulbus level a straight course of the ridges A and B.

If the endocardial bulbar cushions A does not spiral right-left towards the distal B and from the ventricle to the aortic arch, the distal A becomes anterior and the distal B posterior: the flow from the RV will go into the 4th aortic arch and the flow from the left ventricle into the 6th aortic arch forming the TGA phenotype.

According to De la Cruz, in situs solitus the development of a straight conotruncal septum is responsible for the transposition of great vessels **[42-51]**. The truncoconal ridges may develop with an anticlockwise rotation of 180° (normal heart) or in a straight fashion (0° rotation, transposition of great arteries with anterior Aorta or 90°rotation with side by side great arteries) or may not develop at all (truncus arteriosus).

The straight truncal septum in transposition as proposed by De La Cruz according to Chuaqui 1973,1979 **[35,36]** should be regarded as the result and not the cause of the pathogenetic bulbotruncal process.

We argue that the abnormal septation at ventricular level (Malrotation of the posterior endocardial crest of the interventricular foramen) coupled with an arrested bulbar rotation will end to 180° TSM's malrotation observed in formed Transposition of Great Arteries phenotypes.

Embryological Evidence of The Bulboventricular Rotational Process. Laterality And Ptx2 Gene

The heart rotates between Carnegie stages XIV-XIX **[34,66,67]**. During Looping and septation, in an ideal transverse plane, has been documented a rotation of the axis of the semilunar valves of 121° frontal counterclockwise, 196° sagittal counterclockwise and 240° transverse clockwise with a simultaneous lengthening of the great arteries. This will line the muscular Outflow Tract with the ventricular septum.

The ventricle moves ventrally and to the right while the atrium moves dorsally and to the left. That rotation will locate the aorta posteriorly and wedged between the atrioventricular valves and the Outlet and Ventricular Septum (TSM plane in our observations) become aligned.

The valve position in normal hearts were reported similar to the stage XIX whereas in Tetralogy of Fallot was similar to XVIII stage and in transposition of great arteries to XV stage**.** The majority of hearts with DORV resembled stage XVI**.** These data confirm an arrest of the normal rotation at the junction of the Outflow Tract and great arteries leaving the aortic valve over the right ventricle as in Carnegie stage XVI.

During the VI to IX Carnegie stages the arterial orifice is not in one plane: it has a curved and twisted configuration and

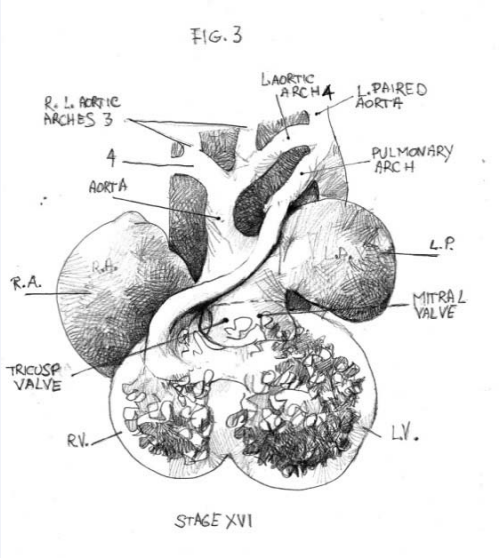


Figure 3 The primary interventricular foramen closes at stage XIX-XX. Grant 1962 [12] Wenink 1977 [13]
Note
1. the widening of the atrioventricular canal and the development of the trabecular zones that gives origin to the ventricles, 2- the knee where the bulbus and the truncus meet (bulbo truncal orifice),
2. the counterclockwise torsion of the ascending Limb at the bulbo truncal orifice up to 150° and the displacement of the Bulbus to the left with clockwise torsion of 45° on the long axis at bulbo metaampullar orifice (Ostium Bulbi).
3. The meeting points of the TSM spiral rotation with the truncal cushions and the bulboventricular flange [32] will pose the pulmonary artery above the RV. The term metampulla is applied by german authors to the ascending limb at the level of the developing right ventricle; the term proampulla applies to the proximal trabeculated area of the primary heart tube.

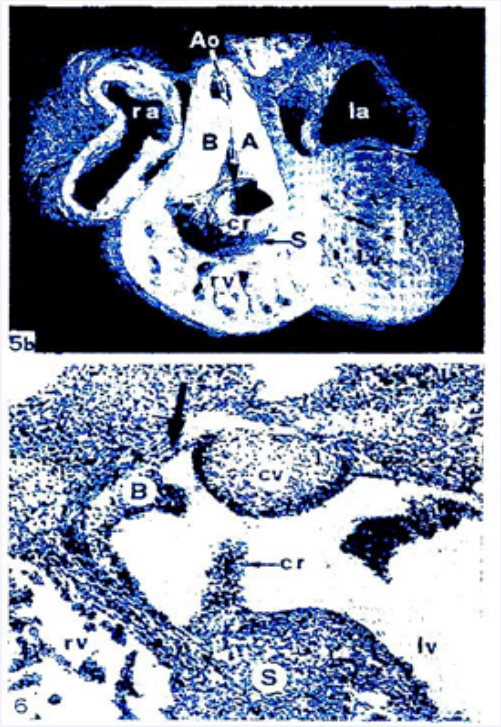


Figure 4 5b: reconstruction: oblique coronal dissection showing the proximal parts of the cushion A (left anterior) and B (right posterior) and the continuity of the part A with the endocardial crest (cr) of the interventricular muscular septum (S) (TSM primordia). The part B (right posterior cushion) in continuity with atrioventricular cuschions cranio ventral and right lateral runs towards the proximal anterior truncal ridge spiraling distally. The aorta (Ao) overrides the interventricular muscular septum (S). The endocardial crest cr spirals right left and develops towards the anterior atrioventricular cushion. 6: oblique coronal section x 70 corresponding to the reconstruction.

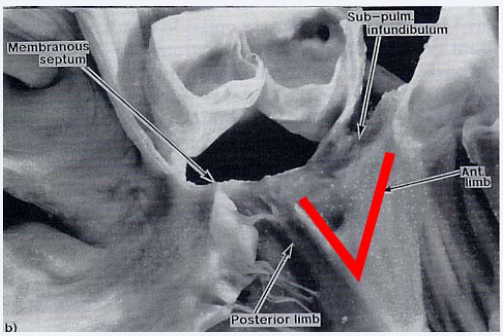


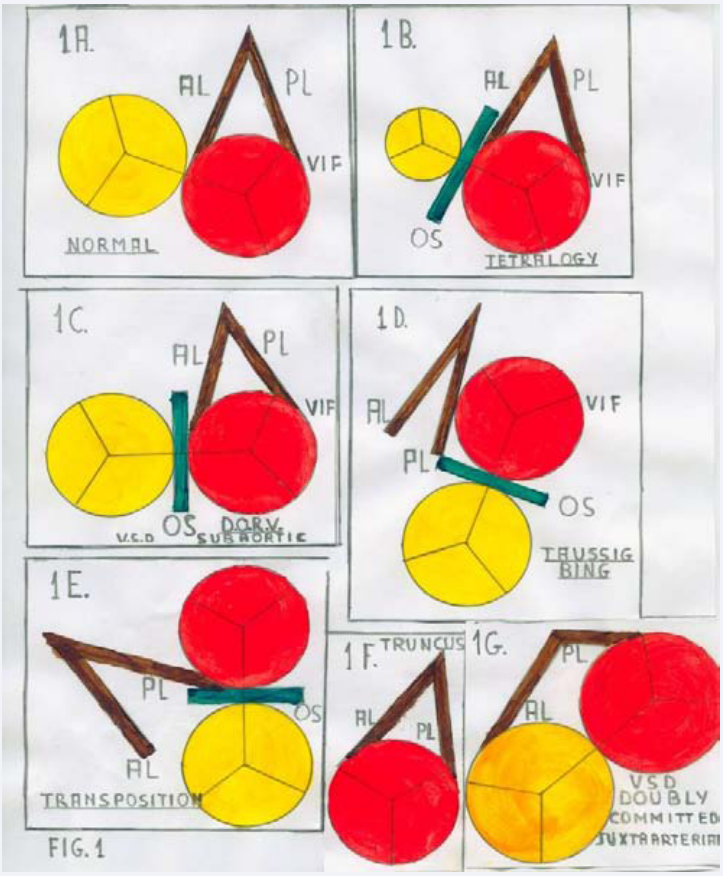
Figure 5 The roof of the right ventricle has been removed. The greatest part of the CSV is the inner curvature of the parietal wall of the RV: the VIF. In the normal heart a very small part of the CSV separates the aortic and pulmonary outflow tracts as free standing subpulmonary Infundibulum or Conus (Outlet Septum): there is no a "real Outlet Septum". Removal of CSV insertion into the interventricular septum creates a hole beneath the anterior coronary cusp. The TSM is the limit between the Outlet and the anatomical RV: the junction between the conus and the trabeculated portion of the RV corresponds to the inferior edge of the CSV and the TSM.

reaches up the origin of the 4th and 6th branch of arch arteries. As a consequence the pulmonary trunk is short and the ascending aorta is long, the pulmonary outlet is long and the aortic outlet is short. The truncal septation incorporate the anterolateral Outlet into the right ventricle and the posteromedial into the left ventricle.

We now know that the Outflow tract is recruited from the secondary heart field **[158-161,162],** however the actual right-left primordia translocation is unknown. We do not know yet the molecular changes involved. Markwald RR, Trusk T, Moreno-Rodriguez R. in 1998 proposed the myocardialisation process **[74];** Pexieder T. in 1975 and Poelmann RE, Gittenberger-de-Groot AC. in 2005 suggested the Apoptosis **[78,146].**

An asymmetric expression of the primitive mesenchyme on the pulmonary side of the outflow tract pushing in frontal position the outflow tract has been recently advocated by others **[148]** and that would eliminate the need of introducing a tissue teratogenic process **[78,145]** in conotruncal inversion hypothesis **[90]**.

Molecular expression analyses have confirmed that the



Scheme 1 On the long septal axis base apex, from normal 1A, to TF 1B, DORV with subaortic VSD 1C, Taussig-Bing 1D, TGA 1E. There is simultaneous counter clockwise rotation of the OS with increasing β angle (ventricular septum-deviated crista) from 30°(normal) to about 180°(TGA) and dextroanterior rotation of the aorta around the pulmonary artery. The VSD is cradled between the TSM limbs. From 1B to 1C the PL is committed to the VIF and the VSD is subaortic, from 1D to 1E the PL is committed to the OS and the VSD is subpulmonary outlining the TSM rotation. In Truncus 1F and Doubly Committed Juxtaarterial VSD there is malrotation of the TSM and absence of the OS. TSM brown, OS green, Aorta red, Pulmonary yellow.

Scheme 2 Simultaneous dextro-anterior counterclockwise rotation of the aorta around the Pulmonary with malrotation of the TSM's limbs and the resulting phenotypes from normal to TF-DORV with subaortic VSD, Taussig-Bing, Transposition. From normal to TF and DORV with subaortic VSD the PL is committed to the Inner Curvature. In Taussig-Bing and Transposition the AL is committed to the Inner Curvature. From the first pathological phenotype to the last anomaly there is about 180° degree rotation. Aorta red, Pulmonary Artery blue, PL green, AL yellow.

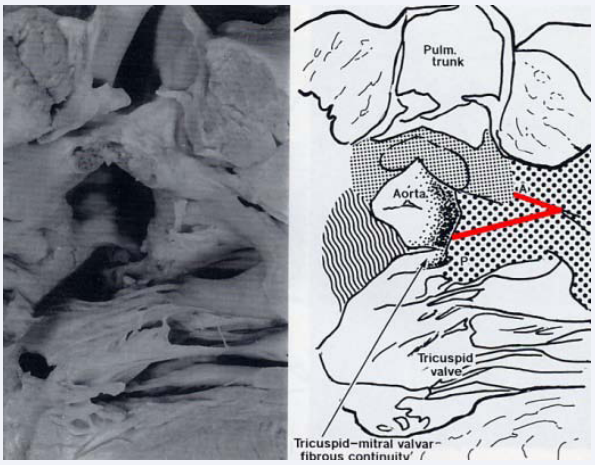


Figure 6 The conal rotation results in dextroposition of the aorta and conal malseptation with anterior deviation of the outlet septum which inserts anterior to the TSM (highlighted red). The OS is deviated anteriorly and is attached to the TSM's AL as a free standing structure producing pulmonary stenosis. The PL is committed to the VIF which stops short of the PL with tricuspid-mitral continuity. Adapted.

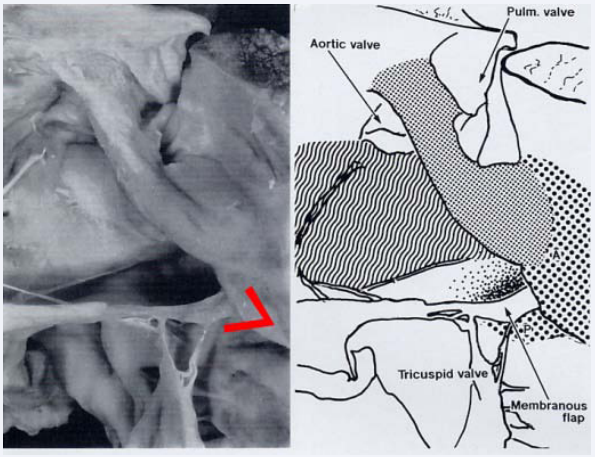


Figure 7 The PL is committed to the VIF. The AL blends with the OS. The VIF is well represented creating a complete muscular antero-posterior subaortic infundibulum. The TSM is highlighted red. Adapted.

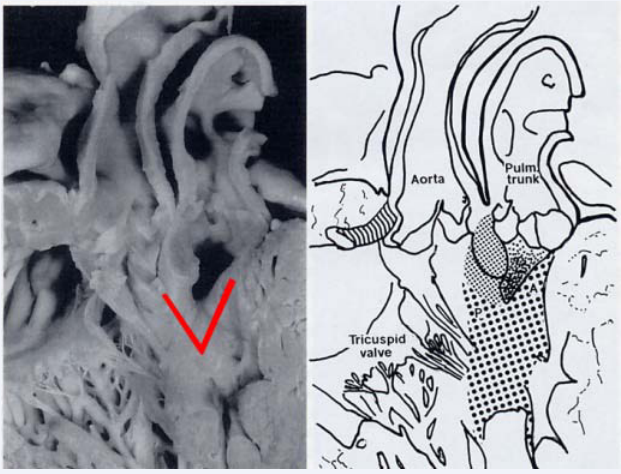


Figure 8 The OS fuses with the PL rather than the AL creating a subaortic infundibulum. The AL is displaced anteriorly in a cephalic position. The great vessels are side by side.

Outflow Tract myocardial wall rotates before and during the formation of great vessels **[163]**. In fact, in hearts with persisting Truncus Arteriosus , DORV and Transposition the rotation is arrested or fails to initiate and 70% of PITX2c gene mutants have TGA morphology. Because the PITX2c is involved in left- right signaling this suggest that the embryonic laterality affects rotation of the myocardial wall during the outflow tract maturation.

Bending is an intrinsic process while dextral torsion is caused by external forces **[154]** as compressive loads **[155]**. Internal and external forces can induce anatomical defects **[164].** Mechanical forces and the directional flow mediated by beating cilia **[164-167]** or chiral spreading of the cells translate into asymmetric cell migration **[167]** resulting in heterotaxis **[168].**

According to Ramsdell 2005, 2017 **[156,157]** errors in left-right axis determination are associated with complex CHD. More than 80 genes are associated with laterality in animal models **[168]** and he majority of genes implicated in the left-right pathway are expressed prior the organogenesis which demonstrate that they are relevant to the formation of Looping **[156].**

The TBx5 gene specifies the left-right ventricles and the ventricular septum position **[172-164]**; PITX2 gene function is associated with abnormal Looping which is linked to VSD, DORV and TGA in formed phenotypes. The PITX2 gene is a source of positional informations for the cells inducing left-right translation into anatomical asymmetry. The symmetry breaking process is followed by the Looping and the remodeling of the left-right PITX2 expression **[157,169-171]**which is essential in modulating the mutations. The modular activation of the gene with distinct roles at different developmental stages is important for understanding the sequential phenotypic expressions at the molecular level.

We believe that the modular activation of PITX2 with distinct roles at different developmental stages [156-157,162,172,169-171]explains the phenotypes heterogeneity.

In our vision the Doerr "similar pathogenetic process" **[53-56]** during the embryonic period is the remodeling at ventricular level and we speculate that the TSM sequential observations in malformed phenotypes under a pathological PTX2 expression recapitulates the embryogenetic process between Streeter's stages XIV-XVI **[1,2]**.

From Classic Diagnostic and Corrective Strategies to New Potential Approaches

Congenital Heart Diseases (CHD) represent about 1-2 % of all live births with a very high human and socioeconomic fallout **[173,174]**. Moreover, the patients with CHD that are seen clinically represent a small percent of all cases: the others died in the first month of life. When this is taken in consideration, CHD proves to be a vastly greater cause of human mortality **[12]**.

The etiology is multifactorial and is in relation to anomalous expression of genes and epigenetic factors. Genetic abnormalities appear to be the primary cause of CHD but identifying precise defect has proven challenging **[175].**

1- We have to consider that: **[176-196]**Numerous signaling pathways regulating anterior-posterior, dorso-ventral and left-right axes are prime targets for genetic and toxic insults in the first two weeks of development.

2- single gene defects can cause both syndromic and isolated CHD,

3- several pathways act during development independently or in combination,

4- a specific signaling pathway vary as development proceed,

5- the same gene or genetic locus or identical mutation may cause different types of CHD even in the same family (phenotypic heterogeneity),

6- the same malformation may result from mutation in different genes (locus heterogeneity).

For these reasons changes in gene function have to be integrated and correlated with morphological changes particularly when viewed over time in living embryos using dynamic imaging approaches **[197]**.

Diagnosis and Treatment

Most congenital malformations originate during primary morphogenesis and can be basically clustered by a pathogenetic process (Clark 1996) **[136]**.

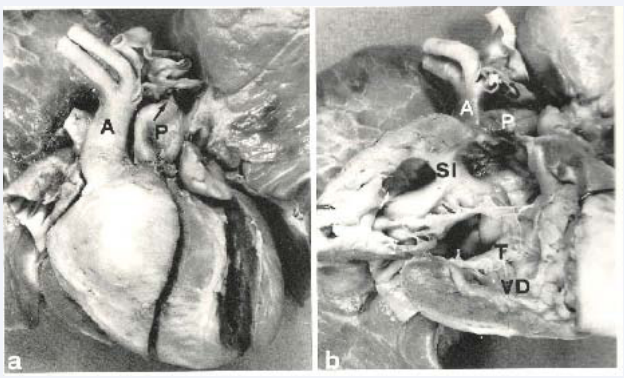


Figure 9 The aorta is to the right of pulmonary artery side by side. There is a large sub-pulmonary VSD, coarctation of the aorta and "banding" of the pulmonary artery. The TSM rotation above 90° is close to the rotation observed in Transposition of Great Arteries. Adapted.

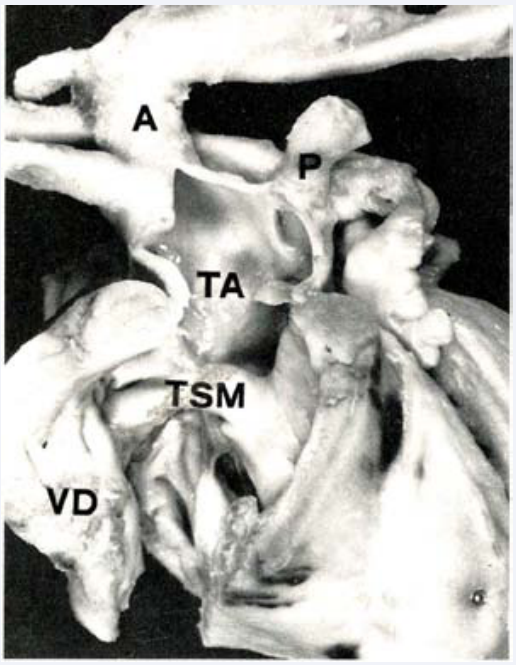


Figure 10 The PL blends with the VIF forming a muscular posteroinferior rim of the doubly committed subarterial VSD separated from the membranous septum by the TSM. There is absence of the OS. The TSM limbs rotation form the anterior cephalic part of the ventricular septum. Adapted.

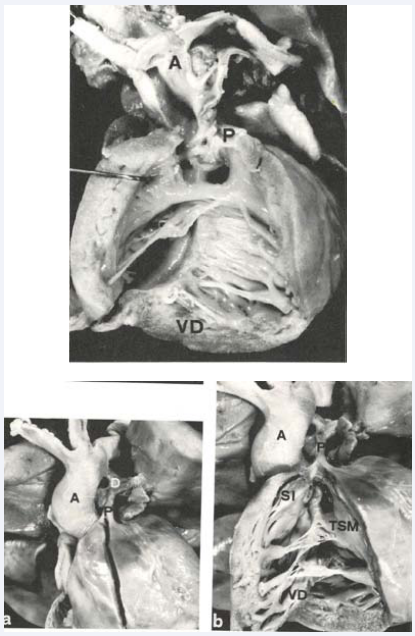


Figure 11 The Outlet Septum is absent and the doubly committed VSD is cradled between the rotated TSM limbs. Note the similarity with Truncus Arteriosus Fig.10. Adapted. In a and b The VSD is perimembraneous. Extreme anterior deviation of the Outlet Septum (SI). Atretic pulmonary infundibulum. The TSM is rotated and displaced in cephalic position. Adapted.

Ultrasound in prenatal screening improves the outcome in CHD providing planned delivery, genetic counseling and perinatal management, however, often represent a diagnostic challenge **[180,198-202]**.

Recent advances on molecular technologies applied to liquid biopsies (maternal blood) and circulating cell free /DNA-RNA molecules **[203-205]** can effectively provide a not invasive access to genetic informations. Non-invasive, liquid biopsy-based diagnostics is currently incorporated into standard healthcare practice and precision medicine.

Two complementary technical advanced technologies **[206-212],** DNA microarrays and massively parallel DNA sequencing,

can provide unprecedented insights into the genome opening to new possibilities for prenatal and postnatal treatments.

Diagnostic Genes panel based approaches (Next-Sequencing platforms) in clinical practice by Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) can provide novel gene discovery **[206-212]**.

The WES (High-troughput sequencing of target-enriched genomic DNA) allows for the detection of small variants missed by WGS **[213]** and has been utilized to identify causative mutation in familial CHD using candidate gene list **[214]**. WES has proven an effective alternative in genetic screening panel based expanding the candidate gene list.

Future Therapeutic Potentialities of Congenital Heart Diseases

Despite terrific advances in diagnosis and treatment, conventional heart surgery still carryes significant mortality and morbidity in severe forms **[215-217]**. For exemple, the estimated mortality in Truncus Arteriosus plus Interrupted Aortic Arch has been reported 29.8%.

Can we do better?

The genetic diagnosis of CHD has to provide targeted curative strategies and, in our vision, the knowledge of the molecular mechanisms determining the heart rotation during embryogenesis will let to interfere with the ongoing process wat we call Molecular Cardiac Surgery **[218-222].**

Nowadays, somatic cells can be programmed into induced pluripotent stem-cells and differentiated cells can be dedifferentiated or transdifferentiated into other types of differentiated cells **[223-224].**

Prenatal cardiac interventions [180,225-226,201]entail risks to the mather and baby and few medical centers have the resources and the skill to perform such procedures. However, fetal cardiac surgery may be considered in fetuses with evolving hypoplastic left heart syndrome or with pulmonary atresia and intact ventricular septum.

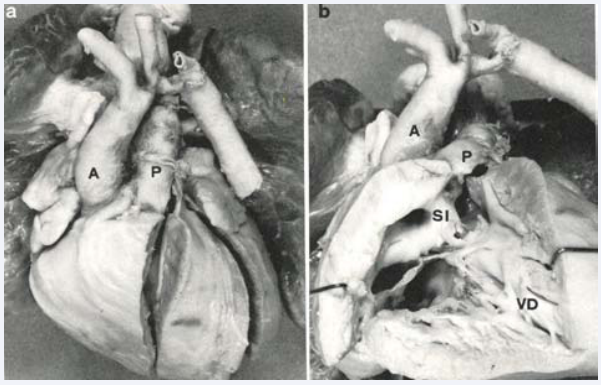


Figure 12 The aorta is posterior and to the right. There is anterior deviation of the OS obstructing the aortic inlet. The VSD is subpulmonary. The pulmonary artery is situated above the VSD which is mainly committed to the right ventricle. Adapted.

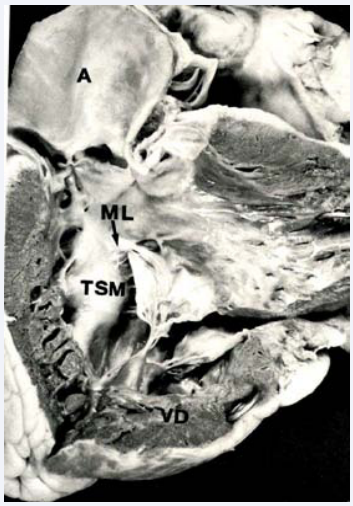


Figure 13 The right atrium connects with the morphological right ventricle through the mitral Valve. The right ventricle is to the left (ML: Lancisi muscle). The pulmonary artery is atretic. The Aorta arises from the left sided right ventricle with distorted TSM and Lancisi muscle (ML). There is a muscular infundibulum between aorta and tricuspid valves. Adapted.

Identifying in the first month after conception the TSM malrotation sequence, may be possible to reactivate the neonatal myocardial plasticity **[231,232]** and /or interfere with the ongoing process by stem-cells **[229-233,223,234]**or CRISPR-Cas9 based techniques **[235-241]**.

Besides, forced expression of the cardiogenic transcription factors holds a potential therapeutic use inducing the cardiac progenitors that control cardiac development early during gastrulation with induction of cardiomyogenesis **[79].**

Knowing the sequential genomic identity we believe that it will be possible to reactivate the embryogenetic myocardial process since the heart retains significant growth plasticity during fetal life **[227-229]** linking embryology to clinical practice **[221,222,242,243,173,174,215]**

The recent CRISPR/Cas9 technique may dramatically interfere with the ongoing cardiogenesis. Although embryo's gene editing raises ethical and technical problems **[235-241]** facing extremely challenging queries for the human being, genome editing (molecular scissors) CRISPR/Cas9 can without doubt cut out and even replace strands of DNA molecules. Moreover CRISPR-Cas9 based techniques have the potential for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis.

There is a lack of models to investigate the pathogenesis of malformed hearts since it is very difficult to reproduce in a significant percentage a specific malformation and it is impossible and arguable to replicate the genetic architecture in a model. In this context, the TSM morphogenetic process has to be considered a "biological model" for investigating and treating the developing heart linking embryology, anatomy and clinical practice **[218-222].**

CONCLUSION

1- The Trabecula Septomatrginalis during the early bulboventricular morphogenetic process miss the appointment with the Outlet Septum. As the two structures divorce, the Trabecula and the Outlet Septum become evident with specific features for each pathological phenotype. The Trabecula progressive malrotation is traceable in all different formed segmental configurations and there is a tight morphological relation with the development of the right ventricle.

2- The conus is not an inseparable part of the morphological

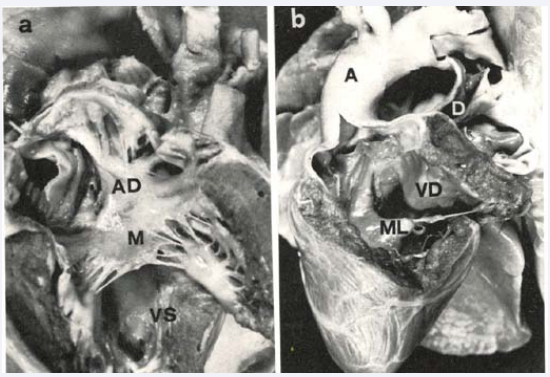


Figure 14 The right atrium connects with the morphological right ventricle through the mitral Valve. The right ventricle is to the left (ML: Lancisi muscle). The pulmonary artery is atretic. The Aorta arises from the left sided right ventricle with distorted TSM and Lancisi muscle (ML). There is a muscular infundibulum between aorta and tricuspid valves. Adapted.

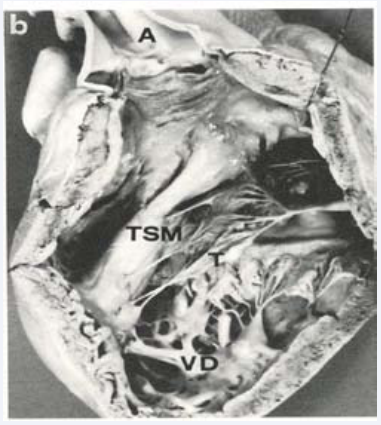


Figure 15 Absent right atrioventricular connection with hypoplastic left venytricle. The left atrium connects to the subaortic morphological right ventricle. Note the distorted TSM with tricuspid chordae insertion. Adapted.

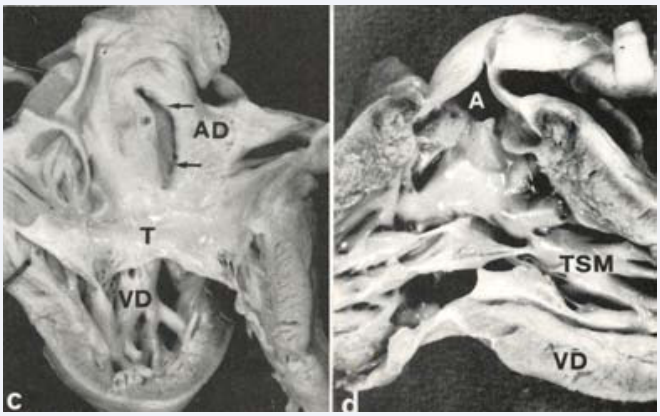


Figure 16 The right atrium connects to the right ventricle with an evident TSM. Note the tricuspid chordae insertion to the interventricular septum and the subaortic infundibulum separating the aorta from the tricuspid valve.

right ventricle and may bear any relationships with the ventricle. The conotruncus may be twisted in one direction and the ventricular loop in the opposite direction as well as the bulbus and the ventricle.

3- The abnormal ventriculoarterial connections originate by a pathological torsion of the primary cardiac tube at the level of the Conus (Infundibulum) and by an abnormal remodelling of the primitive ventricle at the atrioventricular region in relation to an abnormal spiralling of the primary interventricular foramen endocardial crest. Disturbances of the rotation process produce the malformed outlet phenotypes.

4- The key point is the torsion (Looping) of the cardiac tube. Many genes are involved eventually regulated by epigenetic factors.

5- The knowledge and the control of the factors determining the rotation of the TSM will allow to interfere onto the cardiogenesis modifying the ventricular development and finally reducing the incidence and the severity of the resulting pathological phenotypes.

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The reproduced figures are adapted as Author's proof for the Trabecula Septomarginalis rotational concept.

CONFLICTS OF INTEREST

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- 27th Congress of European Society of Pathology, Belgrade Serbia 2015;
- 27th Meeting of the Arab Division of International Academy of Pathology, Dubai 2015;
- 28th Congress of the European Society of Pathology and XXXI Congress of the International Academy of Pathology, Cologne Germany 2016;
- Congress of the Italian Society of Anatomia Patologica SIAPEC and International Academy of Pathology, Genova Italia 2016;
- 7th World Congress of Pediatric Cardiology & Cardiac Surgery, Barcelona Spain 2017;
- 24th Annual Cardiologists Conference, Conferenceseries. com, Barcelona Spain 2018;
- 2019 Joint Conference: Advances in Pediatric Cardiovascular Disease Management, Columbia University, New York City 2019.

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