

Has the Congenitally Malformed Heart Changed Its Face? Journey From Understanding Morphology to Surgical Cure in Congenital Heart Disease

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The incidence of children born with congenitally malformed hearts has changed little over the centuries. Our understanding of the lesions has improved subsequent to analysis in sequential fashion of the cardiac components. Ongoing differences in the approach to naming the lesions can now be resolved by careful application of the new evidence emerging from examination of the developing heart and by noting the lesions produced by genetic manipulation of mice.

The recorded incidence of congenital cardiac malformations has changed little across the ages. At a rough estimate, ≈ 8 infants in every 1000 are born with a congenitally malformed heart, with little difference being found in this number across the World. The lesions themselves have been recognized for centuries. In 1846, for example, Thomas Peacock described a deficiency of the base of the interauricular septum in the heart removed from a patient having a distinctly tricuspid form of the left auriculoventricular valve.¹ It has taken 170 years to re-establish the fact that the left atrioventricular valve in the ostium primum defect is trifoliate, rather than representing a cleft mitral valve. Examples of the lesion we now recognize as tetralogy of Fallot were illustrated well before the description provided by Fallot himself, not least in the atlas of Von Rokitansky.² In his own description, nonetheless, Fallot provided the evidence that should have forestalled another ongoing controversy, namely the association between tetralogy and double-outlet right ventricle, when he described that, in one of the hearts obtained from a patient with *la maladie bleue*, the aortic valve was supported exclusively by the right ventricle.³ Examination of the atlases of Von Rokitansky² and Maude Abbott,⁴ furthermore, provides illustrations of the phenotypic features of most of the lesions that we now recognize as constituting congenital cardiac disease. The lesions themselves, therefore, have not changed with the passage of time. It has been

our ability to recognize the morphological features during life, along with the outcomes of treatment, which have been transformed over the past half century. In this respect, it salutary to realize that surgical treatment for so-called transposition did not begin in earnest until the mid 1960s. Surgical repair of tetralogy of Fallot at the end of the 1960s still carried a significant risk of operative death, whereas surgical options for repair of hypoplasia of the left heart had yet to be introduced. In respect of diagnosis and treatment, therefore, the changes have been revolutionary. And, although the lesions have been recognized for centuries, there has also been a revolution in the way they have been approached by morphologists. Such anatomic contributions have played their own part in underscoring the clinical advances. It remains the case, nonetheless, that consensus has yet to be reached on optimal classification and description of all the lesions. The advances made thus far in understanding the detailed anatomy, furthermore, have yet to be fully appreciated by those who have introduced similar revolutions in the understanding of the genetics and molecular biology of the developing heart, be it growing in normal or abnormal fashion.

What Underscored Changes in Anatomic Description?

By the mid 1960s, the morphology of the different individual lesions was well understood. Complex lesions, however, still tended to be grouped together as miscellaneous. The introduction of the segmental approach then showed how all hearts could be analyzed in comparable fashion, with the establishment of the location of the chambers and arterial trunks setting the scene for ongoing descriptions.⁵⁻⁷ The widespread adoption of the concept by clinicians has subsequently created some problems in providing precision in description. For example, in the majority of the patients born with transposition, the aortic root is positioned anterior and rightward within the cardiac base relative to the pulmonary root. In most patients having congenitally corrected transposition, in contrast, the aortic root is positioned anteriorly and leftward. It is now customary to describe these entities as d-transposition or l-transposition. Regular transposition, in its mirror-imaged variant, however, is properly represented as transposition {I,L,L} when using segmental codification. This is l-transposition, but the lesion is not congenitally corrected. The segmental notation for the mirror-imaged variant of congenitally corrected transposition is transposition {I,D,D}. Here, there is congenitally corrected transposition

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in the setting of the d variant. The shorthand terms currently used by clinicians, therefore, are not always accurate. Even in patients with regular transposition, furthermore, the aortic root can be positioned anterior and leftward in some patients having usual atrial arrangement. It was considerations of these kinds that stimulated the European group of investigators, of which I was one, to emphasize the importance of distinguishing not only the topological arrangement of the components of the cardiac segments, but also their connections and relations.⁸⁻¹⁰

Connections Versus Alignments

We were surprised that our suggested modification of the segmental approach, which we termed sequential segmental analysis, proved problematic for Van Praagh, who had introduced the segmental approach. Only several years later did we become aware that we had ourselves misinterpreted the essence of segmental notation. In the sets that form the essence of the Van Praaghian notation, the combinations account only for the topologic arrangement of each segment, rather than indicating how they are joined together. {S,D,*}, for example, indicates situs solitus in the setting of a right-handed ventricular loop, irrespective of the junctions between the atrial and ventricular segments. It is {S,D,*}, and {I,L,*} that represent atrioventricular concordance in the segmental system, with {S,L,*} and {I,D,*} accounting for atrioventricular discordance.⁷ We should not, therefore, have used the terms concordance and discordance to describe the normal and abnormal connections between the segments, nor to distinguish these from abnormal arrangements such as double-inlet ventricle, or classical tricuspid atresia. Both double-inlet left ventricle {S,D,D} and tricuspid atresia {S,D,D} are appropriately described in Van Praaghian terminology as having atrioventricular concordance. In our modification, we focused on the junctions between the segments, describing them in terms of connections. Van Praagh et al¹¹ subsequently introduced the notion of atrioventricular alignments for this feature, arguing that the atrial and ventricular segments were separated by 2 additional connecting segments, namely the atrioventricular canal and the conus. So as to avoid any confusion, we now always describe the union between the cavities of the atrial chambers in terms of concordant atrioventricular connections, with the reversed arrangement being described as discordant connections. This approach then distinguishes unequivocally between the concordant and discordant variants, as opposed to double-inlet ventricle, absence of 1 atrioventricular connection, or the mixed arrangement to be found when there are isomeric atrial appendages (see below).

Do New Developmental Findings Impinge on This Potential Disagreement?

During cardiac development, it is possible to recognize the atrioventricular canal and to define the proximal part of the developing outflow tract as the embryonic conus (Figure [A]). With ongoing development, the musculature of the atrioventricular canal becomes incorporated into the atrial chambers, whereas the conus is transformed into the ventricles as the subvalvar outflow tract.¹² During development, furthermore, the cavities of the right atrium and ventricle become connected together, although this is not initially the case (Figure [B]). In the early stages, the right atrium is aligned appropriately to the developing right ventricle, but there is no connection between their cavities. Alignment, therefore, is

not an appropriate synonym for connection. The developmental evidence also pertains to continuing controversies on the univentricular heart. The small chamber as seen in the setting of double-inlet left ventricle is still considered by some to represent no more than an infundibulum or conus.¹¹ From the first stages, nonetheless, the developing right ventricle possesses an apical component, with the heart itself, at this early stage, exhibiting double-inlet left ventricle, and double outlet from the developing right ventricle to a common outflow tract (Figure [B]). The resemblance between the developing right ventricle and the small chamber found in the presence of classical tricuspid atresia is striking, as its resemblance to the small chamber seen in the setting of double-inlet left ventricle, recognizing that the latter chamber most usually gives rise to the aorta, rather than the pulmonary trunk.

What Else Has Changed?

The segmental approach contributed markedly to our improved understanding of congenital cardiac malformations. Understanding is now further facilitated by the advances made in molecular biology, coupled with genetic manipulation of mice. These changes are well seen in the setting of the disturbed laterality currently described in terms of heterotaxy. In the original segmental approach, the so-called splenic syndromes were grouped together in terms of ambiguous situs.⁷ Recent findings show that their phenotypic features are those of isomerism, as opposed to lateralization, of the thoracic organs.¹³ For the heart, however, it is only the atrial appendages that are truly isomeric. By perturbing the genetic cascades responsible for producing morphologically rightness or leftness, it is now possible to generate mice with either isomeric right (Figure [C]) or left (Figure [D]) atrial appendages. And it is the appendages that are the most constant atrial components. As such, when applying the so-called morphological method, established by Van Praagh et al¹⁴ as the best way of defining cardiac structures, it is the atrial appendages that provide the best guide to atrial morphology. When analyzed on this basis, all hearts, be they normal or congenitally malformed can be categorized as having usual or mirror-imaged atrial arrangement, as opposed to isomerism of the left or right atrial appendages. This approach now sets the scene for optimal discrimination of the subsets of the patients with the so-called heterotaxy, recognizing that the isomeric features do not always correspond between the appendages and the other thoracic organs, but that correspondence in this regard is appreciably better than that with splenic anatomy.¹⁵ Description of any variations should they exist, combined with full description of the intracardiac variations, serves to dispel any perceived notion of ambiguity.¹³

Current Face of the Congenitally Malformed Heart

Thanks to the advances made in clinical imaging, the most subtle details of cardiac anatomy can now be recognized during life. When using the segmental approach to diagnosis, therefore, as modified to take note of the connections between the cardiac segments, even the most complex cardiac malformations can now be described in simple, accurate, and unambiguous fashion. These changes have contributed in no uncertain fashion to the amazing results of treatment now achieved for patients born with congenital cardiac lesions, helping to bring so many of these patients to the attention of the adult cardiologist. When molecular biologists and embryologists, in turn,

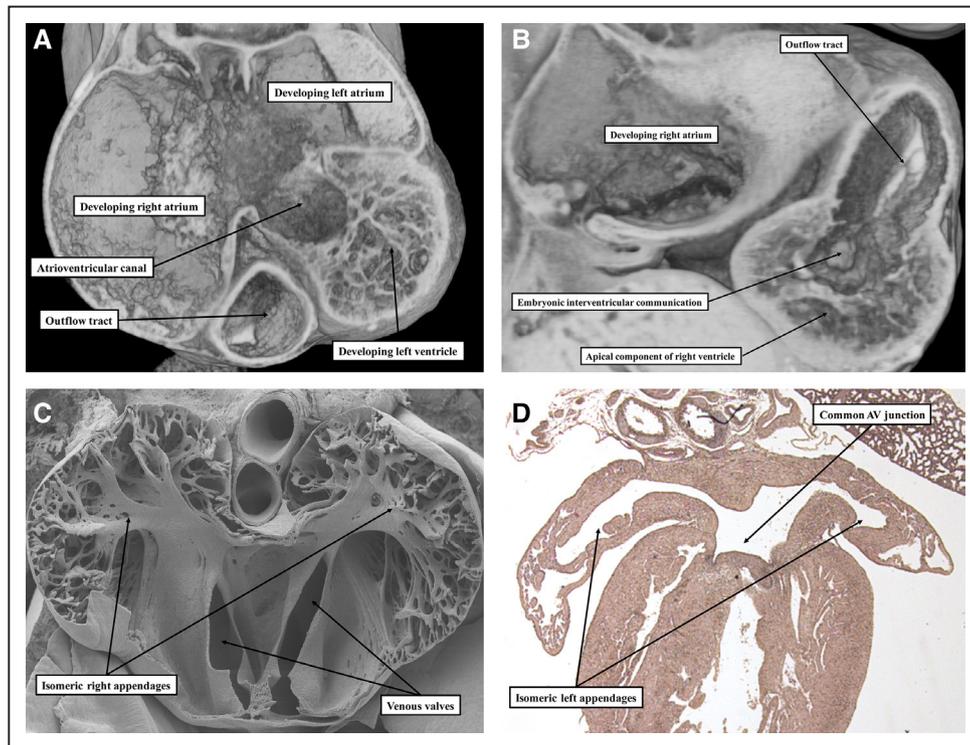


Figure. A, Section from an episcopic data set prepared from a human embryo at Carnegie stage 14. The developing atrial chambers at this early stage are connected by the musculature of the atrioventricular canal to the developing left ventricle. The proximal part of the outflow tract is recognizable as the so-called conus. **B**, From another data set, this time from a human embryo at Carnegie stage 13. It confirms that, although the developing right atrium is aligned in normal fashion to the developing right ventricle, as yet there is no communication between their cavities. The blood from the developing left ventricle enters the developing right ventricle through the embryonic interventricular communication. **C**, Scanning electron microscopic image of the short axis of the atrial chambers of a developing mouse heart in which the *Pitx2* gene has been knocked out. Both atrial appendages are morphologically right. There is also bilateral symmetry of the venous valves. **D**, Histological section through the atrial chambers of a mouse embryo in which the *Lefty1* gene has been knocked out. Both appendages are morphologically left, and there is a common atrioventricular junction.

embrace the approach to diagnosis pioneered by Van Praagh et al,⁵⁻⁷ we can anticipate clarification of the morphogenesis of the various lesions, with the improved knowledge then contributing to optimal genetic counseling.

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Disclosures

None.

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