Abnormal Laterality and Congenital Cardiac Anomalies

Relations of Visceral and Cardiac Morphologies in the iv/iv Mouse

Jeong-Wook Seo, MD; Nigel A. Brown, PhD; Siew Yen Ho, PhD, MRCP; and Robert H. Anderson, MD, FRCP

Background. In the management of hearts with deranged laterality, it is essential that the left and right atrial chambers are correctly identified. There are two major approaches, which are based on venous connections or on the morphology of the atrial appendages, and there is no consensus as to which is the most useful. We used the iv/iv mouse mutant, which is known to be pertinent to this problem, to evaluate the relations of cardiac defects with atrial, venous, and other visceral morphologies.

Methods and Results. The morphology of the heart and other organs was examined in 275 iv/iv mice using criteria based on abnormal laterality in humans. The arrangement of the atrial appendages was determined by morphological examination of the junction between the appendage and the venous component of the atrium. On this basis, 45.1% of cases were shown to have usual atrial arrangement, 50.2% had mirror imagery, 1.5% had right isomerism, and 3.3% had left isomerism. Every case of atrial isomerism had a cardiac lesion; the morphological types were similar to those seen in human cases. Of cases with either usual or mirror-image arrangement of the appendages, 33.2% had abnormal spleens, but only 3.1% had cardiac defects. Similarly, venous abnormalities were much more common (30.1%) than cardiac defects.

Conclusions. Study results endorse the importance of the morphology of atrial appendages in predicting cardiac abnormalities and point to the marked inconsistency of the arrangement of other organs, including the spleen and the connections of the systemic veins. (Circulation 1992;86:642–650)

Key Words • isomerism • atrial appendages • heterotaxy

The entire normal human body, including the heart, has obvious handed laterality. Thus, the left side of the body is consistently different from the right. Nevertheless, the mechanisms that control the development of laterality remain obscure.1-2 The great majority of the population has an arrangement of the thoracoabdominal organs, including the atrial chambers, that is called “situs solitus,” or the usual arrangement. A very small proportion, fewer than one in 6,000–8,000, have all of the thoracoabdominal organs arranged in mirror-image fashion, which is called “situs inversus.”3 A larger proportion, however, have their organs arranged in neither usual nor mirror-image fashion. These are the persons who have been described as showing heterotaxy,4 or “situs ambiguus.”5 It is this arrangement that is particularly significant for the heart because the heterotaxic pattern of the organs is known to be the harbinger of severe congenital cardiac malformations.6,7

There currently is no consensus as how best to describe and analyze this abnormal laterality in the heart and other organs. For example, some would consider isomerism of the lungs automatically to predict cardiac isomerism, whereas others would draw the same conclusion from the morphology of the spleen. Correct classification of abnormalities of laterality is of obvious importance for the management of cardiac defects. There have been two major approaches to classification. One is based on the morphology of the atrial appendages, and the other emphasizes the connections of systemic veins and other visceral morphologies.8-11

The only genetic animal model of abnormal laterality of which we are aware is the mouse iv mutation. On simple analysis, half of iv/iv mice show mirror-image body plan,12 and it has been hypothesized that laterality is determined randomly in these animals.13 A more complete analysis,14-19 however, shows that many iv/iv mice show so-called heterotaxy and therefore may be a good model of abnormalities of laterality in humans. As yet, there has been no systematic analysis of cardiac defects in iv/iv mice in relation to heart and visceral morphology, although there has been progress in mapping the mutation.20,21 In this study, therefore, we conducted a detailed study of the arrangement of the

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Animals

SI/Ca iv/iv mice, originally from the Jackson Laboratory (Bar Harbor, Me.), were maintained in a reversed-light room. For timed matings, three to five female adults (unselected for the arrangement of organs, or “situs”) were housed with an unselected male during the dark cycle. The study included 275 mice (Table 1). Adults were 48–320 days old, and all had a healthy appearance. Fetuses were collected on the 18th or 19th day of gestation, with the date on which a plug was observed counted as day 1; neonates were collected on the first or second day after birth. The identification of the mating partner of the plugged female was marked, and the phenotypes of parents were analyzed with those of their offspring. We were able to match both parents in six groups of fetuses and in four groups of neonates. Only the mother could be matched in nine groups of fetuses and in two groups of neonates.

Morphological Criteria

In describing cardiac morphology, we use the anatomic orientation usually followed for humans. Thus, the cephalocaudad axis of the mouse is described as superoinferior and so on.

Atrial chambers. Morphological criteria were used to determine the laterality of the atrial appendages. As in the human, the morphologically right atrium of the mouse has a broad triangular appendage and a wide junction with the venous component of the atrium, the demarcation between the two being the terminal groove (sulcus terminalis, Figure 1A). The morphologically left atrium, seen in lateral aspect, also has a large appendage, with pectinate muscles similar to the right atrium, but the junction between the appendage and venous component is narrow and deeply excavated, especially at its superior crest (Figure 1B). The venous component of the left atrium is broad in the lower part, and the pulmonary veins drain into it. The left superior caval vein runs across the posterior margin to the left atrium to connect to the venous component of the morphologically right atrium through the coronary sinus.

Spleen. We classified spleens into five categories (Figure 2). The normal spleen was flat and bar shaped with an even thickness and width. Fissured spleens were slightly shorter than normal and of nearly normal configuration but with a fissure on the convex side running half the length of the spleen. Bilobed spleens were pyramidal but had two components that were separated longitudinally by an omental membrane. Elongated spleens were 1.5-fold to twofold longer than normal. They were usually impacted deeply within the posterior abdominal cavity and had a horseshoe shape. The fifth category was absence of spleen.

Liver. The usual normal liver had a transverse fissure in its right lower lobe, and the mirror-imaged liver had the fissure in the other side. An abnormal liver was defined when such lateralization was absent or when the organ was bilaterally fissured.

Veins. An abnormal ventral portal vein ran anterior to the first part of duodenum in contrast to the usual location, which was behind the duodenum. The inferior caval vein normally drained into the right atrium via its hepatic portion. This portion was interrupted in some animals, being connected to the heart along the posterior wall of the thoracic cavity via either the left or right azygous systems.

Lungs. Pulmonary laterality was initially determined by the pattern of bronchial bifurcation and the number of lobes. In cases that were not usual or mirror imaged, the relation between the pulmonary arteries and the upper lobar bronchus was used to confirm laterality. Normally, the pulmonary artery on the left side was above the upper lobar bronchus, whereas the artery was anterior to the bronchus on the right.

Heart defects. The internal anatomy of the heart was studied by microsurgical dissection and reconstruction of serial histological sections of the whole heart and lungs. Incision of the heart along the paraseptal free wall of atria and ventricles exposed the interatrial and interventricular septal surfaces. The movements of blood and air under the dissecting microscope were examined to determine the connection of segments and presence of any defects. An interatrial communication with intact rims of the oval fossa was considered a normal finding in fetuses and neonates unless the defect was larger than one third the area of the fossa. Patency of arterial duct was considered normal in the fetus and neonate unless the duct was short and unequivocally wide.

Histological sectioning was carried out in 11 cases found to have isomerism of the atrial appendages and in 12 cases with lateralized atria, including six cases with interruption of the inferior caval vein and continuation through the azygous venous system.

Statistical Analysis

Differences of the proportions of certain phenotypes by sex and age groups were assessed using the \( \chi^2 \) test. The number of fetuses, resorptions, and total implantations by the phenotypes are expressed as mean±SEM. Their differences were assessed by one-way ANOVA.

Results

Proportions of Morphological Types of Organs by Sex and Age

The arrangement of the atrial appendages was, in most cases, either usual (45.1%) or mirror imaged (50.2%) (Table 2). Among the 275 mice, there were nine cases of isomerism of left atrial appendages (3.3%) and four cases of isomerism of the right appendages (1.5%). The incidence of isomerism of the atrial appendages was significantly higher in females (7.4%)

<table>
<thead>
<tr>
<th>Table 1. Number of Animals Used in Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Fetus</td>
</tr>
<tr>
<td>Neonate</td>
</tr>
<tr>
<td>Adult</td>
</tr>
<tr>
<td>All</td>
</tr>
</tbody>
</table>

*Twenty-nine neonates were born to six mothers.
than in males (1.6%, $p<0.05$) and in fetuses (12.0%) than in adults (1.4%, $p<0.01$).

The splenic morphology was abnormal in 36.4% of mice; the proportions of morphological types are listed in Table 3. An abnormal spleen was seen more often in females (44.6%) than in males (26.8%, $p<0.01$). Abnormal arrangement of the liver was also more common in females (42.6%) than in males (26.8%, $p<0.01$).

A ventral portal vein or an abnormal connection of the inferior caval vein was seen in 26.6% and 17.8% of cases, respectively. The incidence of a ventral location of the portal vein was significantly higher in females
FIGURE 2. Morphology of the spleen in adults and fetuses. Outer (upper row) and inner (lower row) surfaces of usual, fissured, bilobed-pyramidal, and elongated spleens (from left to right).

(33.1%) than in males (18.9%, p<0.01), whereas an abnormal arrangement of the inferior caval vein was significantly more common in fetuses (29.3%) than in adults (15.0%, p<0.05). The locations of abnormal connections of the inferior caval vein are shown in Tables 4 and 5.

The laterality of the lungs in 12 cases (4.4%) could not be determined by counting the number of lobes but rather was determined from bronchoarterial relations (see below).

There were 21 cases (7.6%) with cardiac lesions. The cardiac lesions were significantly more common in females (11.5%) than in males (3.1%, p<0.01) and in fetuses (16.0%) than in adults (3.6%, p<0.01). The cardiovascular lesion in animals with either usual or mirror-image arrangement of the appendages was more common in females (six cases) than in males (two cases).

Relations of Morphological Arrangements Between Organs

The relations of splenic morphology and the arrangement of the inferior caval veins to the arrangement of the atrial appendages are listed in Tables 3 and 4.

Of hearts with usual or mirror-imaged appendages, 67.9% had normal hepatic morphology. Every case with isomerism of appendages, however, had an abnormal liver. A normal liver with a normal spleen was seen in 61.8% of all mice, a normal spleen but an abnormal liver were seen in 1.8%, an abnormal spleen with a normal liver was seen in 2.9%, and 33.5% had both an abnormal liver and an abnormal spleen.

A ventral portal vein was present in 25.6% of mice with hearts with lateralized appendages and in 46.2% of cases with isomeric appendages. Of the total, a normal spleen and normal systemic veins were seen in 61.5%, normal systemic veins but an abnormal spleen were seen in 6.5%, a normal spleen but abnormality in either of the systemic veins were seen in 2.2%, and 29.8% had both an abnormal spleen and abnormal systemic veins (Table 5).

Overall, 39.2% had some kind of abnormal laterality that could be categorized into four groups. Lateralized atria with abnormal morphology of liver and/or spleen but with normal systemic veins were found in 4.7%. Lateralized atria with abnormal morphology of either the portal vein or the inferior caval vein were seen in 18.5% of cases. Lateralized atria with abnormalities observed in both of the systemic veins were found in 10.2%. Finally, the mice with isomerism of the atrial appendages made up 4.7% of the total.

Cardiac lesions were seen in 2.4% of hearts with the usual atrial arrangement and in 3.6% of those with mirror-imaged atria. Every case with isomerism of right or left atrial appendages had a cardiac lesion (see below).

Parental and Offspring Phenotypes

There were fewer implantation sites in mothers with certain phenotypes. For example, mothers with bilobed spleens (5.3±1.3, p<0.05) had significantly fewer implantations than those with normal (9.0±0.6) or fissured spleens (8.0±1.5). Mothers with abnormal livers (6.6±1.1, p<0.05) also had significantly fewer implantations than those with normal livers (9.1±0.5). There were no significant relations between parental phenotype and the phenotypes of offspring.

Morphology of Isomerism of Atrial Appendages

Both appendages resembled the pattern of a normal left appendage in nine mice. The venous components

<p>| Table 2. Arrangement of Atrial Appendages According to Age Groups |
|------------------|-----------------|-----------------|-----------------|-----------------|-------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Atria</th>
<th>Fetus</th>
<th>Neonate</th>
<th>Adult</th>
<th>All (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual</td>
<td>34</td>
<td>24</td>
<td>66</td>
<td>124</td>
<td>(45.1)</td>
</tr>
<tr>
<td>Mirror image</td>
<td>32</td>
<td>34</td>
<td>72</td>
<td>138</td>
<td>(50.2)</td>
</tr>
<tr>
<td>Right isomer</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Left isomer</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>(3.3)</td>
</tr>
<tr>
<td>All</td>
<td>75</td>
<td>60</td>
<td>140</td>
<td>275</td>
<td>(100.0)</td>
</tr>
</tbody>
</table>

*Percentage of animals with each type of atrial arrangement (row percent).
were broad, and their junctions with the trabeculated appendages were deeply excavated (Figure 3). Similarly, each appendage in four additional mice had features of the morphologically right appendage, with a terminal groove and a wide junction on each side (Figure 4).

The posterior aspect of the hearts showed striking differences in the venous components, both between the left and right atria in lateralized hearts and between hearts with isomerism of the left or right appendages. On the morphologically left side, the superior caval vein descended obliquely, and there was a wide gap between the caval vein and the morphologically left appendage (Figure 5). The venous component on the morphologically right side, in contrast, was vertical, being characterized by wide incorporation into the atrium close to the junction between the two atria. Thus, the angle of insertion of the left and right superior caval veins in lateralized atria was markedly different but symmetrical in those with isomeremic appendages (Figure 6).

In the great majority of cases (268 of 275), the apex of the heart was on the same side of the body as the stomach. All exceptions had isomerism of the atrial appendages. Four cases of left isomerism had the apex on the left but a right-sided stomach. Two cases with right isomerism had a left-sided apex and stomachs on the right. One additional case of right isomerism had a right-sided cardiac apex and a left-sided stomach. All mice with the cardiac apex oriented to the left had right-handed ventricular topology, whereas every case with a rightward pointing apex had left-hand ventricular topology.

The morphological diagnosis of the cardiac lesions are given in Table 6.

**Discussion**

Our study has shown that the *iv*/*iv* mouse is a useful model of abnormal laterality within the heart. At present, however, there is no universally accepted system with which to classify such abnormalities of cardiac laterality. Previously, the morphology of the spleen,7,22 the connections of the systemic veins,8 or the direction of the cardiac apex23,24 were used as markers for categorization and analysis of cardiac features. The concept of overall abnormalities of lateralization also is controversial,8–11 and although often called heterotaxia, there is no agreement on the precise meaning of this term. Cases described as heterotaxic by some have been said by others to display "partial mirror imagery." Such confusion can readily be avoided simply by analyzing each organ in its own right and by accepting that changes in one system of organs need not necessarily be accompanied by comparable changes in others.8,10,25,26

The main findings of this study, therefore, are that atrial morphology in the mouse is very similar to that in the human, a feature recently shown by Icardo and Sanchez de Vega,19 and that the appendages are the most reliable indicators of atrial arrangement. Studies of human hearts permit recognition of four basic types of atrial morphology8,25: normal, mirror image, left isomeremic, and right isomeremic. Similar morphological patterns, with small modifications, can be recognized in the mouse (Figure 7). Although the shape and size of the appendages are very similar in the mouse, the distinction between them can be made as in the human,8,27 concentrating on the different morphology of the junction between the appendage and the venous component of its atrium. It is, then, significant that the relation of the right and left pulmonary arteries to their respective bronchi, along with the pattern of bifurcation of these bronchi, showed very close correlation with atrial arrangement as determined from the morphology of the appendages. Of 275 mice, there was only one case in which laterality of lungs and atrial chambers did not concur. The outstanding case had asymmetric bronchi but isomerism of the morphologically left atrial appendages. The cardiac lesions were, however, as expected for left isomerism. Such discordance has also been observed in humans.27

Individual cardiac lesions found in the mouse, as detailed in Table 6, also show a similar spectrum of known malformations in humans. Atrioventricular septal defect, abnormal ventriculoarterial connections, pulmonary atresia, and anomalous pulmonary venous connections are particularly common findings in hearts with isomerism of right appendages in humans.28 The present study of murine right isomerism recapitulates most of this spectrum, albeit that anomalous pulmonary return was not detected. Characteristic lesions also occur in human hearts with left isomerism but are less

**Table 4. Relation Between Atrial Arrangement and Location of Inferior Caval Vein**

<table>
<thead>
<tr>
<th>Atria</th>
<th>Normal (%)</th>
<th>Right azygous</th>
<th>Left azygous</th>
<th>Others</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual</td>
<td>103 (83.1)</td>
<td>6</td>
<td>15</td>
<td>0</td>
<td>124</td>
</tr>
<tr>
<td>Mirror image</td>
<td>119 (86.2)</td>
<td>8</td>
<td>10</td>
<td>1</td>
<td>138</td>
</tr>
<tr>
<td>Right isomer</td>
<td>4 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Left isomer</td>
<td>0 (0.0)</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

All (%) (82.2) (5.8) (11.3) (0.7) (100.0)

*Percentage of normal inferior caval vein in each type of atrial arrangement.

1Drainage of inferior caval vein to bilateral azygous veins or to both hepatic and azygous veins.

**Table 5. Relation Between Splenic Morphology and Abnormal Systemic Venous Connection**

<table>
<thead>
<tr>
<th>Splenic morphology</th>
<th>Normal veins</th>
<th>Ventral portal vein</th>
<th>Azygous continuation*</th>
<th>Both</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>169</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>175</td>
</tr>
<tr>
<td>Fissured</td>
<td>9</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Bilobed</td>
<td>5</td>
<td>24</td>
<td>12</td>
<td>33</td>
<td>74</td>
</tr>
<tr>
<td>Elongated</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Absent</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>All</td>
<td>187</td>
<td>39</td>
<td>15</td>
<td>34</td>
<td>275</td>
</tr>
</tbody>
</table>

(68.0) (14.2) (5.5) (12.4) (100.1)

*Percentage of normal inferior caval vein and azygous continuation.
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Superior Posterior Anterior Inferior

**Figure 3.** Morphology of the right-sided morphologically left atrium in a case with isomerism of the left atrial appendages and the cardiac apex pointing to the left. The junction between the appendage and the broad venous component is deeply excavated. Through an incision in the venous component, the common atrial chamber and common atrioventricular (AV) valve are seen. Two interatrial communications are divided by a bridging strand of atrial septum.

severe. Again, the present study revealed similar findings in mice. The cardiac lesions in cases with usual or mirror-image appendages are quite different from those seen in the isomeric setting, in both this experimental model and human cases. Thus, the cardiac lesions found in hearts with isomeric appendages are not only more common but also more severe than in hearts with lateralized appendages.

The arrangement of the venous system has been used previously as one criterion for categorization of laterality. Thus, the atrial connection of the inferior caval vein, or its suprahepatic segment, was taken as the major

**Figure 4.** Morphology of the left-sided morphologically right atrial appendage in a case with right isomerism and the cardiac apex pointing to the left. The junction between the atrial appendage and venous component is wide and indistinct vertically. Left superior caval vein is inserted high to the common atrium.
Inferior view of a heart of a fetus with isomerism of left atrial appendages. There is a gap, on each side, between the superior caval vein and the morphologically left appendage (arrowheads). Superior caval veins are distinctly posterior to the atria. The lungs are bilaterally single lobed.

Marker for rightness of the atrium, whereas interruption of the inferior caval vein, along with its azygous continuation, is recognized as a hallmark of “polysplenia.” The shape of the atrial appendages, in contrast, was purported to be related to embryonic hemodynamics. This convention does not withstand rigorous analysis. Our observations of the iv/iv mouse have shown that more than one fourth of all animals have interruption of the inferior caval vein but with usual or mirror-image arrangement of the atrial appendages. Similar examples are well recognized in humans. This observation alone shows that the systemic venous pathways and their atrial connections are unreliable markers for the recognition of the atrial morphology, whereas the concept based on fetal hemodynamics ignores totally the fact that in the fetal circulation, flow from the inferior caval vein is directed to the left rather than the right atrium.

It should be noted, nevertheless, that the types of splenic abnormalities seen in the iv/iv mouse have some similarity with abnormalities found in humans. The bilobed spleens in the mice with left isomerism are reminiscent of polysplenia in humans. The absence of splenic tissue observed in three mice with isomerism of the right appendages clearly is the counterpart of asplenia as seen in humans. The fissured and the elongated spleens, however, as far as we know, have no human equivalent.

There is no doubt that abnormal patterns of splenic development can be associated with abnormal laterality.
TABLE 6. Incidence of Cardiac Lesions in Each Group of Atrial Arrangement and Morphological Diagnoses of Lesions

<table>
<thead>
<tr>
<th>Arrangement</th>
<th>Morphological diagnosis</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual arrangement</td>
<td>Oval fossa defect</td>
<td>(3/124; 2.4%) 3</td>
</tr>
<tr>
<td>Mirror-image arrangement</td>
<td>Oval fossa defect</td>
<td>(5/138; 3.6%) 2</td>
</tr>
<tr>
<td></td>
<td>Ventricular septal defect</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Double-outlet right ventricle</td>
<td>1</td>
</tr>
<tr>
<td>Isomerism of right atrial appendages</td>
<td>Atrioventricular septal defect</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Discordant VA connections</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Discordant VA connections and pulmonary stenosis</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Double-inlet left ventricle</td>
<td>1</td>
</tr>
<tr>
<td>Isomerism of left atrial appendages</td>
<td>Ventricular septal defect</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Atrial septal defect</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Interruption of aortic arch</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Right ventricular hypoplasia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Atrioventricular septal defect</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Interruption of aortic arch</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Right ventricular hypoplasia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Discordant VA connection</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Double-outlet right ventricle</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic left heart syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

VA, ventriculoarterial.

of both the heart\textsuperscript{26} and the body\textsuperscript{34} in humans and in the iv/iv mouse. Splenic morphology, nevertheless, is frequently discordant with the arrangement of the atrial appendages.\textsuperscript{10,27} These discordances with splenic arrangement, like those with venous connections, are sufficiently frequent to make their usefulness as a marker of atrial morphology unacceptable in either humans or mice.

Among the small number of our cases observed with isomerism of the atrial appendages, the incidence of left is much higher than the incidence of right isomerism. A separate study, based on the criterion of pulmonary lobation, showed similar results.\textsuperscript{14} In contrast, two other animal models\textsuperscript{35,36} show the opposite trend, with $\approx$4% showing right isomerism and $<$1% having left isomerism. The prevalence of mirror-image atria was similar in these two studies (1.2%) and much lower than in the iv/iv mouse. The low incidence of right isomerism in our study probably is related to the stage of development (18 or 19 days) examined. In a study of fetuses at 14 days, resorption was found to be less common and cardiac lesions were twice as frequent as found in our specimens.\textsuperscript{17} It is likely that deaths occur in later fetal life due to the severity of cardiovascular lesions, thus reducing the apparent frequency of right isomerism.

FIGURE 7. Diagram showing the characteristic patterns of the atrial appendages seen in iv/iv mice.
Fetal death may also explain the higher incidence of defects in female than in male iv/iv mice. We observed a higher incidence of abnormal atrial appendages, spleens, livers, ventral portal veins, and cardiac malformations in females. A similar sex bias has been suggested previously for iv/iv mice but not confirmed. There were significantly more female than male fetuses and neonates in this present study and in previous investigations of iv/iv mice (N.A. Brown, unpublished data). This suggests that some deaths occur during fetal life of males with severe lesions. Isomerism of the morphologically right type is more common in human males, and the afflicated neonates are more likely to die because of the more severe associated cardiac lesions. We suspect, therefore, that early deaths during fetal life in our animal model may result in removal of males with right isomerism.

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