Arrested rotation of the outflow tract may explain double-outlet right ventricle

Mathias P. G. Bostrom, B.A., and Grover M. Hutchins, M.D.

ABSTRACT In a previous study the possibility that tetralogy of Fallot and transposition of the great arteries may arise as a result of embryonic arrests in the normal rotation of the junction of the outflow tract and the great arteries was investigated. The results suggested that the development of other transposition complexes such as double-outlet right ventricle might also be related to arrests in this process of rotation. To further study this question 20 normal hearts and 15 hearts with double-outlet right ventricle obtained at autopsy were studied. The angle of the aortic-to-pulmonary valve axis relative to the inferior surface of the heart, as viewed from apex to base, was measured from postmortem radiographs. For normal hearts the mean angle was 81 ± 4(SE) degrees. For 13 of the 15 hearts with double-outlet right ventricle the mean angle was 4 ± 7(SE) degrees. Two hearts with double-outlet right ventricle showed markedly divergent aortic-to-pulmonary valve angles, with a mean of 228 ± 11(SE) degrees, and were therefore grouped separately. Although direct comparison of hearts and embryos is difficult because of the differences in methods of determining angles, the valve positions in normal hearts was most similar to Carnegie stage 19, as found in an earlier study. The majority of the hearts with double-outlet right ventricle resembled stage 16 embryos. The results of this study, as well as those of the earlier studies, support the hypothesis that a spectrum of cardiac anomalies with anomalous origin of great vessels arises as arrests in the normal rotation of the semilunar valve region during embryogenesis.

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In a study using three-dimensional computerized reconstructions of serially sectioned human embryos it was possible to show quantitatively that the junction of the outflow tract and the great arteries undergoes a rapid rotation between Carnegie stages 15 and 19. This finding led to an examination of the possibility that an arrest in the rotation of the outflow tract may result in certain cardiac malformations such as tetralogy of Fallot and transposition of the great arteries. It was shown that the positions of the semilunar valves in hearts with transposition of the great arteries resembled those in stage 15, whereas the semilunar valve positions in hearts with tetralogy of Fallot resembled those in stage 18. The semilunar valve positions in normal hearts were found to be most similar to those in stage 19, a period when normal cardiogenesis is largely complete. These results suggested that these anomalies arise as arrests in the normal rotation of the semilunar valve axis. The results also suggested that other transposition complexes, such as double-outlet right ventricle, might also be caused by arrests in the rotation of the semilunar valve axis. The present study was undertaken to further study this question.

Materials and methods

Since the term double-outlet right ventricle was first used in 1957 by Witham, a variety of workers have defined the term differently. Although the definition that deemphasizes the importance of aortic-mitral discontinuity, proposed separately by Anderson and Levy and their colleagues, may be more useful from a clinical perspective, the more rigid criteria set forth by Neufield et al. and Van Praagh et al. were used in this study. Thus, the hearts with double-outlet right ventricle in this study had both great vessels taking origin from the right ventricle and no fibrous continuity between semilunar and atrioventricular valves.

Fifteen hearts with double-outlet right ventricle as defined above were examined. Thirteen of these were obtained from patients undergoing autopsy at The Johns Hopkins Hospital between 1948 and 1984. The remaining two hearts were from outside hospitals. Cases with asplenia or polysplenia syndrome were excluded from this study. Two hearts with mitral atresia and a single, morphologically right ventricle were, however, included. Twenty normal hearts were also examined. Usually the hearts had been distended in 3.7% formaldehyde solution before dissection. Two thin metal probes were inserted across each semilunar valve ring so as to form a cross with the center of the cross coinciding with the center of each valve. Stereoscopic radiographs of the hearts were then prepared. The centers of the aortic and pulmonary valves were located on the radiograph and
a line from the aortic valve to the pulmonary valve was drawn. A line parallel to the inferior aspect of the atrioventricular groove was then drawn so as to intersect the aortic-pulmonary line. Viewing the heart in an apical-to-basal direction, the angle of the aortic-pulmonary line was then determined with use of the line parallel to the inferior surface of the heart as the zero line. Additional information about each case was obtained by reviewing the autopsy records.

**Results**

Of the 15 hearts with double-outlet right ventricle that were studied, seven were from male patients, six were from female patients, and in two the sex was unknown to us. Among the 13 patients in whom the age was known, the mean age at the time of death was 78 months and the range was 10 days to 34 years.

There were a number of associated cardiac anomalies found. Although there have been cases of double-outlet right ventricle reported without ventricular septal defects,\(^1\),\(^2\) none of our cases showed this variant. Instead, one doubly committed, six subaortic, and six subpulmonary ventricular septal defects were found. Two hearts had mitral atresia with a single morphologically right ventricle. Eight of the hearts had patent foramen ovales and three had atrial septal defects. Two cases showed persistence of the left superior vena cava and eight hearts showed either infundibular or pulmonary valve stenosis. There were four cases with bicuspid pulmonary valves. Four cases showed coarctation of the aorta and three had patent ductus arteriosus. Two cases displayed a right-sided aortic arch. There was one case with dextrocardia. Table I summarizes the associated anomalies found.

To analyze the hearts with regard to their semilunar valve positions, the 15 hearts were divided into three groups: group I included 11 hearts showing a side-by-side relationship of the great arteries with the aortic valve to the right of the pulmonary valve, group II included two hearts with a side-by-side relationship of the great arteries with the aortic valve to the right of the pulmonary valve and a single ventricle, and group III consisted of two hearts with the aortic valve anterior and to the left of the pulmonary valve.

In group I, the acute angle between the line intersecting the centers of the aortic and pulmonary valves and the line demarcating the inferior surface of the hearts showed a mean of 6 degrees with a range of 327 to 38 degrees. For comparison, the 20 normal hearts had a mean angle of 81 degrees with a range of 48 to 117 degrees (table 2 and figure 1, A). No significant variation in the angles was demonstrated associated with age. The difference in angles between double-

**Table 1**

**Features of the cases studied**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/race/sex</th>
<th>Venous return</th>
<th>Atrial septum</th>
<th>AV valves</th>
<th>VSD</th>
<th>Outflow tract</th>
<th>Semilunar valves</th>
<th>AP angle</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 mo/W/M</td>
<td>—</td>
<td>PFO</td>
<td>SP (T-B)</td>
<td>IS</td>
<td>—</td>
<td>PDA</td>
<td>332</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14 days/W/M</td>
<td>—</td>
<td>PFO</td>
<td>SA</td>
<td>—</td>
<td>—</td>
<td>Coarctation, PDA</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15 years/W/F</td>
<td>—</td>
<td>PFO</td>
<td>SA</td>
<td>IS</td>
<td>BPV</td>
<td>RAA</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10 days/W/M</td>
<td>ASD</td>
<td>SP (T-B)</td>
<td>Subaortic</td>
<td>—</td>
<td>349</td>
<td>PDA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5 years/B/M</td>
<td>—</td>
<td>Malform MV</td>
<td>SA</td>
<td>IS</td>
<td>—</td>
<td></td>
<td>356</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 mo/B/F</td>
<td>PFO</td>
<td>SP (T-B)</td>
<td>SA</td>
<td>IS</td>
<td>BPV</td>
<td>RAA</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9 mo/B/M</td>
<td>—</td>
<td>PFO</td>
<td>SA</td>
<td>—</td>
<td>BPV, PS</td>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>7 mo/W/F</td>
<td>PLSVC</td>
<td>PFO</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Coarctation, PDA</td>
<td>347</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10 days/W/M</td>
<td>PFO</td>
<td>SP (T-B)</td>
<td>SA</td>
<td>—</td>
<td>—</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2 mo/W/F</td>
<td>ASD</td>
<td>SP (T-B)</td>
<td>SA</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>27 years/W/F</td>
<td>ASD repair</td>
<td>SA</td>
<td>PS, BAV</td>
<td>—</td>
<td>327</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group II</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>12</td>
<td>PFO</td>
<td>MV atresia</td>
<td>Single vent</td>
<td>—</td>
<td>—</td>
<td>9</td>
<td>Coarctation, PDA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>PLSVC</td>
<td>MV atresia</td>
<td>Single vent</td>
<td>BPV, PS</td>
<td>346</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>PFO</td>
<td>—</td>
<td>DC</td>
<td>BPV</td>
<td>217</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>34 years/W/F</td>
<td>PFO</td>
<td>SP</td>
<td>PS</td>
<td>238</td>
<td></td>
<td></td>
<td></td>
<td>Dextrocardia</td>
</tr>
</tbody>
</table>

**Notes:**

AP angle = aortic-to-pulmonary valve angle relative to inferior atrioventricular groove (in degrees); ASD = atrial septal defect; AV = atrioventricular; B = black; BAV = bicuspid aortic valve; BPV = bicuspid pulmonary valve; Coarctation = coarctation of the aorta; DC = doubly-committed VSD; DORV = double-outlet right ventricle; IS = infundibular stenosis; MV = mitral valve; PFO = patent foramen ovale; PLSVC = persistent left superior vena cava; PPFO = probe patent foramen ovale; PS = pulmonary valve stenosis; RAA = right aortic arch; SA = subaortic VSD; SP = subpulmonary VSD; (T-B) = Taussig-Bing malformation; VSD = ventricular septal defect; W = white.
outlet right ventricle hearts and normal hearts was highly significant (p<.001) by the Student t test.

The hearts of group II showed a mean angle of 358 degrees, which was not statistically different from that of group I. Although these hearts did not represent pure double-outlet right ventricles due to the associated finding of mitral atresia and single ventricle, their great artery relationship was that of double-outlet right ventricle. Groups I and II were combined, and showed a mean angle of 4 degrees, with a range of 327 to 38 degrees (table 2 and figure 1, B). Statistical analysis also showed this combined group to be highly significantly different from normal hearts (p<.001).

Although separating the hearts of group III from the other two groups may seem artificial, these hearts definitely represent a distinct class (table 2 and figure 1, C). The mean aortic-to-pulmonary valve angle in these two hearts was found to be 228 degrees, which was statistically different from that in both the normal hearts and the other hearts with double-outlet right ventricle (both p<.001). Although rare, similar hearts have been described earlier by Danielson,17 Blanc-quaert,18 Van Praagh,19 Goor,20 and Lincoln21 and their colleagues using a variety of names. Sridaromont et al.16 also referred to five such hearts that were described as having levomalposition of the great vessels.

All these hearts have been described as having viscera and atria in situs solitus, normal ventricular d-loop (i.e., the morphologically right ventricle being right-sided and the morphologically left ventricle being left-sided) and pulmonary stenosis, just as found in our cases. None of the hearts was described as displaying dextrocardia as was found in one of our cases.

Discussion

Although the quantitative approach used in this study to determine the semilunar valve positions in hearts with double-outlet right ventricle is somewhat different, the results of this study are consistent with other qualitative studies. In a series of 33 hearts with

<table>
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<tr>
<th>Table 2</th>
<th>Aortic-to-pulmonary valve angles</th>
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<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Number of cases</td>
<td>20</td>
</tr>
<tr>
<td>Age (months)</td>
<td>265 ± 42</td>
</tr>
<tr>
<td>Range of ages</td>
<td>12 days–39 yr</td>
</tr>
<tr>
<td>Angle (degrees)</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>Range of angles</td>
<td>48–117</td>
</tr>
<tr>
<td>Median</td>
<td>78</td>
</tr>
</tbody>
</table>

*p Mean ± SE.

FIGURE 1. Positions of cardiac valves (A = aortic; P = pulmonary; M = mitral; T = tricuspid) as viewed from apex to base. Numerical value in center of the arc indicates the mean aortic-to-pulmonary valve angle relative to the inferior atrioventricular groove. Values at the ends of the arc indicate range of aortic-to-pulmonary valve angles. A, Normal hearts; B, double-outlet right ventricle with side-by-side semilunar valve relationships (groups I and II); C, double-outlet right ventricle with the aortic valve anterior and to the left of the pulmonary valve.
double-outlet right ventricle obtained at autopsy, Zama- 
ora et al. showed that, although there was some 
variation in the anteroposterior relationship of the two 
great vessels, they generally existed in a side-by-side 
relationship with the aorta to the right. In a larger series 
of autopsied hearts, Sridaromont et al. also found 
that the majority of hearts with double-outlet right 
ventricle showed either a side-by-side or dextromalposi-
tioned great artery relationship. Since the qualitative 
term "side-by-side" corresponds to an aortic-pulmo-

TABLE 3
Comparison of aortic-to-pulmonary valve angles of embryonic and 
postnatal hearts

<table>
<thead>
<tr>
<th>Carnegie stage</th>
<th>Angle (degrees)A,C</th>
<th>Type</th>
<th>Angle (degrees)A,D</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>327 ± 7</td>
<td>TGA</td>
<td>333 ± 3</td>
</tr>
<tr>
<td>16</td>
<td>6 ± 3</td>
<td>DORV</td>
<td>4 ± 7</td>
</tr>
<tr>
<td>17</td>
<td>38 ± 9</td>
<td>TF</td>
<td>48 ± 5</td>
</tr>
<tr>
<td>18</td>
<td>47 ± 2</td>
<td>Normal</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>19</td>
<td>88 ± 34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DORV = double-outlet right ventricle; TGA = transposition of the 
great arteries; TF = tetralogy of Fallot.
A Mean ± SE.
B Angles for TGA and TF derived from an earlier study.
C Aortic-to-pulmonary valve axis relative to frontal plane.
D Aortic-to-pulmonary valve axis relative to inferior atrioventricular 
groove.

great artery showed either a side-by-side or dextromalposi-
tioned great artery relationship. Since the qualitative 

The rotation of the outflow tract region of the em-

bryonic heart has long been recognized. In a pre-

vious study of the outflow tracts of embryos of Carne-
gie stages 15 through 19, the rapid angular rotation of 
the semilunar valve axis that occurs during this period 
of development was described quantitatively. Comparing 
the results of that study with those in the hearts 
with double-outlet right ventricle in this study and 
those in hearts with tetralogy of Fallot and transposi-
tion of the great arteries in a previous study showed 
similarities between the angles in the embryonic and 
postnatal hearts (table 3). These similarities suggest 
that the progenitors of the outflow tract rotation in the 
embryonic heart may subsequently be manifested as rota-
tional anomalies. The hearts with double-outlet right 
ventricle have an angle similar to Carnegie stage 16 
hearts, suggesting that double-outlet right ventricle 
may arise as a result of a reduction in the rotation of the 
semilunar valve axis, leaving it in a position corre-

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several theories as to the cause of arrested development. The 
implications of these theories with respect to the devel-

opment of tetralogy of Fallot and transposition of the 
great arteries have been dealt with previously. Although 
de la Cruz et al. did not specifically address hearts with double-outlet right ventricle in their ontogenetic theory, they thought that incomplete rotation

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of the outflow tract (truncoconal) septum resulted in partial distortions of the great vessels and that delayed disappearance of the interventricular (conoventricular) flange resulted in dextroposition of the outflow tract (truncus-conus). Extrapolating from this theory, hearts with double-outlet right ventricle would be caused by incomplete rotation of the outflow tract and delayed disappearance of the interventricular flange. According to the closely allied “straight septum hypothesis” of Van Mierop et al., persistence of the interventricular (bulboventricular) flange also results in double-outlet right ventricle since it interferes with the transfer of the aortic root to the left ventricle.

Due to inadequacies in these theories, Van Praagh and Van Praagh developed the differential conal growth hypothesis, which proposes that the spectrum of transposition complexes seen are the result of various degrees of subpulmonary or subaortic free wall...
conal development. According to this hypothesis, there must be pulmonary conal free wall development and deficient aortic free wall conal development for the normal great artery relationship to develop. It is this lack of aortic free wall conal development that accounts for the normal mitral-aortic fibrous continuity. The side-by-side great vessel relationship seen in hearts with double-outlet right ventricle is thus the result of either combined aortic or pulmonary free wall conal development or bilaterally deficient free wall conal development.

Van Praagh's differential conal development hypothesis was also believed by many to be inadequate, so a related conal absorption hypothesis developed. This hypothesis, supported by Goor and Edwards, proposes that the definitive shape of the outflow tract is primarily due to three processes: outflow tract (conotruncal) inversion, leftward shift of the outflow tract-ventricular (conoventricular) junction, and absorption of the conus. Thus, in their view, double-outlet right ventricle is due to incomplete outflow tract inversion and failure of leftward shift of the outflow tract. The fibrous discontinuity between mitral and aortic valvular material seen in double-outlet right ventricle is the result of inadequate absorption of the aortic conus. Other authors, such as Anderson et al., support their own variation of the conal absorption hypothesis, placing emphasis on slightly different developmental processes.

A different view of pathogenesis of double-outlet right ventricle and the other transposition complexes suggests that a hemodynamic mechanism related to the amount and direction of blood flow may account for the rotational arrests seen in these anomalies. During Carnegie stages 15 through 19, the maximal rotation of the semilunar valve axis occurs; there is also a dramatic increase in the diameter and length of the great arteries. The third event, which occurs in conjunction with the rotation and artery elongation, is a reduction in the confinement of the heart by the thoracic wall as the ribs develop and the heart comes to lie more freely in the thoracic cavity. It seems probable that the arterial elongation causes the rotation of the outflow tract region. Since it has been observed that both vessel diameter and length are direct functions of blood flow, the rapid growth and elongation of the great arteries can be accounted for by increased blood flow. If blood flow through the great arteries were reduced during this critical period, the time course of great artery growth would be altered. This reduction of great artery growth could cause varying degrees of rotational arrest of the semilunar valve area, depending on the timing and severity of the reduced blood flow. In the case of classical double-outlet right ventricle (group I), alterations of blood flow may cause an arrest in rotation that would correspond to stage 16 of development and subsequently alter the time course of development of the positioning of the ventricles, outflow tract, and the two great arteries. As discussed earlier, reductions in blood flow at different periods or of varying severity may also account for the arrests in rotation seen in tetralogy of Fallot and transposition of the great arteries.

This hemodynamic hypothesis is not consistent with the association of single ventricle with double-outlet right ventricle (group II). In this group of hearts there was an alteration of intracardiac blood flow produced by the mitral atresia. However, reduced blood flow may have caused the arrest in the rotation of semilunar valves during embryogenesis, as suggested for group I hearts. Single or common ventricle has been noted in a high percentage of hearts with malpositioned great arteries.

The above discussion deals with 13 of the 15 hearts with double-outlet right ventricle in this study, specifically those showing classical double-outlet right ventricle (group I) and those with a single ventricle and double-outlet right ventricle (group II). So far, however, little has been said about the two hearts in group III with the aorta anterior and to the left of the pulmonary artery, i.e., the hearts with aortic-to-pulmonary valve angles of 217 and 238 degrees. As mentioned earlier, similar hearts have been described in the literature. Several possible pathogenetic explanations for these hearts have also been proposed. One tentative explanation for this malformation is that the aortopulmonary septum that separates the fourth (aortic) and sixth (pulmonary) aortic arches fuses with the outflow tract (conotruncal) septum in reverse. As Lincoln et al. point out, however, such an argument is closely related to the straight septum hypothesis of Van Mierop et al., which has been found to be inadequate. Goor and Edwards have proposed that complete isolated conal inversion in reverse would produce this anomaly. They also propose that this type of double-outlet right ventricle, which they refer to as double-outlet right ventricle with L-transposition of the great arteries and D-loop, fits into a spectrum of anomalies along with anatomically corrected transposition, the developmental difference between the two being that in anatomically corrected transposition the outflow tract has undergone the appropriate leftward shift, whereas in this type of double-outlet right ventricle it has not.

Another possible explanation for the position of the
semilunar valves in these cases is a hemodynamic one in which the ventricular ejection stream of the embryonic heart preferentially flows through the left fourth aortic arch instead of the sixth aortic arch as found normally.\textsuperscript{41,42} This preferential flow would then result in an altered torsion on the growing great arteries. Since great artery growth and elongation may be responsible for the rotation of the semilunar valve axis, as described above, this alteration in torsion could arrest the normal counterclockwise rotation of the semilunar valve axis and reverse its direction. The primitive aortic valve would then no longer rotate posteriorly and to the left but rather anteriorly and to the right.

In conclusion, we believe that the data from this study and those from our previous studies show that the positions of the great arteries in transposition of the great arteries, double-outlet right ventricle, and tetralogy of Fallot differ significantly from the position of the great vessels in normal hearts and that these anomalies form a spectrum of complexes. In addition, the data support the concept that these malformations represent arrests in the normal rotation of the outflow tract during embryogenesis. Reduced blood flow may provide an explanation for why these developmental arrests occur.

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