isoproterenol as compared to exercise despite greater increment in cardiac output obtained during exertion.

Although isoproterenol and exercise both induced an increase in cardiac output and a decrease in systemic vascular resistance, the magnitude of changes in those parameters was different in the two states. The greater increase in cardiac output with exercise can be explained on the bases of metabolic vasodilatation in the active muscles decreasing systemic resistance while constriction of the systemic veins and the pumping action of the skeletal muscles increases the venous return to the heart. In addition, the potent vasodilator effect of isoproterenol may have contributed to the lower values of systemic arterial pressure obtained with this agent.

The increase in ventricular systolic pressures obtained with mild exercise in our patients was most likely related to an increase in preload as well as an increase in myocardial contractility.

Our data in patients with pulmonary stenosis are in general agreement with the observations of Neal et al. regarding the increase in peak valvular gradient with isoproterenol out of proportion with the increase in cardiac output as compared to exercise. However, despite the differences in mechanisms causing increased semilunar gradients, the effects of exercise and isoproterenol were fairly consistent in patients with pulmonary or aortic valve stenosis at similar increments of heart rate. Individual values fit well to the regression line in both groups of patients (figs. 2 and 3). Thus, the linear regression equations generated from these data can be used to estimate gradients of the stenotic lesion under exercise conditions at an equivalent heart rate.

We believe that exercise studies remain the method of choice for the complete evaluation of patients with aortic or pulmonary stenosis. However, isoproterenol infusion and application of these regression equations constitute a practical and useful alternative when exercise studies cannot be carried out.

References


Congenital Heart Block in Newborns of Mothers with Connective Tissue Disease

CAROLYN M. McCUE, M.D., MICHAEL E. MANTAKAS, M.D., JON B. TINGELSTAD, M.D., AND SHAUN RUDDY, M.D.

SUMMARY Of 22 children with congenital complete heart block (CCHB) available for study, 14 (63.6%) were born to 11 mothers with clinical or laboratory evidence of connective tissue disease, primarily lupus erythematosus (LE). Seven mothers had both clinical and laboratory evidence of disease while four had only positive laboratory studies including fluorescent antinuclear antibody, rheumatoid factor, and depressed complement levels.

In adults with systemic LE, pathologic changes in the collagen surrounding the conduction system have led to fibrosis and death from heart block. Antinuclear antibodies of the IgG class cross the placental barrier and newborn infants have been reported with transient skin lesions of lupus. Placental transmission of such antibodies may affect the fetal cardiac conduction system, surrounding collagen, and myocardium, leading in some cases to CCHB. This is probably one important etiologic factor in CCHB even though the mother is asymptomatic during her pregnancy.

CONGENITAL COMPLETE HEART BLOCK was reported by Morquio 1 75 years ago as a syndrome with a slow pulse, attacks of syncope, and sudden death, often occurring in families. Since then small series and individual cases have been reported, 2 but the comprehensive cooperative study of the European and American Pediatric Cardiologists in 1972, 7 presenting the results of studies on 599 infants and children, provided a clearer picture of the clinical aspects of congenital complete heart block. There were 14 families with two siblings with heart block and two families with three siblings, but no maternal history is given and the etiology of this rare condition remained obscure.

A coincidence of observing several cases of congenital heart block within a few months at the Medical College of Virginia prompted a review of the clinical findings in all children with congenital heart block seen at the Medical College of Virginia during the preceding 12 years. Since a
lupus-like illness was seen in one infant with congenital heart block born to a mother with known systemic lupus erythematosus, we looked for connective tissue disease in mothers of the other children with congenital heart block. Our objective was to ascertain whether clinical and laboratory evidence of connective tissue disease could be related to the cardiac conduction abnormalities in the infants. The results, presented here, indicate an extraordinarily high frequency of either overt connective tissue disease or abnormal serologic tests for such disease in these mothers, and suggest that transplacental transfer of abnormal antibodies may be of pathogenic importance in some cases of congenital complete heart block.

Case Report

In October of 1975 a 36-weeks-gestational age female infant was born at the Medical College of Virginia Hospital to a para IV, abortions II, 26-year-old mother. The birth weight was 3270 g. The physical examination revealed a hypotonic, massively edematous baby in acute distress; pulse 140, respirations 40, and blood pressure 60 mm Hg, systolic, by palpation in arms and legs. The clinical picture was dominated by ascites. The liver was palpable 3 cm and the spleen 4 cm below the costal margin. She had no cardiac murmur.

Family history. A 5-year-old brother had complete congenital heart block without associated heart defects. Her mother revealed a 10-year history of butterfly rash and arthritis with positive laboratory findings over the previous six years including antinuclear antibody (ANA) titer of 1:1600. She easily met the established criteria for lupus erythematosus.8 During her pregnancies she took only occasional aspirin and the disease was relatively quiescent. Ten years earlier lupus was diagnosed in the maternal grandmother.

Laboratory studies. The blood analyses revealed the following data: hemoglobin, 11.4 g/dl; white blood count, 7.0 x 10^9/L; polymorphonuclears 32%, bands 7%, lymphocytes 55%, monocytes 5%, metamyelocytes 1%; platelets, 100 x 10^9/L, BUN, 44 mg/dl. The chest roentgenogram revealed diffuse cardiomegaly with evidence of pulmonary edema. The electrocardiogram showed atrioventricular dissociation briefly which changed to 1:1 atrioventricular block with a slower rate. The IgM level was 23 mg/dl. Viral titers on mother and infant showed no significant rise. Urinalyses and an intravenous pyelogram were negative. An angiocardiogram made during the first week of life disclosed a large right atrium but no other abnormalities. An echocardiogram was normal except for a mild right ventricular overload and did not suggest an Ebstein's deformity. The initial blood gases showed a PaO_2 of 45 mm Hg which rose in 90% oxygen with intensive supportive therapy to 99 torr.

Course. An immediate paracentesis removed 250 cc of fluid and this procedure was repeated several times during the next two weeks. The infant was also treated with diuretics and digitalis. Severe respiratory distress required mechanical ventilatory assistance for about one week and careful regulation of electrolytes. The anasarca disappeared over a two week period with a weight loss of 1350 g and the gastrointestinal bleeding, presumably due to low platelets, resolved. At 1 month of age the infant developed a discoid skin rash (fig. 1A) consistent with lupus by biopsy (fig. 1B). The ANA at four months of age was weakly positive (1:20) and of a diffuse nuclear pattern.

By six months she was free of edema, without organomegaly, and in normal sinus rhythm. The rash was fading. Since then she has shown steady improvement and now has no murmur and a normal heart size by chest X-ray. Her excellent progress continues at 12 months of age but a few telangiectatic areas on the face persist.

Materials and Methods

A search of the records at the Medical College of Virginia revealed 24 children with congenital heart block seen in the past 12 years. A sibling of one of our patients was studied in Indiana by Dr. Roger Hurwitz. Another affected child was referred by Dr. Lewis Scott from Washington, D.C.; they are included in the total group of 26 children born to 23 mothers. The history, physical findings, and electrocardiogram of each infant were reviewed and tabulated. Nineteen mothers who could be located were recalled for history of connective tissue disease or other diseases, and hospital and physicians' records were reviewed when available. During 1976 blood specimens were drawn from 18 mothers and 18 children for immunologic studies, including antinuclear antibodies,8 latex, human and sheep cell tests for rheumatoid factor,10 and C3 and C4 complement.11 One mother, from whom no blood was obtained, had severe lupus encephalitis in a Washington, D.C., hospital; her hospital record included a positive lupus erythematosus (LE) cell preparation as early as 1954. Two children who died prior to 1976 and two who refused venipuncture could not be tested. Results of earlier tests on mothers were tabulated where available.

Results

The 23 mothers of 26 children with congenital complete heart block were categorized as noted in table 1. In group A are 11 mothers who have evidence of connective tissue disease; they have a total of 14 children with congenital complete heart block. In seven mothers of nine children (group A-1) the disease is overt and symptomatic, whereas four mothers with five children (group A-2) have only laboratory evidence of connective tissue disease. In group B are eight mothers with neither symptoms nor laboratory evidence of connective tissue disease; each has one child with congenital complete heart block. The four mothers in group C are not available for study at this time.

The seven mothers in group A-1 (table 2) have children whose ages now range from 5 months to 24 years. Three mothers had pronounced clinical manifestations of systemic lupus erythematosus and positive laboratory findings, including LE cell preparations. Three others had mild clinical symptoms and positive laboratory tests. One mother, now age 53, has had progressively severe rheumatoid arthritis for 30 years. The laboratory studies on five of these seven mothers showed a peripheral pattern of antinuclear antibodies, consistent with antibodies to native DNA and systemic lupus erythematosus.

Of the nine group A-1 children two have died; one at 18 months in Indiana during surgery to implant a pacemaker...
and one at eight years in Virginia when a previously inserted pacemaker failed in 1964 (table 3). All but one had undergone cardiac catheterization and one had a necropsy as well, but the only underlying pathology discovered in the hearts has been fibroelastosis with secondary mitral insufficiency and/or a small patent ductus arteriosus. The oldest patient, now 24 years of age, has tolerated two pregnancies herself without need for a pacemaker. Her two children are well.

In group A-2 are four asymptomatic mothers who have laboratory findings of connective tissue disease as shown in table 4. All have recently denied any symptoms of skin rash, joint pains, or unexplained fevers, yet all have positive latex tests and three have positive tests for antinuclear antibody. Their children now range in age from one to 20 years (table 5). Three have had cardiac catheterization and one has died. Fibroelastosis and mitral insufficiency were verified in one living case and two others have L-transposition of the great arteries with associated defects. It is interesting that the twins both had congenital heart block recognized at birth, and although one is asymptomatic, the other, with L-transposition, ventricular septal defect, coarctation, and hypoplastic right ventricle died at 15 days of age, in spite of a pacemaker and vigorous medical support.

The group B mothers, with the same laboratory studies entirely negative, denied all symptoms of connective tissue disease. They have given birth to eight infants with congenital complete heart block, who now range in age from 3 months to 15 years (table 6). One died at birth with polysplenia and complex congenital heart disease. Four others underwent cardiac catheterization. Case 5 had L-transposition of the great arteries, a ventricular septal defect, and pulmonary hypertension along with his congenital heart block. His ventricular septal defect was corrected at 22 months of age and he now has a pacemaker not required preoperatively. Case 2 had a small patent ductus ligated.

The children and their mothers in group C are older. The children range in age from 6 to 21 years. All reside outside Virginia and are not available for study at this time. The mother of one patient is known to have heart block and a pacemaker.

The present age range of the total group is 5 months to 24 years, with a mean of five years. The sexes are almost equally represented with 12 males and 14 females; four children are

---

**TABLE 1. Summary Data of Children with Congenital Complete Heart Block**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of mothers</th>
<th>No. of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1)</td>
<td>Mother with overt LE</td>
<td>7</td>
</tr>
<tr>
<td>2)</td>
<td>Mother with positive lab findings only</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic mother, negative lab findings</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>Not available for recall</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>23</td>
<td>26</td>
</tr>
</tbody>
</table>
block. Seventeen have undergone diagnostic cardiac catheterization. Complex associated heart disease was present in four of the children, two of whom have died. Significant cardiomegaly is present now in six, all of whom have fibroelastosis and mitral insufficiency by cineangiography. Seven others had cardiomegaly in infancy. A total of four children have died, two with pacemaker problems and two, noted above, with complex congenital heart disease. The diagnosis of heart block was made before birth in six infants, in the neonatal period in ten, under six months of age in two others, and after two years of age in four. Assays of antinuclear antibodies and rheumatoid factors were made in all living children except two, and all were negative except those of two infants who had transiently positive ANA titers of 1:20 and 1:200 respectively during the first month of life. Their mothers' ANA tests were strongly positive. Both infants had negative tests at four months of age.

Several additional electrocardiographic variations in the children, especially during infancy, have been noted and may be explained by the spectrum of pathology involving the sinoatrial and atrioventricular nodes. They have included sporadic episodes of sinus rhythm alternating with heart block (fig. 2A), an ectopic atrial pacemaker (fig. 2B), transient atrial flutter (fig. 2C), varying width of the QRS, and ventricular premature beats. All of these were transient except the single patient described in the introduction who had an A-V dissociation initially, followed by a 1° A-V block for about six months, but did not have a permanent complete heart block. No major differences in the electrocardiographic pattern of the complete heart block of the children in groups A, B, and C could be perceived, once the rhythm became established.

The obstetrical history of mothers available for study reveals that among 55 live births, 22 or 40% had congenital heart block and 33 had no cardiac abnormalities. Of the 14 children with heart block in group A, ten were the youngest in birth order, three the oldest, and one a middle child. No serologic studies at the time of each pregnancy are available, but no clear relationship of the mothers' symptoms of illness could be associated with the birth of infants with heart block, in contrast to siblings without heart block. Connective tissue diseases are, however, well known for their exacerbations and remissions in symptoms and in serology. The nine abortions in these mothers are consistent with the known high fetal loss, which is approximately 30% in mothers with lupus erythematosus.
TABLE 3. **Group A-1 Infants With Congenital Complete Heart Block Whose Mothers Have Overt Connective Tissue Disease**

<table>
<thead>
<tr>
<th>Case</th>
<th>Race</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Casa</th>
<th>Assoc. heart disease</th>
<th>Age CCHB found</th>
<th>V*</th>
<th>A*</th>
<th>QRS</th>
<th>Transient variations</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CC</td>
<td>W</td>
<td>M</td>
<td>3</td>
<td>No</td>
<td>?</td>
<td>&lt; B</td>
<td>45</td>
<td>135</td>
<td>0.08</td>
<td>Brief sinus rhythm, 1 day. CCHB since.</td>
<td>Excellent</td>
</tr>
<tr>
<td>2 DG</td>
<td>W</td>
<td>M</td>
<td>5/12</td>
<td>Yes</td>
<td>EFE</td>
<td>B</td>
<td>60</td>
<td>160</td>
<td>0.06</td>
<td>Occasional PVC 1st week.</td>
<td>Mild CF responded to digitalis. ANA positive 1:200 as newborn with depressed C4. ANA negative at 4 mos. Sib. of Case 3.</td>
</tr>
<tr>
<td>3* GG</td>
<td>W</td>
<td>F</td>
<td>1½§</td>
<td>Yes</td>
<td>EFE</td>
<td>FO</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>PVCs</td>
<td>Syncopa and death at surgery to implant pacemaker at 18 mos. in Indiana. Sib. of case 2.</td>
</tr>
<tr>
<td>4 JL</td>
<td>W</td>
<td>M</td>
<td>6</td>
<td>Yes</td>
<td>EFE</td>
<td>&lt; B</td>
<td>46</td>
<td>60</td>
<td>0.12</td>
<td>Varying width QRS, AV dissociation at birth. 1° block for 6 mos. Now sinus rhythm without block.</td>
<td>Excellent. Sib. of Case 5.</td>
</tr>
<tr>
<td>5† AL</td>
<td>W</td>
<td>F</td>
<td>10/12</td>
<td>Yes</td>
<td>No</td>
<td>B</td>
<td>140</td>
<td>120</td>
<td>0.05</td>
<td>Brief flutter in infancy. Varying QRS width .05 to .10. Intermittent RBBB since 1974.</td>
<td>Excellent. Tolerated 2 pregnancies. Stress test normal.</td>
</tr>
<tr>
<td>6 WR</td>
<td>B</td>
<td>M</td>
<td>8½</td>
<td>Yes</td>
<td>EFE</td>
<td>MI</td>
<td>50</td>
<td>120</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 RER</td>
<td>W</td>
<td>F</td>
<td>24</td>
<td>Yes</td>
<td>No</td>
<td>B</td>
<td>40</td>
<td>60</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 JV</td>
<td>W</td>
<td>F</td>
<td>8‡</td>
<td>Yes</td>
<td>No</td>
<td>B</td>
<td>45</td>
<td>80</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9‡ KL</td>
<td>W</td>
<td>M</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>B</td>
<td>35</td>
<td>155</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Case history and pathology from Dr. L. Hurwitz.
†Only case in which heart block was not permanent and complete.
‡Patient of Dr. L. Scott.
§Died.

**Abbreviations:** CF = cardiac failure; <B = before birth; EFE = endocardial fibroelastosis; FO = foramen ovale; JRA = juvenile rheumatoid arthritis; MI = mitral insufficiency; PDA = patent ductus arteriosus; PVC = premature ventricular contraction; V and A = ventricular and atrial rate, respectively, in beats/min.

**Discussion**

Serology

The highly significant laboratory studies on the mothers of our patients were performed in August 1976 and are reported in tables 2 and 4. Among mothers of infants with congenital complete heart block seven of the 19 for whom information was available had systemic lupus or rheumatoid arthritis. Four other mothers

**Table 4.** **Group A-2: Asymptomatic Mothers With Positive Laboratory Findings of Connective Tissue Disease Whose Infants Have Congenital Complete Heart Block**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at infant's birth</th>
<th>Pattern</th>
<th>Complement (percent)</th>
<th>Rheumatoid factor</th>
<th>With heart block block</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>L</td>
<td>B</td>
<td>56</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>1 TB</td>
<td>21</td>
<td>25</td>
<td>3+, peripheral, diffuse</td>
<td>1/80</td>
<td>128</td>
</tr>
<tr>
<td>2 LG</td>
<td>29</td>
<td>34</td>
<td>Negative</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3 PS</td>
<td>33†</td>
<td>34</td>
<td>Negative</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4 RP</td>
<td>33</td>
<td>50</td>
<td>2+, peripheral, diffuse</td>
<td>1/20</td>
<td>104</td>
</tr>
</tbody>
</table>

*Values in parenthesis indicate earlier results.
†Normal values: C3 = 60-150%; C4 = 55-160%.
‡Twin birth.

**Abbreviations:** SHC = sensitized human cell titer.
had positive laboratory abnormalities suggesting connective tissue disease. Although reliable figures for frequency of symptomatic connective tissue disease among mothers in the obstetrical population at the Medical College of Virginia are not known, comparative data are available. In 1966 Waller, in a child development study, found that of 1,027 obstetrical patients, 2.5% manifested a positive latex fixation test. Using the technique employed for the present study only one of 253 normal females had an ANA titer greater than 1:20. In a separate study of 30 post partum mothers of children without heart defects all had normal C4 values. Thus, the frequency of laboratory abnormalities in these 19 mothers is clearly excessive. In general, the ANA test is positive in 98-100% of patients with active lupus erythematosus and 0-4% of the normal population. Although antinuclear antibodies may be found in other connective tissue diseases, lupoid hepatitis, and drug reactions, the peripheral pattern of fluorescence, indicative of antibodies to native DNA, is rarely seen in these diseases and is strongly suggestive of systemic lupus erythematosus. The depressed C3 and C4 complement levels are also found more commonly in systemic lupus erythematosus than in those other diseases. Furthermore, there was no clinical evidence of those other diseases in our mothers.

Both the increased frequency of connective tissue disease and the increase in laboratory abnormalities among mothers of infants with congenital complete heart block suggest that infants born to mothers with such diseases or laboratory ab-

<table>
<thead>
<tr>
<th>Case</th>
<th>Race</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Cath</th>
<th>Assoc. heart disease</th>
<th>Age CCHD found</th>
<th>V</th>
<th>A</th>
<th>QRS</th>
<th>Transient variations</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 TB</td>
<td>W</td>
<td>F</td>
<td>4</td>
<td>Yes</td>
<td>EFE</td>
<td>&lt; B</td>
<td>40</td>
<td>150</td>
<td>0.06</td>
<td>Occasional PVCs</td>
<td>Cardiac enlargment, CF in infancy. Improved with digoxin.</td>
</tr>
<tr>
<td>2 HG</td>
<td>W</td>
<td>F</td>
<td>4½</td>
<td>No</td>
<td>No</td>
<td>&lt; B</td>
<td>48</td>
<td>70</td>
<td>0.06</td>
<td>None known</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>3 DS*</td>
<td>W</td>
<td>F</td>
<td>NB†</td>
<td>No</td>
<td>LTGA</td>
<td>B</td>
<td>58</td>
<td>145</td>
<td>0.06</td>
<td>PVCs</td>
<td>Premature; wt. 1720 gm. CF, respiratory distress. Pacemaker implanted. Died at 15 days.</td>
</tr>
<tr>
<td>4 DS*</td>
<td>W</td>
<td>F</td>
<td>1</td>
<td>Yes</td>
<td>EFE</td>
<td>B</td>
<td>60</td>
<td>136</td>
<td>0.04</td>
<td>None known</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>5 SP</td>
<td>W</td>
<td>M</td>
<td>20</td>
<td>Yes</td>
<td>LTGA</td>
<td>8 yrs</td>
<td>50</td>
<td>110</td>
<td>0.08</td>
<td>None known</td>
<td>Excellent. Stokes-Adams once 6 years ago. Pacemaker, 1976.</td>
</tr>
</tbody>
</table>

*Twins.  †Died.

| Abbreviations: CF = cardiac failure; EFE = endocardial fibroelastosis; LTGA = left transposition of great arteries; MI = mitral insufficiency; PDA = patent ductus arteriosus; PVCs = premature; VSD = ventricular septal defect; for others see previous tables. |

Table 5. Group A-2: Infants With Congenital Complete Heart Block of Asymptomatic Mothers Having Positive Laboratory Findings of Connective Tissue Disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Race</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Cath</th>
<th>Assoc. heart disease</th>
<th>Age CCHD found</th>
<th>V</th>
<th>A</th>
<th>QRS</th>
<th>Transient variations</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BA</td>
<td>B</td>
<td>M</td>
<td>NB†</td>
<td>No</td>
<td>Yes</td>
<td>B</td>
<td>60</td>
<td>130</td>
<td>0.08</td>
<td>None</td>
<td>Polysplenia, situs inversus with levocardia, common A-V orifice, complete transposition and pulmonary atresia. TAPVR. Died 24 hrs.</td>
</tr>
<tr>
<td>2 TB</td>
<td>B</td>
<td>F</td>
<td>1/4</td>
<td>Yes</td>
<td>PDA</td>
<td>B</td>
<td>105</td>
<td>160</td>
<td>0.04</td>
<td>None</td>
<td>Mild CF in infancy, digitalis responsive. Excellent. Small ductus repaired.</td>
</tr>
<tr>
<td>3 MB</td>
<td>B</td>
<td>M</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>B</td>
<td>43</td>
<td>60</td>
<td>0.08</td>
<td>2:1 block briefly in infancy</td>
<td>Found in Child Develop. Clinic. No symptoms. SC anemia. Occasional syncope in infancy. No problems.</td>
</tr>
<tr>
<td>4 PP</td>
<td>W</td>
<td>F</td>
<td>15</td>
<td>Yes</td>
<td>MI</td>
<td>6 yrs</td>
<td>50</td>
<td>82</td>
<td>0.06</td>
<td>None</td>
<td>CCHB pre-op. Corrected VSD, 22 mos. Pacer post-op. Much improved, normal PVR.</td>
</tr>
<tr>
<td>5 DH</td>
<td>W</td>
<td>M</td>
<td>5</td>
<td>Yes</td>
<td>LTGA</td>
<td>2 wks</td>
<td>76</td>
<td>150</td>
<td>0.08</td>
<td>None</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>6 TJ</td>
<td>W</td>
<td>F</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>6 wks</td>
<td>45</td>
<td>95</td>
<td>0.04</td>
<td>2:1 block, 6 wks.</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>7 DL</td>
<td>W</td>
<td>F</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>6 wks</td>
<td>48</td>
<td>80</td>
<td>0.06</td>
<td>None</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>8 WH</td>
<td>W</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>2 yrs</td>
<td>50</td>
<td>80</td>
<td>0.05</td>
<td>None</td>
<td>No symptoms.</td>
</tr>
</tbody>
</table>

* Died, 1 day.

Table 6. Group B: Infants With Congenital Heart Block Whose Mothers Have No Laboratory or Clinical Evidence of Connective Tissue Disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Race</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Cath</th>
<th>Assoc. heart disease</th>
<th>Age CCHD found</th>
<th>V</th>
<th>A</th>
<th>QRS</th>
<th>Transient variations</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BA</td>
<td>B</td>
<td>M</td>
<td>NB†</td>
<td>No</td>
<td>Yes</td>
<td>B</td>
<td>60</td>
<td>130</td>
<td>0.08</td>
<td>None</td>
<td>Polysplenia, situs inversus with levocardia, common A-V orifice, complete transposition and pulmonary atresia. TAPVR. Died 24 hrs.</td>
</tr>
<tr>
<td>2 TB</td>
<td>B</td>
<td>F</td>
<td>1/4</td>
<td>Yes</td>
<td>PDA</td>
<td>B</td>
<td>105</td>
<td>160</td>
<td>0.04</td>
<td>None</td>
<td>Mild CF in infancy, digitalis responsive. Excellent. Small ductus repaired.</td>
</tr>
<tr>
<td>3 MB</td>
<td>B</td>
<td>M</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>B</td>
<td>43</td>
<td>60</td>
<td>0.08</td>
<td>2:1 block briefly in infancy</td>
<td>Found in Child Develop. Clinic. No symptoms. SC anemia. Occasional syncope in infancy. No problems.</td>
</tr>
<tr>
<td>4 PP</td>
<td>W</td>
<td>F</td>
<td>15</td>
<td>Yes</td>
<td>MI</td>
<td>6 yrs</td>
<td>50</td>
<td>82</td>
<td>0.06</td>
<td>None</td>
<td>CCHB pre-op. Corrected VSD, 22 mos. Pacer post-op. Much improved, normal PVR.</td>
</tr>
<tr>
<td>5 DH</td>
<td>W</td>
<td>M</td>
<td>5</td>
<td>Yes</td>
<td>LTGA</td>
<td>2 wks</td>
<td>76</td>
<td>150</td>
<td>0.08</td>
<td>None</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>6 TJ</td>
<td>W</td>
<td>F</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>6 wks</td>
<td>45</td>
<td>95</td>
<td>0.04</td>
<td>2:1 block, 6 wks.</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>7 DL</td>
<td>W</td>
<td>F</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>6 wks</td>
<td>48</td>
<td>80</td>
<td>0.06</td>
<td>None</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>8 WH</td>
<td>W</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>2 yrs</td>
<td>50</td>
<td>80</td>
<td>0.05</td>
<td>None</td>
<td>No symptoms.</td>
</tr>
</tbody>
</table>

* Died, 1 day.

Abbreviations: CF = cardiac failure; EFE = endocardial fibroelastosis; LTGA = left transposition of great arteries; MI = mitral insufficiency; PDA = patent ductus arteriosus; PVCs = premature; VSD = ventricular septal defect; SC = sickle cell.
normalities may be at increased risk for congenital complete heart block.

Pathology

During fetal development the A-V node and the His bundle originate as separate structures and later join together. Previous authors have explained congenital complete heart block as a failure to develop a connection between the A-V node and His bundle. The heart is well-formed and the sinus node can be found by the sixth to eighth week of age in the fetus. We feel there may be damage to the conduction system of great importance later in pregnancy. Pathologic changes in the A-V node or the bundle of His in patients with congenital complete heart block have been demonstrated in selected necropsy specimens by James, Lev, and Sotelo-Avila.

Lev's detailed pathologic studies on specimens from seven cases of fatal congenital heart block by serial sections of the conduction system revealed that in three the A-V node was absent, in three it was present but "in a sea of dense connective tissue," and in one case only a fragment of tissue was present which was difficult to recognize as node or bundle. Hypertrophy and fibroelastosis were striking and all seven cases had in common a lack of or diminished connection between the atrial musculature and the A-V node.

Lupus erythematosus in the adult affects the heart, especially the collagen framework around the SA and A-V nodes, causes endocarditis, pericarditis, arteritis, and arrhythmias. Moffitt and Becker have reported heart block in adults with systemic lupus erythematosus also. In eight adults with lupus erythematosus who had arrhythmias, James found cystic degeneration of collagen around the SA node. Bharati et al. reported a 12-year-old girl with lupus and heart block whose A-V and SA nodes had been replaced by granulation tissue. Similar pathology has been found in adults with rheumatoid arthritis. Although the studies came from different institutions and different populations, all have in common the damage and replacement of conduction tissues by connective tissue, a finding similar to the pathology reported by Lev in cases of congenital complete heart block.

Placental Transmission

The effect of maternal lupus on the infant's heart may be significant. Both the LE factor and antinative DNA are IgG antibodies which may pass the placental barrier. Placental transmission of an abnormal IgG, including the LE factor and antinuclear antibodies, has been verified in the sera of many infants born to mothers with lupus erythematosus, although overt disease in the infant is rare. In 1976 Vonderheur described four infants with neonatal lupus manifested by discoid skin lesions whose mothers had systemic lupus, and a search of the literature disclosed 11 similar case reports. In many of these, placental transfer of antibodies was verified. The rash usually disappeared in a few months without further evidence of disease in the infant. Case 2, in group A-1, is an example of such transplacental passage. Initially her ANA was positive at 1:200 and her C4 depressed; by four months of age, however, both were normal. Other antibodies against platelets, leukocytes, or even red cells may also cross the placenta, and newborns of mothers with such antibodies have been occasionally reported with thrombocytopenia, anemia, and leukopenia.

In view of the increased prevalence of systemic lupus among mothers of children with congenital complete heart block.
block, and the similarity of pathologic changes in the collagen surrounding the conduction tissue in both systemic lupus and congenital complete heart block, transplacental transfer of an abnormal antibody from a mother with systemic lupus might play a pathogenetic role in the development of complete heart block in her infant.

Similar Cases Previously Reported

A review of the literature has revealed five case reports of congenital complete heart block in infants of mothers with lupus erythematosus. The relationship was recognized in 1966 by Hull who described a mother with active lupus, two of whose children were normal, one had skin lupus, and one died at 25 minutes of age with congenital heart block. The necropsy on Hull’s infant and that performed on a similar patient of Hoge disclosed marked collagen destruction and fibroelastosis. Both of these mothers were ill during pregnancy and under treatment. Three siblings with congenital heart block, born to a mother who died of lupus erythematosus, were reported by Wright et al. and Plant et al. Although the authors emphasized the pathologically diffuse endocardial fibroelastosis they did not appreciate the connection with maternal lupus.

Electrocardiographic Variations and Fibrosis

One of the authors (MEM) recognized that the electrocardiographic patterns in our children changed transiently, usually early in life but on some occasions at a later age, findings that are consistent with a diffuse pathologic process that is frequently progressive in the endocardium and myocardium surrounding the conduction system (fig. 2A, B, C). Levy, by careful monitoring of 20 patients with congenital complete heart block, found varying arrhythmias, including high atrial rates, exit block, and varying R-R intervals. This diversity might reflect the varied pathology in the endocardium surrounding the conduction pathways. James, in his recent report of late onset of congenital complete heart block in a 30-year-old patient emphasizes the dynamic nature of this pathologic process. Disruptive fibrosis may progress within the His bundle for many years. It is not surprising that the electrocardiographic conduction abnormalities vary with time. Necropsy studies of patients with complete heart block by Levy, Bharati, James, Becker, Hoge, Hull, and Sotelo-Avila have all recorded necrosis and fibrosis in the endocardium and myocardium as well as in the conduction system.

Conclusion

This clinical study suggests an increased risk of congenital complete heart block in children born to mothers with systemic lupus erythematosus, whether overt or detected only by serologic abnormalities; the extent of the increased risk cannot be estimated from these data. Only a prospective study of such mothers’ pregnancies will afford such an estimate. Meanwhile, a careful scrutiny of the mother for both clinical and laboratory evidence of connective tissue disease, especially lupus erythematosus, is strongly indicated if the infant has congenital heart block.

Acknowledgments

The authors express appreciation to Dr. H. P. Mauck, Jr., and Dr. Louise Robertson, who contributed catherization data, and to many referring physicians who assisted in the recall of the mothers. Dr. Kenneth Blaylock and Dr. Edward Abell assisted with a valuable dermatologic consultation and the biopsy. Dr. Marion Waller and Mrs. Nellie Curry were very helpful in the laboratory studies. Dr. Peter Schur checked many of the antinuclear antibody tests. Mrs. Carol Nance’s editorial suggestions and Miss Joanna Woodward’s secretarial assistance were appreciated.

References

CONGENITALLY COMPLETE HEART BLOCK results from failure of communication between the atrial and ventricular myocardial tissues as a consequence of lack of continuity of the atrioventricular conducting system across the fibrous atrioventricular anulus. It has been argued that, in an otherwise normal heart, such lack of continuity can either result from post-formative disruption of a normally developed conducting system or failure of fusion during development of parts of the conducting system derived from different embryological sources. Histopathological studies of congenital heart block, as reported in a recent review article, tend to support the latter concept, particularly since the studies of Lev and his colleagues have shown that there are two basic divisions of the dysrhythmia.

The first is that in which the atrial myocardial tissues fail to contact the compact atrioventricular node. The second group comprises those hearts in which a normally formed atrioventricular node is separated by fibrous tissue from the ventricular conducting tissues and myocardium. We recently examined an example of the first variety of complete heart block and suggested that such hearts were indeed best explained on the basis of interposition of fibrous tissue septa between differing embryological components of the specialized junctional tissues. We espoused a similar explanation for the second type of block, but at that time we were unable to explain why fibrous tissue should form between the different components of the node and bundle. We have now studied three further cases of congenitally complete heart block, and in the light of the findings in these hearts we have re-examined the embryological material at our disposal. We believe that our findings endorse the hypothesis of nodal development previously advanced and show why fibrous tissue can form between the different conducting tissue components and thus produce congenitally complete heart block. At the same time our findings provide information regarding the development of the central fibrous body relative to the atrioventricular node and penetrating atrioventricular bundle of the normal heart.

SUMMARY Three cases of congenitally complete heart block are described in hearts in which other minor congenital malformations were not in themselves severe enough to disrupt the atrioventricular conduction system. The cases fitted well into the categorization of complete heart block suggested by Lev. Two exhibited lack of communication between the atrial and conducting tissues, the other had discontinuity of the penetrating atrioventricular bundle. In an attempt to explain why this discontinuity between different segments of the conducting tissues occurs, we re-examined several series of graded human embryos. This investigation suggested that the anulus fibrosus in the normal heart is derived from sulcus tissue of the atrioventricular junction, the endocardial atrioventricular cushions playing a minor role in the separation of atria from ventricles. The relationships between the sulcus tissues and the different components of the atrioventricular junctional area are discussed in terms of an explanation both for the existence of different types of congenitally complete heart block and for persistence of Mahaim (nodo-ventricular and nodo-fascicular) fibers.

From the Departments of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London, England; Anatomy, State University of Leiden; Paediatrics, Binnen Gasthuis, University of Amsterdam; and Pathology, Wilhelmina Gasthuis, University of Amsterdam, The Netherlands.

Dr. Anderson was a Medical Research Council Travelling Fellow, U.K., during the course of this investigation. He is now a British Heart Foundation Senior Research Fellow.

Address for reprints: Dr. Anton E. Becker, Department of Pathology, Wilhelmina Gasthuis, Eerste Helmerstraat 104, Amsterdam, The Netherlands.

Received December 7, 1976; revision accepted February 14, 1977.
Congenital heart block in newborns of mothers with connective tissue disease.
C M McCue, M E Mantakas, J B Tingelstad and S Ruddy

_Circulation_. 1977;56:82-90
doi: 10.1161/01.CIR.56.1.82

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/56/1/82

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/