Disharmonious Patterns of Heterotaxy and Isomerism
How Often Are the Classic Patterns Breached?

Deane Yim, MBchB; Hazumu Nagata, MD; Christopher Z. Lam, MD; Lars Grosse-Wortmann, MD; Mike Seed, MBBS; Edgar Jaeggi, MD; Shi-Joon Yoo, MD

Background—It is advocated that heterotaxy should be segregated into right or left isomerism according to atrial appendage morphology. However, atrial situs determination is often based on the pattern of associated findings rather than on atrial morphology itself, which can be difficult to define. The objective was to assess how often concordant patterns of isomerism classified by atrial appendage morphology, bronchopulmonary pattern, and splenic status are breached using cardiac magnetic resonance or computed tomography. The secondary objective was to determine the feasibility of defining atrial appendage morphology using cardiac magnetic resonance or computed tomography.

Methods and Results—Retrospective review of 114 pediatric patients (median, 2.4 years; range, 1 day–17.9 years) with heterotaxy who underwent cardiac magnetic resonance or computed tomography was performed to evaluate atrial appendage, bronchopulmonary, and visceral organ arrangements. Atrial appendage and splenic anatomy were not definable in 17 of 114 (15%) and 4 of 114 (3.5%) patients, respectively. In the remaining 93 patients, 39% had classic right isomerism (bilateral right atrial appendages, right bronchopulmonary pattern, and asplenia) and 40% had classic left isomerism (bilateral left atrial appendages, left bronchopulmonary pattern, and polysplenia). Classic pattern of isomerism was breached in 20 of 93 (21.5%) patients: 13 (65%) displayed incongruent abdominal situs, 5 (25%) incongruent bronchial situs, 1 (5%) had discrepant appendage morphology, and 1 (5%) incongruent situs at all levels.

Conclusions—Atrial appendage morphology is difficult to assess and not always indicative of bronchopulmonary or abdominal situs. Discordance between bronchopulmonary branching, atrial appendage arrangement, and splenic status was identified in >20% patients with heterotaxy. Independent description of each organ system is required when arrangements are disharmonious among different organ systems. **(*Circ Cardiovasc Imaging*. 2018;11:e006917. DOI: 10.1161/CIRCIMAGING.117.006917.)**

Key Words: atrial appendage ■ heart atria ■ heterotaxy syndrome ■ isomerism ■ magnetic resonance imaging ■ tomography, X-ray computed

An abnormal arrangement of the internal organs is a harbinger of congenital heart diseases that are frequently complex. This condition has been described using contentious terms: heterotaxy and isomerisms.[1] As these terms have not been used uniformly, the International Society for Nomenclature of Paediatric and Congenital Heart Disease proposed the following definitions in 2007[2]:

See Editorial by Sanders and Geva
See Clinical Perspective

> *Heterotaxy is an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body. By this Committee convention, heterotaxy does not include normal and mirror-imaged arrangements of the internal organs that are also known as "situs solitus" and "situs inversus."*
>
> *Isomerism in the context of the congenitally malformed heart is a situation where some paired structures on opposite sides of the left-right axis of the body are, in morphologic terms, symmetrical mirror images of each other.*
>
> *Situs ambiguus is an abnormality in which there are components of situs solitus and situs inversus in the same person. Therefore, the thoraco-abdominal organs are positioned in such a way that they have neither normal nor mirror-imaged arrangements.*

In general, heterotaxy encompasses 2 separate entities, right and left isomerisms, the former being usually associated with asplenia and the latter with polysplenia. As the International Society for Nomenclature of Paediatric and Congenital Heart Disease pointed out, however, there are cases that breach the general rules of left versus right isomerism.[2] In day-to-day practice with cross-sectional imaging, we

Received July 20, 2017; accepted December 21, 2017.

From the Labatt Family Heart Centre (D.Y., H.N., L.G.-W., M.S., E.J., S.-J.Y.) and Department of Diagnostic Imaging (C.Z.L., L.G.-W., M.S., S.-J.Y.), The Hospital for Sick Children, Toronto, Canada; and Department of Pediatrics, University of Toronto, Canada (L.G.-W., M.S., E.J., S.-J.Y.).

Correspondence to Shi-Joon Yoo, MD, Department of Diagnostic Imaging, The Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada M5G 1X8. E-mail shi-joon.yoo@sickkids.ca

have experienced that not all heterotaxy cases are consistently classifiable as right or left isomerism, therefore falling into the category of situs ambiguus as defined above. Moreover, it is a challenging task to assess the shape of the atrial appendages and distribution of the pectinate muscles as Uemura et al[3,4] and Anderson[5] have proposed by echocardiography and cross-sectional imaging. Therefore, in vivo atrial situs determination seems to be based more on the general pattern of the associated cardiovascular and noncardiovascular findings than on the actual assessment of the atrial morphology.

In this article, we sought to assess how frequently the general rules of heterotaxy and isomerisms are breached and how reliable and feasible it is to define the atrial appendage morphology using cardiovascular magnetic resonance (CMR) or computed tomography (CT).

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. In this retrospective study, we reviewed all pediatric patients diagnosed with heterotaxy that underwent CMR, CT, or both at our institution between 1991 and 2016. A systematic search for patients from the institutional radiology database with the terms heterotaxy, isomerism, asplenia, or polysplenia was conducted. All cases were reviewed case-by-case to determine the arrangements of bronchopulmonary segments, the lengths of main bronchi, the morphology of the atrial appendages, and the arrangement of the visceral organs. Excluded were patients with studies of insufficient image quality or coverage to allow for detailed segmental analyses. The study was approved by the institutional research ethics board.

Assessment of Atrial Appendages

Each case was assessed by consensus among 2 observers (D.Y. and S.J.Y.) whether they had morphologically right or left atrial appendages by CT and CMR as determined by the shape of the appendage and extent of the pectinate muscles, following descriptions by Uemura et al[3,4] and Anderson.[5] The appendages were further assessed using multiplanar reformatting if their morphology was not evident from standard imaging planes (Figure 1). The cases where the atrial appendage morphology was not able to be defined by cross-sectional imaging were recorded.

Assessment of Bronchopulmonary Arrangement

The bronchopulmonary relationship was assessed using CT or CMR images obtained or reconstructed in coronal or oblique coronal planes, and cases were categorized into situs solitus, situs inversus, right isomeric, and left isomeric patterns. If it was not possible to define the bronchial branching pattern, it was considered to be indeterminate. A right side pattern of bronchopulmonary relationship was defined as the descending branch of the pulmonary artery coursing backward below the upper lobar bronchus (hypbronchial pulmonary artery—eparterial bronchus).[6,7] Conversely, a left-sided pattern of the bronchopulmonary relationship was defined as the pulmonary artery coursing backward over the upper lobar bronchus (epbronchial pulmonary artery—hyparterial bronchus).

Assessment of Bronchial Length

The lengths of the right and left bronchi were measured from the tracheobronchial bifurcation to the origins of the upper lobar bronchi. The bronchial lengths were considered symmetrical if the ratio between the 2 was <1.5 and asymmetrical when ≥1.5.[8] Asymmetrical bronchial length has been proposed to be typical of situs solitus or inversus of the bronchi.[8] Cases where the bronchial length was incongruent with the bronchopulmonary pattern were noted.

Assessment of Splenic Status

The splenic status was defined by the number and the configuration of the spleen or spleens. Multiple discrete spleens were defined as polysplenia. A single spleen with a lobulated or round contour was regarded as a variant of polysplenia.[9] The spleen was considered to be normal when a single spleen showed smooth and crescentic configuration.

Diagnosis of Left or Right Isomerism

The diagnosis of heterotaxy was based on the abnormal viscero-atrial-thoracic arrangement across the left–right axis of the body.[9,10] Patients were classified to have classic features of right isomerism if they exhibited a bilateral eparterial bronchial branching pattern, bilateral morphological right atrial appendages, and abnormal visceral arrangement with asplenia (Figure 2A and 2B). Features considered in classic left isomerism included a bilateral hyparterial bronchial branching pattern and morphological left atrial appendages and polysplenia (Figure 3). The cases that deviated from these 2 classic patterns of heterotaxy were studied.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY). Results are presented as median with ranges or numbers with percentages as appropriate.

Results

There were 150 cases that returned from our search criteria of key words. Cases were excluded if they were mistakenly diagnosed as heterotaxy (n=15), did not have sufficient coverage to determine thoracic and abdominal situs (n=14), or if the imaging quality was insufficient (n=7). The remaining 114 cases with heterotaxy, with a median age of 2.4 years (range, 1 day–17.9 years) at the time of cross-sectional imaging, were included. Thirty-five patients had CTs available, 50 patients had CMR studies, and the remaining 29 had both CT and CMR studies. The indications for cross-sectional imaging included anatomic delineation, assessment of pulmonary arteries or veins, pre-Glenn or Fontan operations, assessment of the post-Fontan circulation, or as a work-up before cardiac transplantation.

Classic Versus Deviating Isomeric Patterns

The splenic anatomy could not be reliably defined in 4 (3.5%) cases, and the atrial appendage morphology was undefinable in 17 (15%) by CT or CMR (Figure 4). In the remaining 93 patients, classic right or left isomerism of the atrial appendages, bronchopulmonary branching, and splenic arrangement was present in 36 (38.7%) (Figure 2A and 2B) and 37 (39.8%) patients, respectively (Figure 3). The remaining 20 (21.5%) displayed breach to the classic patterns of right or left isomerism (Table 1; Figures 5–8). Among these 20 patients, 16 had polysplenia, 1 asplenia, and 3 had a normal single spleen. Inconsistent abdominal situs, bronchial situs, or atrial situs respectively from classic isomerism was observed in 13 (65%), 5 (25%), and 1 (5%) case while 1 (5%) had discordant situs arrangements at all 3 levels (Figure 5). All cases showing a laterialized situs, that is, solitus or inversus of either atrial appendage or bronchopulmonary arrangement (or both) were associated with polysplenia, which was the most common combination (Table 1).

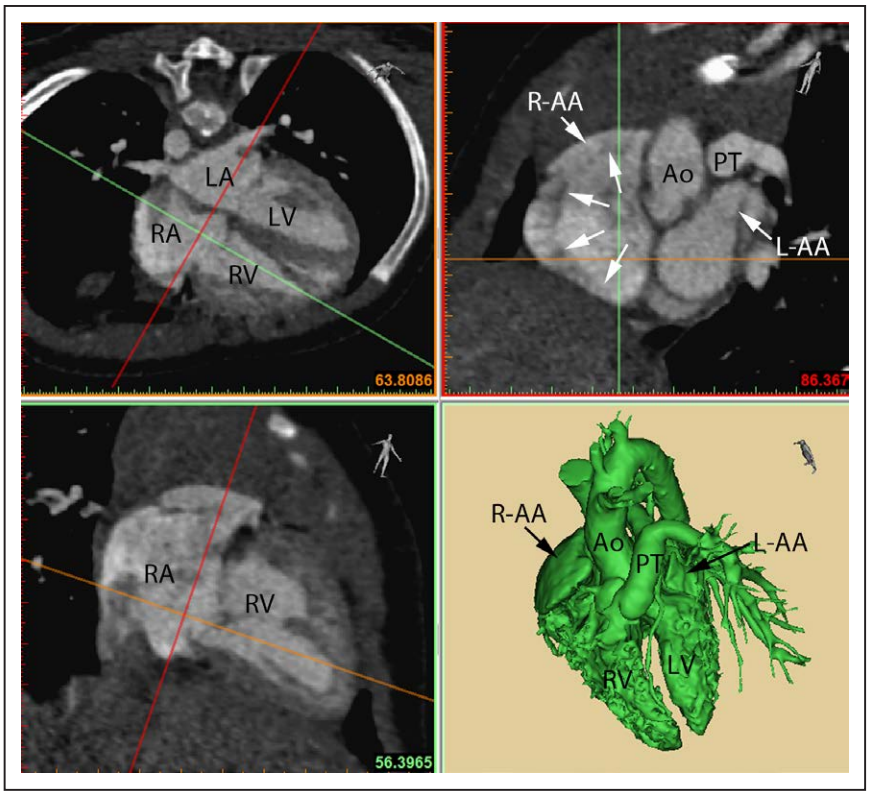


Figure 1. Multiplanar reformat and 3-dimensional volume-rendered images of a case of situs solitus with tetralogy of Fallot. The short-axis image on the right upper panel was obtained through the lower part of the atrium immediately above the atrioventricular junction. The imaging plane is marked with a red line on the 4-chamber image and 2-chamber image of the right ventricle on the left hand panels. The right atrial appendage (R-AA) is triangular in shape, and its pectinate muscles (**arrows**) are seen all around the right atrial wall. The left atrial appendage (L-AA) is narrow and elongated. There are no identifiable pectinate muscles along the left atrial wall. Ao indicates aorta; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; and RV, right ventricle.

Variations in Segmental Findings

Bronchopulmonary Pattern and Bronchial Length

The bronchopulmonary relationship and bronchial lengths were able to be reliably assessed in all patients. In 103 of 114 (90%) of cases, the bilateral eparterial or hyparterial locations of the upper lobe bronchi were consistent with a right (n=54) or left (n=49) isomeric pattern, respectively (Figures 2 and 3). In the remaining 11 (10%), the bronchopulmonary relationship was either normal (n=7) or inverted (n=4; Figure 6), all in the presence of abnormal abdominal visceral arrangement with polysplenia. In 8 (7%) cases, the lengths of the bronchi were significantly different despite the classic isomeric relationship between the bronchi and pulmonary arteries (Figure 7A and 7B). In these cases, the bronchial length ratio was >1.5, indicating a situs solitus or inversus pattern by way of length despite an isomeric right (n=4) or left (n=4) bronchopulmonary relationship.

Splenic Status

The distribution of cases according to the splenic status is outlined in Figure 8. Asplenia was found in 43 of 110 (39%) patients with definable splenic anatomy, and this was associated with right isomeric pattern of bronchopulmonary branching in all. After exclusion of 6 patients with asplenia with nondefinable atrial appendage morphology, there was concordance between asplenia and right isomerism of atrial appendages in 36 of 37 (97%) patients. One patient with asplenia had left-isomeric atrial appendages and right isomeric bronchopulmonary branching (Figure 7B; Table 1).

Polysplenia was found in 63 of 110 (57%) patients with definable anatomy and consisted of multiple spleens in 56 (89%) and a single lobulated or round spleen in 7 (11%). Polysplenia was associated with a left bronchopulmonary branching pattern in 47 (75%) patients, right bronchopulmonary pattern in 5 (8%), and a normal (n=7) or inverted (n=4) branching pattern in the remaining 11 patients (17%). After exclusion of 10 patients who had nondefinable atrial appendage morphology, polysplenia was associated with left isomerism of the atrial appendages in 42 of 53 (79%) patients, right isomerism in 3 of 53 (6%), and normal or inverted arrangement in 8 of 53 (15%).

Four patients (4%) had a solitary spleen with a smooth crescentic contour that was small or normally sized (Figures 4 and 7A). Of these patients, right isomeric bronchopulmonary branching and atrial appendages were observed in 2 patients, and left-isomeric bronchopulmonary branching and atrial appendages were present in 1 patient (Table 1 and Figure 8). The remaining case of a solitary spleen displayed a right isomeric bronchopulmonary branching pattern and appendages of undetermined morphology.

Overall, asplenia was associated with classic right isomerism of bronchopulmonary branching and atrial appendages in all except 1 while polysplenia was associated with breached bronchopulmonary branching pattern in 16 of 63 (25%) and breached arrangement of the atrial appendages in 11 of 53 (21%).

Cardiac Abnormalities

The majority of cases with classic or nonclassic heterotaxy patterns had complex cardiac disease. Dextrocardia was present in 40 of 114 (35%) of the cohort and was observed in 14 of 36 (39%) and 11 of 37 (30%) with classic right and left isomerism, respectively. An interrupted inferior vena cava was present in 29 of 37 (78%) of classic left isomerism and no cases of right isomerism. Bilateral superior vena cavae were seen in 19 of 36 (53%) and 17 of 37 (46%) of classic right and left isomerism cases, respectively.

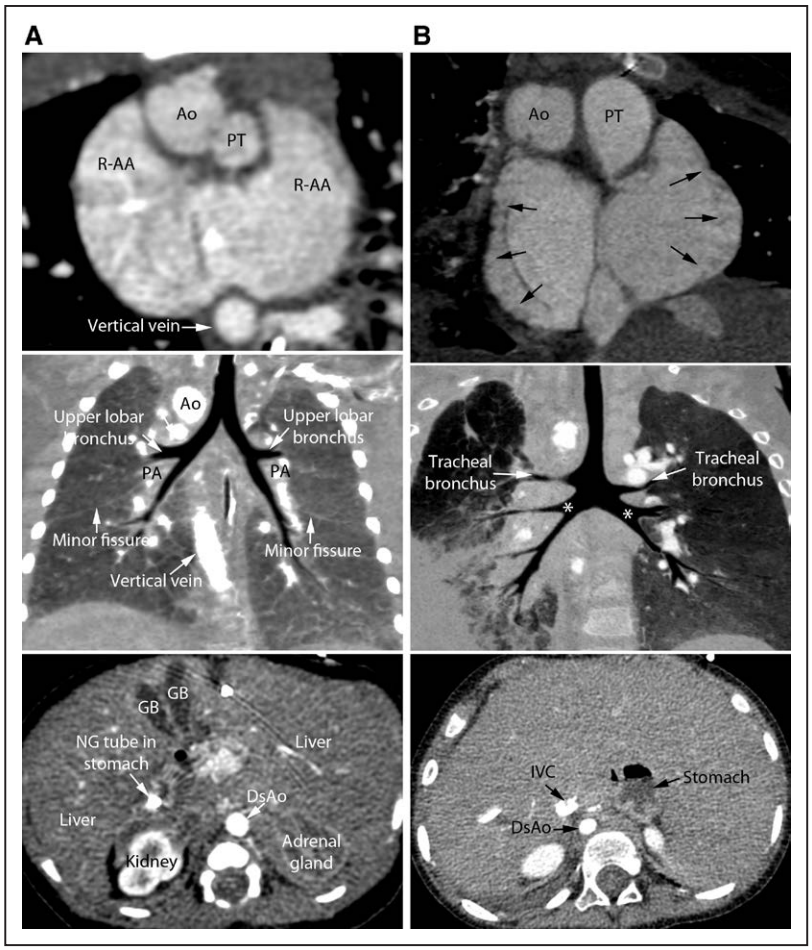


Figure 2. A, Heterotaxy with classic right isomerism and asplenia. Note the symmetrical hypbronchial pulmonary arteries (PA) and eparterial upper lobar bronchi. Both side atrial appendages are triangular in shape with a wide orifice. The right lobe of the liver wraps around the tiny stomach (microgastria). There are duplicated gallbladders (GB). **B**, The pectinate muscles (**arrows**) are seen along the wall of both atria. The airway branching is symmetrical with bilateral tracheal bronchi and short lengths of the main bronchi (*). The liver extends around the stomach. The abdominal aorta (DsAo) and the inferior vena cava (IVC) are on the same side of the spine, which is seen in the majority of the cases of right isomerism. Ao indicates aorta; NG, nasogastric; PT, pulmonary trunk; and R-AA, morphologically right atrial appendage.

Classic right isomerism was associated with an atrioventricular septal defect in 35 of 36 (97%) cases, and 1 patient had a double inlet ventricle of indeterminate morphology. Double outlet right ventricle was observed in 26 of 35 (72%), discordant connections in 6 of 36 (17%), and concordant ventriculoarterial connections in 4 of 36 (11%) patients. Pulmonary stenosis or atresia occurred in 28 of 36 (78%) patients with classic right isomerism.

Classic left isomerism was associated with an atrioventricular septal defect in 25 of 37 (68%) patients, atrial and ventricular septal defects in 8 of 37 (22%), hypoplastic left heart syndrome in 2 of 37 (5%), dextrocardia or levocardia with otherwise normal intracardiac anatomy in 2 of 37 (5%). Left isomerism was associated with concordant ventriculoarterial connections in 22 of 37 (59%) patients, double outlet right ventricle in 13 of 37 (35%), and discordant connections in 2 of 37 (5%) patients. Pulmonary stenosis or atresia occurred in 12 of 37 (32%) patients, and aortic stenosis or atresia was found in 7 of 37 (19%) with classic left isomerism. Arrhythmias, predominantly complete heart block, were more common in patients with left isomerism (10 of 37; 27%) than with right isomerism (2 of 35; 6%).

Discussion

Despite the fact that Aristotle observed the existence of asplenia and polysplenia and that the terms heterotaxy, isomerism, and bilateral right or left sidedness have been used for >60 years,[11–14] there have been ongoing debates and controversies on the concept of isomerism and how to describe cases with an abnormal arrangement of the body organs.[2,15–17] Although we do not know the exact pathogenesis, there are individuals who demonstrate dominance or duplication of normally right- or left-sided structures resulting in right or left-isomeric patterns of paired visceral organs, including lungs, bronchi, pulmonary arteries, and atrial appendages. In addition, nonpaired organs also tend to demonstrate right or left side dominance. When the right side dominates, the liver is usually large and transverse, the normally right-sided structures, such as sinoatrial node and gallbladder, can be duplicated (Figure 2A), and the spleen, a normally left-sided organ, is usually not formed. Interestingly, additional abnormalities, such as tracheal bronchus, can be seen on both sides[17,18] (Figure 2B). When the left side dominates, multiple spleens are commonly formed along the greater curvature of the stomach, the liver tends to be transverse and small, and the normally right-sided structures, such as gallbladder, biliary tree, and portal vein, can be absent, atretic or hypoplastic. Indeed, such interesting associations are the foundation of the fascinating concept of right and left isomerisms or bilateral right and left sidedness.[11–13]

It is, however, important to highlight that isomerism does not mean that every body organ is arranged symmetrically. Although the concept of isomerism does facilitate general understanding of abnormal organ arrangement, it is not always possible to define the situs unequivocally in terms

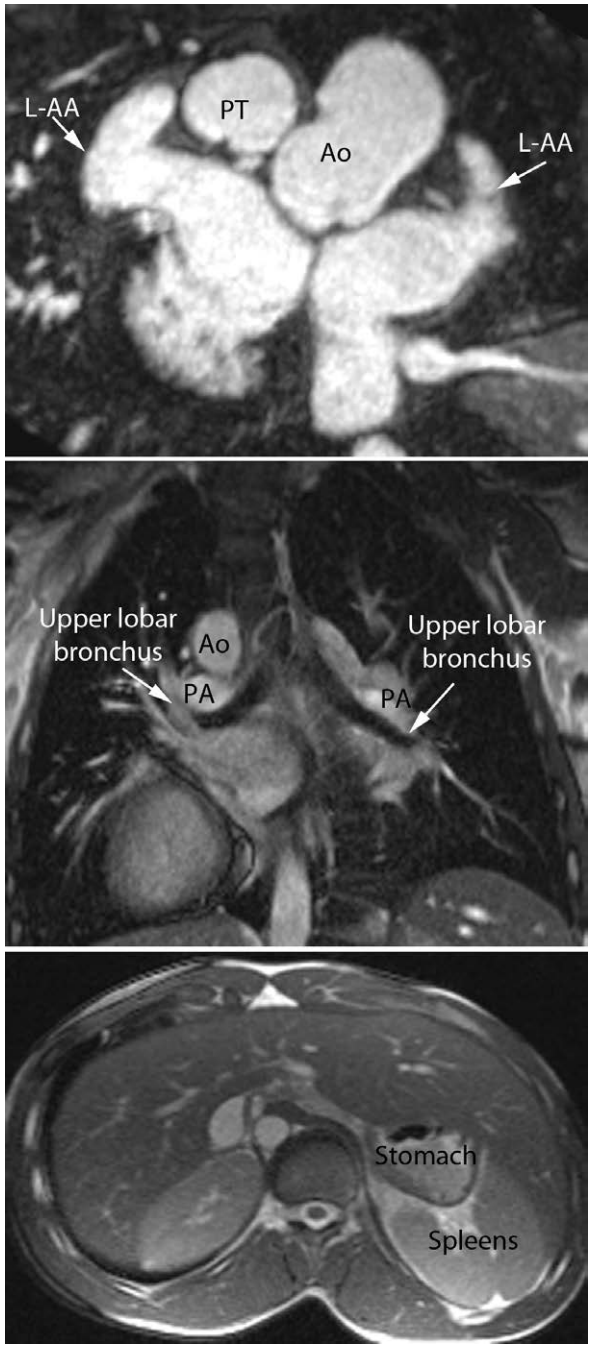


Figure 3. Heterotaxy with classic left isomerism and polysplenia. Both side atrial appendages are long and narrow. No pectinate muscles are seen along the wall of either atrium. The main bronchi are symmetrically long. Note the epbronchial pulmonary arteries (PA) and the hyparterial upper lobar bronchi. Two spleens are seen along the posterolateral wall of the stomach. Ao indicates aorta; DsAo, descending aorta; IVC, inferior vena cava; and PT, pulmonary trunk.

of isomerism. Exceptions to these general rules are not infrequent.[4,6,17] Our assessment of a relatively large patient cohort showed that the general features of classic isomerism were breached in >20% of cases with heterotaxy and far more commonly with polysplenia than with asplenia. The modest association between polysplenia and hyparterial bronchi with bilateral bilobed morphologically left lungs is similarly found in other studies.[9,19] However, compared with left bronchopulmonary isomerism, right isomerism of bronchopulmonary branching was more commonly associated with a breach of the thoraco-atrial-visceral concordance rule. In addition, 7.5% of cases with definable anatomy at all levels showed discrepancy between the arrangement of the atrial appendages and the bronchopulmonary branching pattern. The terms heterotaxy and isomerism are not interchangeable as a fair number of cases with heterotaxy do not show either right or left isomerism, as listed in Table 1 and exemplified by the cases shown in Figures 6 and 7. Although the International Society for Nomenclature of Paediatric and Congenital Heart Disease defined those cases as having situs ambiguus,[2] the situs in these cases are not ambiguous or uncertain per se but instead can be described without ambiguity if the thoraco-abdominal organ arrangement is independently described. Our article supports the findings outlined by the International Society for Nomenclature of Paediatric and Congenital Heart Disease that independent description of each system of organs removes any potential ambiguity when arrangements are disharmonious among different systems of organs (Table 2).[2]

A widely adopted school of teaching situs assessment emphasizes that all heterotaxy cases should be subcategorized according to the morphology of the atrial appendages.[1–5,15] Most recently, Tremblay et al[17] were able to segregate all 188 postmortem specimens obtained from patients with heterotaxy into either right or left isomerism based on the atrial appendage morphology. If all heterotaxy cases were to be segregated into either right or left isomerism based on the same criteria, the cases illustrated in Figures 5 and 6 would not have any entity to be classified into. However, it is wondered whether noninvasive imaging in living patients can consistently and accurately assess the morphology of the atrial appendages. In this study using CMR or CT, the morphology of the atrial appendages could not be defined in 15% of patients. Furthermore, it is doubtful whether we truly rely on the atrial situs assignment based on the shape of atrial appendages and the distribution of the pectinate muscles in our daily practice. Quantitative measurements of atrial appendages are difficult given the degree of appendage variation and the complexity of its shape and morphology. As is commonly the case in our institution, the atrial situs is often assumed based on or with the cognizance of other cardiovascular and noncardiovascular key findings.[2,6] Given the fact that the atrial appendages are of little functional significance, and there is significant limitation in assessment of the atrial appendages,[20,21] it is neither logical nor always possible to categorize heterotaxy cases into the right or left isomerism of the atrial appendages. In fact, it should be acknowledged that the atrial appendage is only one of several other organ systems with a strong tendency toward symmetrical arrangement and therefore, does not represent the whole spectrum of segmental abnormalities.

Although the use of atrial appendages in atrial situs determination by noninvasive imaging is debatable, the Bostonian school uses the venous criteria for atrial situs determination; the atrium taking the drainage of all systemic veins or

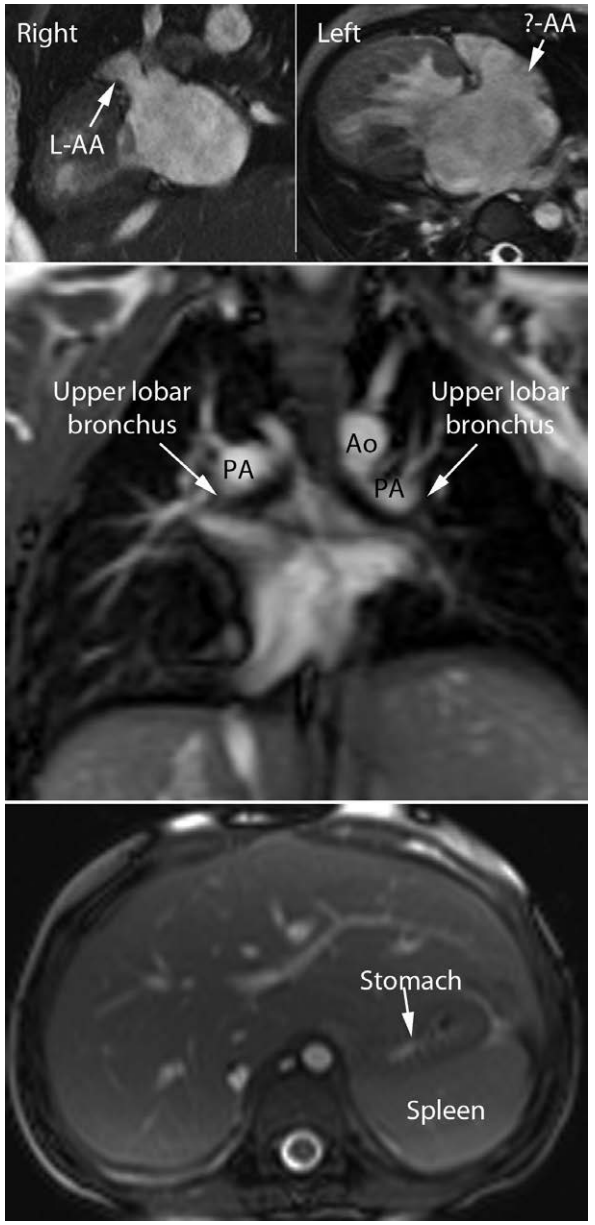


Figure 4. Uncertain morphology of an atrial appendage. The right-sided atrial appendage shows typical shape of the morphologically left atrial appendage (L-AA). The left-sided atrial appendage (?-AA) shows ambiguous morphology. Note that the abdominal situs seems to be situs solitus with a single spleen. However, the airway showed a left-isomeric pattern. Ao indicates aorta; and PA, pulmonary artery.

coronary sinus being regarded as the right atrium while the atrium not taking any systemic veins (with an exception of the superior vena cava associated with unroofed coronary sinus) but taking all or half of the pulmonary veins being regarded as the left atrium.[16] In this regard, it would be clinically relevant and important to describe the systemic and pulmonary venous connections in terms of normal, mirror imaged or inverted, or neither normal nor mirror imaged (Table 2). However, it should be noted that the pulmonary and systemic venous drainage (including separate hepatic veins and coronary sinus) is extremely variable in patients with heterotaxy.

Table 1. Details of Cases Breaching the Classic Patterns of Heterotaxy and Isomerism

Case No	Arrangement of the Atrial Appendages	Bronchopulmonary Situs	Splenic Status	Level of Breaching
1	Right isomerism	Right isomerism	Polysplenia	Abdominal
2	Right isomerism	Right isomerism	Polysplenia	Abdominal
3	Right isomerism	Right isomerism	Polysplenia	Abdominal
4	Right isomerism	Right isomerism	Normal spleen	Abdominal
5	Right isomerism	Right isomerism	Normal spleen	Abdominal
6	Left isomerism	Left isomerism	Normal spleen	Abdominal
7	Left isomerism	Right isomerism	Asplenia	Appendages
8	Left isomerism	Right isomerism	Polysplenia	Bronchi
9	Left isomerism	Solitus	Polysplenia	Bronchi
10	Left isomerism	Solitus	Polysplenia	Bronchi
11	Left isomerism	Inversus	Polysplenia	Bronchi
12	Left isomerism	Inversus	Polysplenia	Bronchi
13	Solitus	Right isomerism	Polysplenia	All
14	Solitus	Solitus	Polysplenia	Abdominal
15	Solitus	Solitus	Polysplenia	Abdominal
16	Solitus	Solitus	Polysplenia	Abdominal
17	Solitus	Solitus	Polysplenia	Abdominal
18	Solitus	Solitus	Polysplenia	Abdominal
19	Inversus	Inversus	Polysplenia	Abdominal
20	Inversus	Inversus	Polysplenia	Abdominal

In our experience, the bronchopulmonary relationship and bronchial lengths could be defined in all patients using CT or CMR. As the bronchopulmonary relationship is more consistently predictive of the splenic status and arrangement of the atrial appendages than the bronchial length ratio, the former is the preferred criterion for bronchopulmonary situs determination. Loomba et al[6] found discordances between the identified bronchial isomerism and the presumed arrangement of the atrial appendages in ≈20% of the patients while our clinical study and Tremblay et al's[17] pathological study found discordances in 7.5% and 5%, respectively. The difference between our and Loomba's study may have arisen from the imaging modalities used and methods of assessment. Loomba included plain chest radiographs as well as cross-sectional images, used bronchial lengths and angles, and assessed the atrial appendage morphology with inference to other cardiovascular and noncardiovascular findings.[6] In contrast, we relied strictly on CMR and CT for assessment of the bronchopulmonary relationship and determined atrial situs by observing the shape of the appendages and distribution of pectinate muscles on CMR and CT images with multiplanar reconstruction.

Limitations

This was a retrospective review of patients with heterotaxy that underwent a cardiac CT or CMR as part of their clinical

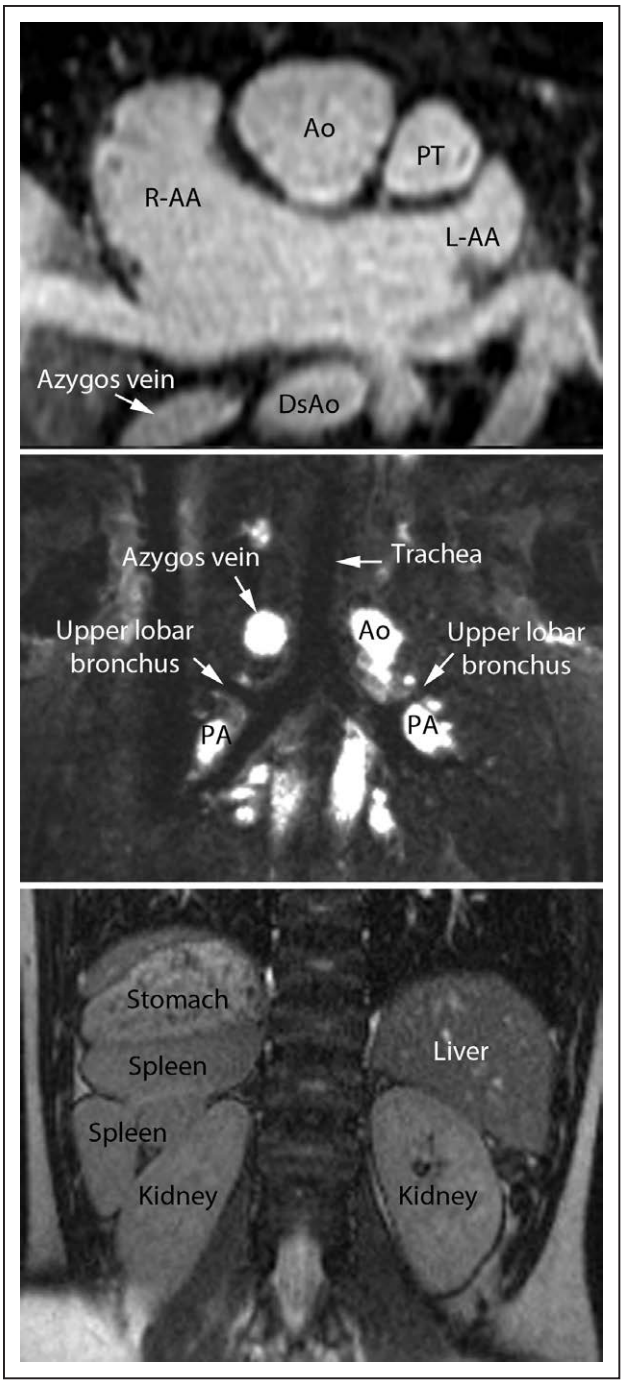


Figure 5. Disharmonious situs at all 3 levels. The atrial appendages show normal arrangement, the bronchopulmonary branching shows right isomeric pattern, and there is right-sided polysplenia. The interrupted inferior vena cava connects to the dilated azygos vein. Ao indicates aorta; DsAo, descending aorta; L-AA, morphologically left atrial appendage; PA, pulmonary arteries; PT, pulmonary trunk; and R-AA, morphologically right atrial appendage.

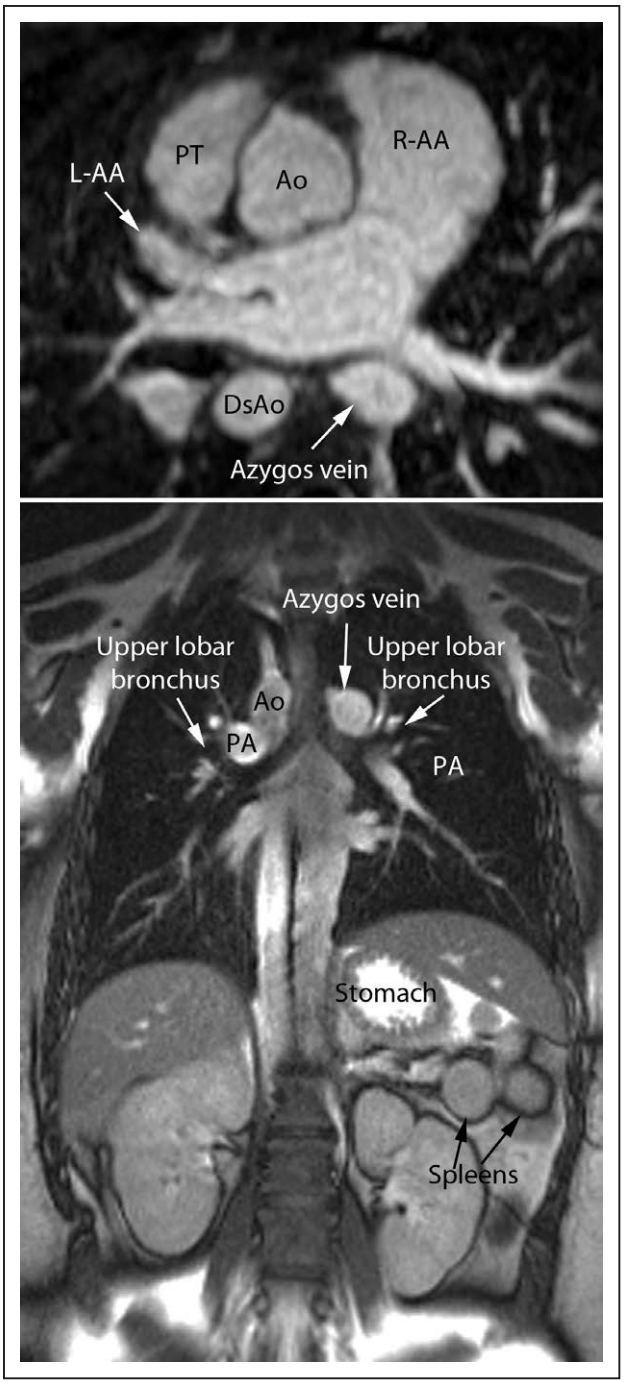


Figure 6. Disharmonious abdominal situs. The atrial appendages and bronchi show situs inversus arrangement while there is left-sided polysplenia. The interrupted inferior vena cava connects to the dilated azygos vein. Ao indicates aorta; DsAo, descending aorta; L-AA, morphologically left atrial appendage; PA, pulmonary arteries; PT, pulmonary trunk; and R-AA, morphologically right atrial appendage.

work-up. Cases without cross-sectional imaging were excluded from the study. Cases were identified using key words associated with heterotaxy in imaging reports, thus patients with heterotaxy may not have been accounted for if these key words were not used in the report. Nevertheless, our patient group is most likely representative of the larger cohort given the size and wide spectrum of heterotaxy features observed in our study population. In addition, appendage determination was subjective and based on a qualitative approach using our knowledge of appendage shape and pectinate muscle extension. Although a quantitative morphometric approach could be useful to standardize appendage geometry, it was not applied in this multimodality study given its uncertain applicability in

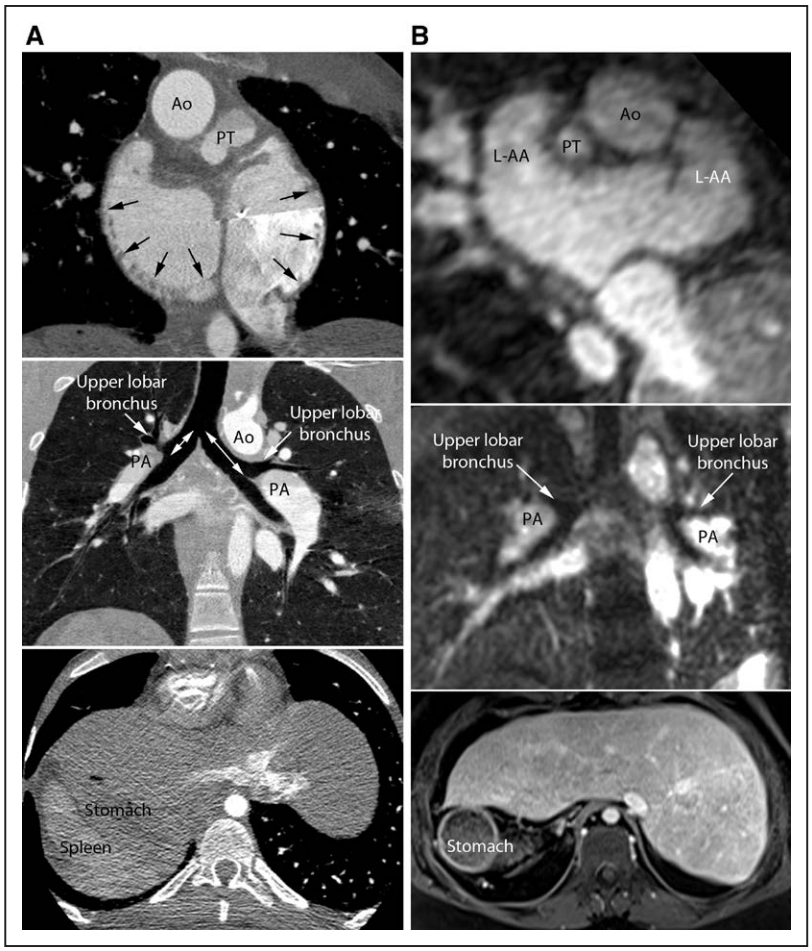
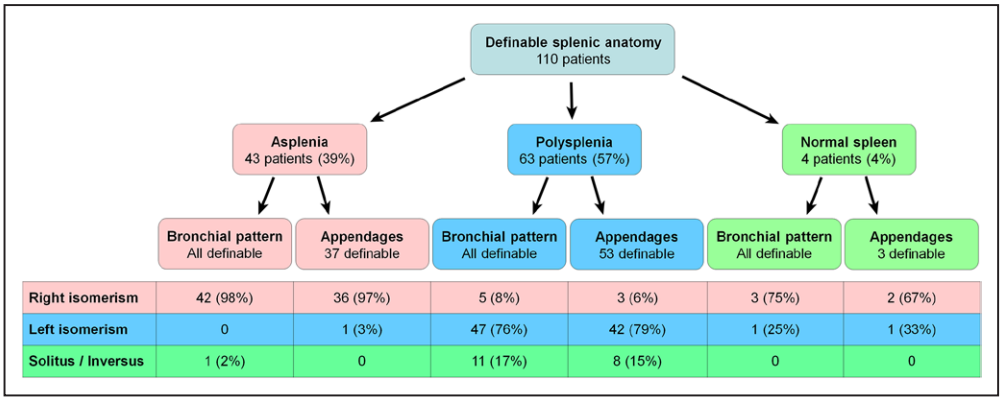


Figure 7. A, Disharmonious abdominal situs. The atrial appendages show typical right isomeric arrangement. The relationship between bronchi and pulmonary arterial (PA) branches is that of right isomerism. However, the bronchial length is not symmetrical. The abdominal organs show situs inversus arrangement. **B**, The atrial appendages show left-isomeric arrangement. The bronchopulmonary branching is right isomeric. There is asplenia. Ao indicates aorta; DsAo, descending aorta; L-AA, morphologically left atrial appendage; and PT, pulmonary trunk.

daily practice. One potential method to obtaining consistent measurements is performing multiplanar reconstructions of the appendages using 3-dimensional volume-rendered data; however, not all of our cases had 3-dimensional volume data sets available.

Summary

Although isomeric patterns of bronchopulmonary branching and arrangement of atrial appendages do exist and are related strongly with the splenic status, the exceptions to the general rules of heterotaxy and isomerisms are seen in >20% of patients with neither situs solitus nor situs inversus. As not all patients with heterotaxy show isomeric patterns, the term heterotaxy cannot be replaced by the term isomerism. Although the bronchopulmonary relationship can be accurately assessed by CMR or CT, atrial appendage morphology is difficult to assess and often unreliable. Independent description of each organ system is required when arrangements are disharmonious among different organ systems.



Right isomerism	42 (98%)	36 (97%)	5 (8%)	3 (6%)	3 (75%)	2 (67%)
Left isomerism	0	1 (3%)	47 (76%)	42 (79%)	1 (25%)	1 (33%)
Solitus / Inversus	1 (2%)	0	11 (17%)	8 (15%)	0	0

Figure 8. Distribution of the cases according to splenic status.

Table 2. Proposed Diagnostic Approach to Heterotaxy

Bronchopulmonary Relationship	Arrangement of Atrial Appendages	Splenic Status	Systemic and Pulmonary Venous Connections
Normal (solitus)	Normal (solitus)	Single left, normal	Normal*
Mirror imaged (inversus)	Mirror imaged (inversus)	Single right, normal	Mirror imaged†
Right isomerism	Right isomerism	Absent	Neither normal nor mirror imaged
Left isomerism	Left isomerism	Multiple Single lobulated or round	Neither normal nor mirror imaged
Uncertain	Uncertain	Uncertain	Uncertain
Not assessed	Not assessed	Not assessed	Not assessed

*Systemic veins including coronary sinus and pulmonary veins connecting to the right-sided and left-sided atria, respectively.
†Systemic veins including coronary sinus and pulmonary veins connecting to the left-sided and right-sided atria, respectively.

Disclosures

None.

References

1. Cohen MS, Anderson RH, Cohen MI, Atz AM, Fogel M, Gruber PJ, Lopez L, Rome JJ, Weinberg PM. Controversies, genetics, diagnostic assessment, and outcomes relating to the heterotaxy syndrome. *Cardiol Young*. 2007;17(suppl 2):29–43. doi: 10.1017/S1047951107000114X.
2. Jacobs JP, Anderson RH, Weinberg PM, Walters HL 3rd, Tchervenkov CI, Del Duca D, Franklin RC, Aiello VD, Béland MJ, Colan SD, Gaynor JW, Krogmann ON, Kurosawa H, Maruszewski B, Stellin G, Elliott MJ. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. *Cardiol Young*. 2007;17(suppl 2):1–28. doi: 10.1017/S1047951107001138.
3. Uemura H, Ho SY, Devine WA, Kilpatrick LL, Anderson RH. Atrial appendages and venoatrial connections in hearts from patients with visceral heterotaxy. *Ann Thorac Surg*. 1995;60:561–569. doi: 10.1016/0003-4975(95)00538-V.
4. Uemura H, Ho SY, Devine WA, Anderson RH. Analysis of visceral heterotaxy according to splenic status, appendage morphology, or both. *Am J Cardiol*. 1995;76:846–849.
5. Anderson RH. Atrial structure in the presence of visceral heterotaxy. *Cardiol Young*. 2000;10:299–302.
6. Loomba RS, Pelech AN, Shah PH, Anderson RH. Determining bronchial morphology for the purposes of segregating so-called heterotaxy. *Cardiol Young*. 2016;26:725–737. doi: 10.1017/S1047951115001195.
7. Landing BH, Lawrence TY, Payne VC Jr, Wells TR. Bronchial anatomy in syndromes with abnormal visceral situs, abnormal spleen and congenital heart disease. *Am J Cardiol*. 1971;28:456–462.
8. Partridge JB, Scott O, Deverall PB, Macartney FJ. Visualization and measurement of the main bronchi by tomography as an objective indicator of thoracic situs in congenital heart disease. *Circulation*. 1975;51:188–196.
9. Peoples WM, Moller JH, Edwards JE. Polysplenia: a review of 146 cases. *Pediatr Cardiol*. 1983;4:129–137. doi: 10.1007/BF02076338.
10. Rose V, Izukawa T, Moës CA. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. *Br Heart J*. 1975;37:840–852.
11. Brandt HM, Liebow AA. Right pulmonary isomerism associated with venous, splenic, and other anomalies. *Lab Invest*. 1958;7:469–504.
12. Van Mierop LH, Wiglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. *Lab Invest*. 1962;11:1303–1315.
13. Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral "left-sidedness". *Circulation*. 1967;36:789–799.
14. Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood; an analysis of the heart malformations in the splenic agenesis syndrome, with fourteen new cases. *Acta Paediatr Suppl*. 1955;44(suppl 104):7–110.
15. Loomba RS, Hlavacek AM, Spicer DE, Anderson RH. Isomerism or heterotaxy: which term leads to better understanding? *Cardiol Young*. 2015;25:1037–1043. doi: 10.1017/S1047951115001122.
16. Van Praagh R, Van Praagh S. Atrial isomerism in the heterotaxy syndromes with asplenia, or polysplenia, or normally formed spleen: an erroneous concept. *Am J Cardiol*. 1990;66:1504–1506.
17. Tremblay C, Loomba RS, Frommelt PC, Perrin D, Spicer DE, Backer C, Anderson RH. Segregating bodily isomerism or heterotaxy: potential echocardiographic correlations of morphological findings. *Cardiol Young*. 2017:27:1470–1480.
18. Ming Z, Hong S, Biao J. Images in cardiovascular medicine. Asplenia syndrome with bilateral tracheal bronchi. *Circulation*. 2008;118:196–197. doi: 10.1161/CIRCULATIONAHA.107.763458.
19. Tawfik AM, Batouty NM, Zaky MM, Eladalany MA, Elmokadem AH. Polysplenia syndrome: a review of the relationship with viscero-atrial situs and the spectrum of extra-cardiac anomalies. *Surg Radiol Anat*. 2013;35:647–653. doi: 10.1007/s00276-013-1100-x.
20. Wang JK, Li YW, Chiu IS, Wu MH, Chang YC, Hung CR, Lue HC. Usefulness of magnetic resonance imaging in the assessment of venoatrial connections, atrial morphology, bronchial situs, and other anomalies in right atrial isomerism. *Am J Cardiol*. 1994;74:701–704.
21. Macartney FJ, Zuberbuhler JR, Anderson RH. Morphological considerations pertaining to recognition of atrial isomerism. Consequences for sequential chamber localisation. *Br Heart J*. 1980;44:657–667.

CLINICAL PERSPECTIVE

The diagnosis of heterotaxy in clinical practice is frequently inferred from other cardiovascular and noncardiovascular findings rather than on atrial morphology, which can be difficult to define. Our focus was to determine how frequently classic patterns of left and right isomerism are breached and how reliable and feasible it is to define atrial appendage morphology using cardiac magnetic resonance or computed tomography. In this study of 114 children diagnosed with heterotaxy, the atrial appendage morphology was not definable in 15%. Of the patients who had definable atrial appendages, 39% had classic right isomerism (bilateral right atrial appendages, right bronchopulmonary pattern, and asplenia) and 40% had classic left isomerism (bilateral left atrial appendages, left bronchopulmonary pattern, and polysplenia). A discordant pattern of organ arrangement from the classic left or right isomerism was found in 21.5%. Given the frequency of disharmony and practical difficulties in assessing appendage morphology, an independent description of organ systems is recommended in cases that breach the classic pattern of isomerism.

Circulation
Cardiovascular Imaging

Disharmonious Patterns of Heterotaxy and Isomerism: How Often Are the Classic Patterns Breached?

Deane Yim, Hazumu Nagata, Christopher Z. Lam, Lars Grosse-Wortmann, Mike Seed, Edgar Jaeggi and Shi-Joon Yoo

Circ Cardiovasc Imaging. 2018;11:
doi: 10.1161/CIRCIMAGING.117.006917
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080