Classifying Heterotaxy Syndrome
Time for a New Approach

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Heterotaxy syndrome is a complex set of abnormalities related to abnormal left–right axis patterning. Although rare (occurring in just over 1 in 10 000 live births[1]), congenital heart defects associated with heterotaxy syndrome carry a disproportionate burden of morbidity and mortality.[2,3] Despite numerous investigations on the genetic underpinning, epidemiology, anatomic pathology, diagnostic imaging, and management, agreement regarding the best method to classify patients with heterotaxy continues to elude our field.[4] Specifically, a growing body of experience has noted that the 2 most common methods of classifying patients with heterotaxy—based on the status of the spleen or on the morphology of the atrial appendages—is frequently incongruent with the expected pattern of cardiac and noncardiac anomalies,[5] is difficult to ascertain clinically, and may not be helpful in guiding clinical management.[2–4]

See Article by Yim et al

In this issue of *Circulation: Cardiovascular Imaging*, Yim et al[6] provide further evidence that the prevailing classification schemes used in heterotaxy syndrome are flawed. In a retrospective analysis of noninvasive imaging data from 114 patients with heterotaxy, they noted that the classic pattern of isomerism was breached in 1 of every 5 patients. Furthermore, they documented the limited clinical utility of relying on atrial appendage morphology or the status of the spleen and observed that the former could not be classified in 15% of patients and the latter in 3.5%. Notably, Figures 4 and 5 in the article by Yim et al highlight the challenges in assigning atrial appendages as left or right, despite excellent in vivo imaging by cardiac computed tomography and magnetic resonance imaging. Indeed, the challenge is not related to imaging technique as illustrated by the study of Calder, who examined 56 autopsy cases of heterotaxy syndrome and 205 autopsy cases with atrial situs solitus.[5] Similar to Yim et al, atrial appendage morphology and bronchial pattern were discordant in 16% of patients with heterotaxy. As with previous postmortem studies, the author identified several other deviations from the expected pattern of visceral and cardiac anatomy, irrespective of classifying patients based on the status of the spleen or atrial appendages.

Substantial progress has been made in recent decades in understanding how lateralizing information is transmitted to the lateral plate mesoderm, the 2-cilia model[7] being most widely accepted. Around the end of gastrulation, motile cilia in the pit of the node at the rostral end of the primitive streak normally establish flow of extracellular fluid across the node from right to left. This stimulates receptor cilia at the leftward edge of the node, initiating a transcription cascade that instructs the left lateral plate to generate left-sided structures. Right-sided structures appear to develop from the right lateral plate by default. For such a fundamental process, left–right axis establishment is remarkably complicated, with multielement effector and receptor cilia leading to expression of distinct chains of essential gene products on either side of the embryo. Consequently, the variability in heterotaxy syndromes, well recognized by generations of pediatric cardiologists and documented by Yim et al,[6] should not be surprising.

Although there are statistical associations among various cardiac and extracardiac anomalies (eg, asplenia, bilaterally right atrial pectinate muscle architecture, common atrioventricular canal defects, transposition of the great arteries or double-outlet right ventricle, and pulmonary stenosis or atresia), recognized since Ivemark,[8] these are merely associations and not rules. Yim et al have done us a service by quantifying the exceptions to the syndromes or sets of associated defects, confirming and emphasizing the variability and unpredictability encountered in these complex hearts. Accurate diagnosis of complex heart defects, especially heterotaxy syndromes, requires knowledge of the nearly limitless anatomic possibilities. The realization that almost anything can happen should serve as fair warning to the diagnostician to avoid becoming entrapped by labels.

The variability of heterotaxy syndromes likely reflects the complexity of the developmental biology of lateralization. A large number of genes and regulatory pathways are involved. Mutation at any given point in a pathway might produce a specific phenotypic pattern. Interactions between genes in pathways directly involved in lateralization and background genes are also likely important and might explain some of the intersubject phenotypic variability, despite mutation of a common gene. Recently, copy number variation of significant genes has been found in patients with heterotaxy syndrome[9] so that variable gene dosage might also be an important cause of phenotypic variability.

Advances in developmental biology have tied together mechanistically some of the ostensibly disparate defects seen in heterotaxy syndromes. For example, Ivemark questioned why there should be the frequent association

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between conotruncal anomalies (transposition or double-outlet right ventricle) and atrioventricular canal defects.[8] He concluded that it was likely because of an abnormality of the gelatinous reticulum—the name applied to the material making up both the atrioventricular cushions and the outflow ridges. More recent data, not available to Ivemark, indicate that the second heart field (the source of most of the right ventricle, the outflow tract, and parts of the atria) is highly prepatterned.[10] Specifically, the infundibular muscle underlying the pulmonary artery in the normal heart derives from a group of cells most likely on the left side of the posterior second heart field. These cells proliferate and develop under the influence of left-sided transcription factors and are necessary for normal outflow development. Further, cells in the same area contribute to the complex of tissues (dorsal mesenchymal protrusion or vestibular spine) important for septation of the atria and division of the atrioventricular canal.[11] Abnormal development of this part of the second heart field provides the most likely link between abnormalities of the outflow and atrioventricular canal. Abnormal development of the subpulmonary myocardium is associated with subvalvar and valvar pulmonary stenosis as well.[10]

The study by Yim et al is not only a useful reminder for practicing cardiologists that the currently used classification schemes do not work but also emphasizes the importance of an individualized approach to diagnosis based a systematic segment-by-segment analysis of each part of the cardiovascular system. In addition, the study might also provide clues to geneticists and developmental biologists studying the causes and developmental mechanisms of congenital heart defects. Looking ahead, the article by Yim et al highlights the need for our field to move past reliance on atrial appendage morphology or splenic status and to develop a new paradigm for classifying patients with heterotaxy based on biological and novel imaging biomarkers.

Disclosures

None.

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