Cardiol Young 2001; 11: 689–690

ISSN 1047-9511

Letter to the Editor

On the value of morphogenetic classifications of hearts with double outlet right ventricle

Dear Sir,

I read with pleasure the article of Anderson et al.[1] concerning double outlet right ventricle, in which they reviewed various aspects of this peculiar diagnostic group of congenital cardiac malformations for the purpose of continuing medical education. I congratulate the authors on writing an excellent overview on these historical and pathomorphological aspects of the entity relevant to clinical disciplines dealing with congenital cardiac disease. With respect to the present discussion on the value of double outlet as a diagnostic term, however, I would like to add some comments on a closely related matter. At first sight, this may seem to be merely of interest to some of the preclinical disciplines. I refer to the value of the term "conotruncal malformations" as an overarching diagnosis to include double outlet along with other major congenital cardiac defects. This topic might be of minor practical relevance to those clinicians primarily dealing with the diagnosis and treatment of congenital cardiac disease. It has, however, some relevance for the interpretation of epidemiologic and molecular genetic data, the correct interpretation of which might lead to the development of strategies for the prevention of some congenital cardiac malformations.

In contemporary articles on congenital cardiac disease, the anatomically heterogeneous group of defects with the ventriculo-arterial connection of double outlet is frequently classified as a subgroup of the class of "conotruncal malformations".[2–5] This implies that the morphogenetic origin of the particular cardiovascular malformation is an abnormality in the development of the outflow region, specifically the "conotruncus" of the embryonic heart, whatever that might be. Besides double outlet, the grouping of "conotruncal malformations" includes defects such as Fallot's tetralogy, complete and corrected transposition, and common arterial trunk.

Since the introduction of double outlet right ventricle as a diagnostic term by Witham in 1957,[6] we have learnt that it does not define a specific morphological entity, but simply represents the ventriculo-arterial connection in which both arterial trunks arise from the morphologically right ventricle. Anderson and co-authors[1] have nicely demonstrated the remarkable anatomical heterogeneity found within this diagnostic group, as well as the controversies which surround this topic. When I think of the bewildering anatomical variability demonstrated, I wonder why clinicians familiar with such defects do not seem to question the current practice of grouping all these variants into a single morphogenetic class, namely that of the "conotruncal malformations". I especially wonder about this practice, since there is a wealth of published data suggesting that the range of morphogenetic pathways leading to double outlet is not confined to abnormal conotruncal development. Based on the analysis of the pathological anatomy of human specimens with double outlet, for example, several pathologists came to the conclusion that developmental alterations in the endocardial cushions of the atrioventricular canal might be causally involved in the pathogenesis of some of the hearts.[7–9] The fact that anomalies in development of these endocardial cushions seem to be of central importance for the pathogenesis of abnormal ventriculo-arterial connections was, indeed, noted in several embryological studies.[10–12] Moreover, the morphological features of embryonic hearts, in which the double outlet ventriculo-arterial connection seems to have resulted exclusively from abnormal development of the atrioventricular region, have been demonstrated recently by scanning electron microscopy.[13] It appears, therefore, that the diagnostic group of double outlet right ventricle might encompass at least two different morphogenetic classes, a class of "conotruncal malformations" along with a class of "atrioventricular malformations". Knowledge on the presence of at least two different morphogenetic classes of double outlet might be helpful for the interpretation of epidemiologic data. The evaluation of data from the Baltimore–Washington Infant Study, for example, led to the distinction of two diagnostic subgroups, one with abnormally related great arteries with anterior aorta, and a second with normally related great arterial trunks.[14] It is tempting to speculate that these two

diagnostic subgroups might correspond to the morphogenetic classes of conotruncal and atrioventricular malformations, respectively.

In summary, it can be stated that, from the standpoint of an embryologist, it is not justified to include the entire group of hearts with double outlet right ventricle within the class of "conotruncal malformations". There is good evidence for classifying some types as "atrioventricular malformations". Furthermore, there is a wealth of data, which space prevents me from detailing, suggesting that defective remodelling of the inner curvature of the embryonic heart is a third important pathway leading to double outlet right ventricle.[15,16] The remarkable anatomical heterogeneity found among congenitally malformed hearts with double outlet right ventricle might be explained by the presence of a corresponding heterogeneity in morphogenetic pathways leading to this peculiar form of ventriculo-arterial connection. Classifying all types of this lesion as "conotruncal malformations" does not favour, but rather hinders the evolution of our understanding of this diagnostic group of congenital cardiac anomalies.

Jörg Männer, Department of Embryology, Georg-August University of Göttingen, Germany

References

1. Anderson RH, McCarthy K, Cook AC. Double outlet right ventricle. Cardiol Young 2001; 11: 329–344.
2. Van Praagh R. Conotruncal malformations. In: Heart Disease in Infancy, Diagnosis and Surgical Treatment. Churchill Livingston, London, 1973, pp 141–188.
3. O'Malley CD, Shaw GM, Wasserman CR. Lammer EJ. Epidemiologic characteristics of conotruncal heart defects in California, 1987–1988. Teratology 1996; 53: 374–377.
4. Paladini D, Rustico M, Todros T, et al. Conotruncal anomalies in prenatal life. Ultrasound Obstet Gynecol 1996; 8: 241–246.
5. Goldmuntz E, Clark BJ, Mitchell LE et al. Jawad AF. Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol 1998; 32: 492–498.
6. Witham AC. Double-outlet right ventricle. A partial transposition complex. Am Heart J 1957; 53: 928–939.
7. McCullough AW, Wilbur EL. Defect of endocardial cushion development as a source of cardiac anomaly. Am J Pathol 1944; 20: 321–328.
8. Angelini P, Leachman RD. The spectrum of double-outlet right ventricle: an embryologic interpretation. Cardiovasc Dis 1976; 3: 127–149.
9. Van Praagh S, Davidoff A, Chin A, Shiel FS, Reynolds J, Van Praagh R. Double-outlet right ventricles: anatomic types and developmental implications based on a study of 101 autopsied cases. Coeur 1982; 13: 389–440.
10. Shaner RF. Malformation of the atrio-ventricular endocardial cushions of the embryo pig and its relation to defects of the conus and truncus arteriosus. Am J Anat 1949; 84: 431–456.
11. Fox MH, Goss CM. Experimental production of a syndrome of congenital cardiovascular defects in rats. Anat Rec 1956; 124: 309–332.
12. Smith WNA. The side of action of Trypan blue in cardiac teratogenesis. Anat Rec 1963; 147: 507–523.
13. Männer J, Seidl W, Steding G. Embryological observations on the morphogenesis of double-outlet right ventricle with subaortic ventricular septal defect and normal arrangement of the great arteries. Thorac Cardiovasc Surg 1995; 43: 307–312.
14. Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD. Genetic and environmental risk factors of major cardiovascular malformations. The Baltimore–Washington Infant Study. Perspect Pediatr Cardiol 5. Futura, New York 1997.
15. De la Cruz MV, Da Rocha JP. An ontogenetic theory for the explanation of congenital malformations involving the truncus and conus. Am Heart J 1956; 51: 782–805.
16. Steding G, Seidl W. Contribution to the development of the heart. Part II. Morphogenesis of congenital heart disease. Thorac Cardiovasc Surg 1981; 29: 1–16.

The Letter was shown to the authors, who responded as follows:

Dear Sir,

We thank Jörg Männer for his perceptive comments. In our opinion, however, he does not go far enough. We would extend his comments to suggest that the term "conotruncal malformations" no longer be used as a diagnostic grouping for postnatal congenitally malformed hearts. As Jörg explains so clearly, there is very strong evidence supporting the notion that double outlet ventriculo-arterial connection can be the consequence of abnormal development of the atrioventricular regions. While the evidence is persuasive that lesions such as tetralogy of Fallot and common arterial trunk are due to abnormal development of the developing outflow tracts, specifically due to abnormal migration of cells from the neural crest, the same cannot be said for the hearts with discordant ventriculo-arterial connections. But, as also pointed out by Männer, it is frequent to include both complete and corrected transposition within the group of purported "conotruncal malformations". In our opinion, it would be a major improvement if we simply grouped these entities together as abnormalities of the ventricular outflow tract. We are now in far better position to dissect out the various abnormal morphogenetic features which produce the differing anatomic manifestations of the lesions, be these an abnormal ventriculo-arterial connection, unexpected relationships between the arterial trunks, or an unusual arrangement of the infundibular musculature. As we emphasised in our review, these are discrete and separate features of the malformed hearts, and require separate description. We infer from Jörg's letter that different embryologic events may underscore these various features. It is now incumbent upon the embryologists to seek to unravel these events, and they now possess the armamentarium for success. But our understanding would be greatly enhanced if, in future, we could describe the entities without recourse to the confusing term "conotruncal malformations".

Robert H. Anderson, Karen McCarthy, Andrew C. Cook, Cardiac Unit, Institute of Child Health, London

https://doi.org/10.1017/S1047951101001147 Published online by Cambridge University Press