Unusual Evolution of Acquired Infundibular Stenosis in Patients with Ventricular Septal Defect

Clinical and Morphologic Observations

By Barry J. Maron, M.D., Victor J. Ferrans, M.D., Ph.D., and Robert I. White, Jr., M.D.

SUMMARY

Hemodynamic and cardiac morphologic observations were made on two patients with ventricular septal defect who showed unusual evolution of obstruction to right ventricular outflow. Both patients developed progressive infundibular stenosis, one in the presence of a spontaneously closing ventricular septal defect and the other after operative closure of the defect. Light and electron microscopic examination of resected infundibular muscle revealed hypertrophy and abnormal shapes and arrangements of cardiac muscle cells. These abnormalities resembled those found in left ventricular outflow tract muscle of patients with idiopathic hypertrophic subaortic stenosis. It is suggested that the patterns of distribution and growth of these abnormal cells in the right ventricular outflow tract may lead to localized hypertrophy and to development of progressive infundibular obstruction in some patients with ventricular septal defect.

Additional Indexing Words:
Ultrastructure  Congenital heart disease

The natural history of ventricular septal defect may involve evolution into Eisenmenger's syndrome,1 spontaneous closure,2,3 infective endocarditis,4 or development of infundibular stenosis with persistence of the ventricular septal defect, leading to an acquired type of tetralogy of Fallot.5 A less well appreciated course in the natural history of ventricular septal defect is the development of infundibular stenosis in association with partial or complete closure of the septal defect.6-8 We have recently seen two children with ventricular septal defect who developed infundibular stenosis, one in the presence of a spontaneously closing ventricular septal defect and the other after operative closure of the defect. In this investigation, light and electron microscopic studies of resected infundibular muscle from these patients were performed to define the structural changes associated with this unusual evolution of infundibular obstruction.

Report of Patients

W.H. was a five pound boy born of a normal term pregnancy and delivery. There was no familial history of congenital heart disease. Clinical findings at five days of age were consistent with a large ventricular septal defect and congestive heart failure. Physical examination revealed a grade 2/6 harsh pansystolic murmur at the lower left sternal border and an apical mid-diastolic flow rumble. Chest radiograph demonstrated cardiomegaly and increased pulmonary vascular markings. Electrocardiogram (ECG) was interpreted as normal. The patient was treated with digoxin and was hospitalized from four to fourteen months of age at a residential treatment hospital. During this time he continued to have mild cardiac failure and frequent respiratory infections. The patient was first seen at the Johns Hopkins Hospital at 15 months of age. At this time cardiac catheterization and angiocardiography demonstrated a defect in the membranous portion of the ventricles septum with a pulmonary-to-systemic flow ratio of 2.6:1 and moderate pulmonary hypertension (table 1). No pressure gradient was present between the right ventricle and pulmonary artery.

Because of cardiac failure, poor growth and recurrent upper respiratory infections, operation was performed at 23 months of age. A large defect in the membranous portion of the ventricular septum was closed with a patch. The crista supraventricularis did not appear to be hypertrophied.
Table 1

Serial Hemodynamic Data in Two Patients with Acquired Infundibular Stenosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>RV body</th>
<th>RV outflow</th>
<th>PA</th>
<th>PSG</th>
<th>LV</th>
<th>Ao</th>
<th>SAO₂(%)</th>
<th>TPR (P.R.U.)</th>
<th>R₁ : Rₗ</th>
<th>Qₗ : Qₘ</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.H.</td>
<td>1.3</td>
<td>68/5</td>
<td>68/5</td>
<td>68/27</td>
<td>0</td>
<td>—</td>
<td>96/68</td>
<td>98</td>
<td>2.2</td>
<td>0.22</td>
<td>2.6:1</td>
</tr>
<tr>
<td>1.9</td>
<td>55/5</td>
<td>30/3</td>
<td>30/10</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>97/71</td>
<td>—</td>
<td>3.6</td>
<td>0.16</td>
<td>1:1*</td>
</tr>
<tr>
<td>2.1</td>
<td>107/10</td>
<td>24/7</td>
<td>24/7</td>
<td>83</td>
<td>120/0-2</td>
<td>120/87</td>
<td>98</td>
<td>3.4</td>
<td>0.21</td>
<td>1:1*</td>
<td></td>
</tr>
<tr>
<td>7.0</td>
<td>47/3</td>
<td>47/3</td>
<td>30/6</td>
<td>17</td>
<td>—</td>
<td>—</td>
<td>90/45</td>
<td>96</td>
<td>2.3</td>
<td>0.16</td>
<td>1:1</td>
</tr>
<tr>
<td>R.B.</td>
<td>0.1</td>
<td>42/5</td>
<td>42/5</td>
<td>30/8</td>
<td>12</td>
<td>80/0-8</td>
<td>80/40</td>
<td>95</td>
<td>4.2</td>
<td>0.10</td>
<td>2.3:1</td>
</tr>
<tr>
<td>4.1</td>
<td>136/4</td>
<td>12/4</td>
<td>11/4</td>
<td>125</td>
<td>90/0-6</td>
<td>96/53</td>
<td>96</td>
<td>3.0</td>
<td>0.10</td>
<td>1:1*</td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>26/4</td>
<td>26/4</td>
<td>22/11</td>
<td>4</td>
<td>83/0-7</td>
<td>88/47</td>
<td>94</td>
<td>1.6</td>
<td>0.08</td>
<td>1:1*</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RV = right ventricular pressure; PA = pulmonary arterial pressure; PSG = peak systolic gradient; LV = left ventricular pressure; Ao = aortic root; SA O₂ = systemic arterial oxygen saturation; TPR = total pulmonary resistance; P.R.U. = pulmonary resistance units; R₁ : Rₗ = pulmonary-to-systemic resistance ratio; Qₗ : Qₘ = pulmonary-to-systemic flow ratio (calculated using the Fick principle); ( ) = mean pressures.

*Small left-to-right shunt demonstrated on an indicator dye dilution curve obtained by injection in the left ventricle and sampling in the pulmonary artery.

†Small ventricular septal defect seen as faint trace of contrast material on left ventricular cineangiogram.

Two months after operation a second cardiac catheterization (table 1) was performed because of persistent cardiomegaly (cardiothoracic ratio 0.63) and a grade 3/6 systolic ejection murmur at the lower left sternal border. A tiny left-to-right shunt was demonstrated only by left ventricular angiocardiogram, which showed a faint wisp of contrast material passing into the right ventricle. A 25 mm Hg peak systolic gradient (PSG) was present between the right ventricular body and infundibulum.

The patient was lost to follow-up until he was examined at six and one-half years of age, when he was considered to have a lesion producing severe right ventricular outflow obstruction. Physical examination disclosed a prominent right ventricular impulse, a grade 3/6 systolic ejection murmur at the lower left sternal border and a decrease in intensity of the pulmonic closure sound. The chest radiograph showed normal heart size and pulmonary vascularity, and prominence of the main pulmonary artery segment. ECG demonstrated right bundle branch block, which resulted from the right ventriculotomy at the time of closure of the ventricular septal defect. A third cardiac catheterization documented systemic pressure in the right ventricle and a PSG of 83 mm Hg between the right ventricular body and infundibulum (table 1). Right ventricular angiocardiogram demonstrated severe, localized narrowing of the right ventricular outflow tract (fig. 1). A very small left-to-right shunt was demonstrated on an indicator.

Figure 1

Lateral view of right ventricular angiocardiogram from patient W.H., 4½ years after closure of a large ventricular septal defect. There is a marked, localized narrowing of the right ventricular outflow tract (arrow) and prominent trabeculations in the right ventricular wall.
dye dilution curve obtained by injection in the left ventricle and sampling in the pulmonary artery. No systolic pressure gradient was present between the left ventricle and ascending aorta. Attempts were not made to provoke left ventricular outflow tract obstruction by the administration of isoproterenol or the Valsalva maneuver. At operation (performed by Dr. Robert Brawley) six months later, greatly hypertrophied and trabeculated muscle of the crista supraventricularis was resected. The site of the ventricular septal defect appeared to be completely closed. No anomalous muscle bands or bundles were present and the pulmonic valve appeared normal. A pericardial patch was used to close the ventriculotomy and to avoid compromising the right ventricular infundibulum.

One year after operation, the patient was asymptomatic. A grade 2/6 systolic ejection murmur was present along the left sternal border and the second heart sound was normal. Cardiac catheterization showed a 17 mm Hg pressure gradient across the right ventricular outflow tract. No ventricular septal defect was demonstrated by angiography or dye dilution curves.

R.B. was a five pound girl born of a normal pregnancy and delivery. There was no familial history of congenital heart disease. Clinical findings at one month of age were consistent with a large ventricular septal defect and congestive heart failure. Physical examination revealed a prominent right ventricular impulse, a harsh grade 3/6 pansystolic murmur at the lower left sternal border, an apical mid-diastolic flow rumble, and a third heart sound gallop rhythm. Chest radiograph showed cardiomegaly and increased pulmonary vascular markings (fig. 2A). ECG revealed combined ventricular hypertrophy. Cardiac catheterization and selective angiography demonstrated an infracristal defect in the membranous portion of the ventricular septum and a pulmonary-to-systemic flow ratio of 2.3:1 (table 1). Pulmonary arterial pressure was 50/8 mm Hg and a 12 mm Hg PSG was present between the right ventricle and pulmonary artery. This gradient was attributed to increased pulmonary blood flow. Right ventricular angiography showed no abnormalities of the outflow tract. The aortic arch was on the right; there was an anomalous right subclavian artery which arose from the descending aorta. The patient was treated with digoxin and was subsequently lost to follow-up for the next four years.

When examined again at four years of age, the child was asymptomatic, but the clinical findings were distinctly different. A harsh, grade 3/6 systolic ejection murmur was present at the second left intercostal space and the pulmonary component of the second heart sound was diminished in intensity. The chest radiograph was normal (fig. 2B). ECG revealed right ventricular and right atrial hypertrophy. A second cardiac catheterization demonstrated suprasystemic right ventricular pressure with a PSG of 125 mm Hg across the right ventricular outflow tract (table 1). A very small left-to-right ventricular shunt was demonstrated on an indicator dye dilution curve obtained by injection in the left ventricle and sampling in the pulmonary artery. Right ventricular angiogram showed severe hypertrophy of the crista supraventricularis, with discrete infundibular narrowing, and a small aneurysm in the membranous portion of the ventricular septum. No systolic pressure gradient was present between the left ventricle and the ascending aorta. Provocation of left ventricular outflow tract obstruction with isoproterenol administration or Valsalva maneuver was not attempted; there was an increase in systemic pulse pressure after premature ventricular beats, which was considered to be a normal response.

At operation (performed by Dr. James Donahoo), the infundibular obstruction appeared to be due to a hypertrophied crista supraventricularis which was covered with fibrous tissue. Several hypertrophied muscular bands, which probably contributed to the obstruction, also were present in the right ventricle. These structures, however, did not appear to be anomalous muscle bundles. The pulmonic valve was normal. Portions of the fibromuscular tissue and muscular bands were excised. A tiny (2 mm in diameter) defect in the membranous portion of the ventricular septum was closed with a single suture.

One year after operation, the patient was asymptomatic. A grade 2/6 systolic ejection murmur was present along the left sternal border and the second heart sound was normal. Cardiac catheterization demonstrated a 4 mm Hg pressure gradient across the right ventricular outflow tract. A small left-to-right ventricular shunt was detected by indicator dye dilution curves, and a small aneurysm of the ventricular septum was shown by left ventricular angiogram.

Materials and Methods

Resected infundibular muscle from patient W.H. was fixed in 10% formalin and embedded in paraffin. Sections were cut at 8 μ thickness and stained with hematoxylin and eosin. Specimens of resected infundibular muscle from patient R.B. were immediately fixed in 3% phosphate-buffered glutaraldehyde, post-fixed in osmium tetroxide and embedded in Maraglas.9 Semithin (0.5 μ thick) sections were stained with alkaline toluidine blue. Measurements of transverse cell diameters were made with a calibrated micrometer eyepiece. Ultrathin sections were cut with uranyl acetate and lead citrate10 and viewed with an RCA EMU-3G electron microscope.

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**Figure 2**

Posteroanterior chest radiographs of patient R.B. (Top) At one month of age showing cardiomegaly and increased pulmonary vascularity. The aortic arch is on the right. (Bottom) At 4 years of age; pulmonary vascularity has decreased, but heart size remains enlarged and unchanged from previous radiograph.

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Morphologic Observations

Histologic study of infundibular muscle from patient W.H. showed muscle cells to be hypertrophied with transverse diameters of 20 to 40 μ (normal, 10-15 μ). The endocardium showed mild thickening by fibrous tissue. Marked disorientation of muscle cells and myofibrils was present in many areas, with myofibrils often forming cross-weaving patterns (fig. 3). For purposes of comparison, a light micrograph of representative infundibular muscle from a patient with typical tetralogy of Fallot is shown in figure 4.

Light and electron microscopic study of resected muscle from the right ventricular outflow tract of patient R.B. showed moderately hypertrophied cells with transverse diameters of 18 to 30 μ. Many areas showed disorientation in the arrangement of muscle cells, with adjacent cells oriented obliquely to each other (figs. 5-8). These changes in the myocardium of patient R.B. were less pronounced than the disorientation of muscle cells present in patient W.H. Within myocardial cells, alignment of myofibrils and myofilaments was normal. Cells were often joined by...
INFUNDIBULAR STENOSIS WITH VSD

Figure 4

Semitthin section of part of the right ventricular outflow tract of a 12 year old female with typical tetralogy of Fallot. Cardiac muscle cells are mildly hypertrophied, have regular rectangular shapes in longitudinal section, and are oriented parallel to each other. (Alkaline toluidine blue stain, × 400.)

Discussion

The clinical courses of the two patients described in this report are distinctly different from those of children with large ventricular septal defects who develop progressive hypertrophy of the crista supraventricularis, without closure of the defect, and become clinically indistinguishable from patients with tetralogy of Fallot. The development of progressive infundibular stenosis in association with partial or complete closure of a ventricular septal defect is a rare phenomenon which has been described only in six other patients (table 2). These six patients and the two reported in this communication had the following features in common: 1) congestive heart failure in infancy associated with clinical and hemodynamic evidence of a large ventricular septal defect; 2) subsequent evolution of this clinical picture into that of obstruction to right ventricular outflow, without the appearance of cyanosis, as the ventricular septal defect closed either partially or completely; 3) infracristal localization of the defect in the membranous portion of the ventricular septum; and 4) localization of obstruction at the level of the crista supraventricularis.

The clinical courses of the six patients previously reported are similar to that of our patient R.B. Patient W.H., however, had a different course in that his ventricular septal defect was operatively closed before infundibular stenosis developed. The exact sequence of events in B.B. and the six patients cited from the literature is not known because significant periods of time (three to nine years) passed between serial hemodynamic measurements. Therefore, it is not possible to determine definitely...
whether spontaneous closure of the ventricular septal defect preceded, paralleled or followed the development of infundibular stenosis in these patients. The latter possibility appears unlikely, however, because cyanosis was not observed in either of our two patients or the six patients reported in the literature. The three patients of Jain, Subramanian and Lambert may differ from the other patients in that the obstructing lesions were considered fibromuscular in two patients and fibrous in one. In the other three patients in whom a description of the right ventricular outflow tract was given (our two patients and that of Watson et al.) massive hypertrophy of the crista supraventricularis was responsible for the infundibular obstruction. Since fibrous, thickened endocardium is commonly found overlying a hypertrophied crista supraventricularis it is difficult to determine the relative importance of muscular and fibrous components in the obstructive lesions reported by Jain, Subramanian and Lambert.

It has been suggested that increased blood flow and pressure in the right ventricular outflow tract acts as the initial stimulus for hypertrophy of the crista supraventricularis in patients with ventricular septal defect and markedly increased pulmonary blood flow. This mechanism may have been involved in seven (patient R.B. and the six patients in the literature) of the eight cases reviewed above. In the remaining patient (W.H.) infundibular stenosis developed after operative closure of the ventricular septal defect and, therefore, could not have been influenced by increased pulmonary blood flow.

A different hypothesis was presented by Grant, Downey and MacMahon, who believed that infundibular stenosis was a basic part of the growth abnormality in ventricular septal defects rather than a secondary adaptation of the heart to the abnormal hemodynamics of a left-to-right-shunt. They suggested that infundibular stenosis was the consequence of a distinctive and complex type of hypertrophy involving the bulbar musculature, but did not describe in detail the anatomic features of this type of hypertrophy. Grant’s concept was based primarily on gross dissections of hearts, which precludes a direct comparison of his data with ours.

Abnormal orientation of muscle cells was the prominent morphologic feature of resected right ventricular outflow tract muscle in our two patients. Patient W.H., in particular, showed severe mal-orientation of myofibrils and muscle cells. In our experience, this combination of abnormalities is rarely found in myocardial hypertrophy due to causes other than idiopathic hypertrophic subaortic stenosis (IHSS). In an ultrastructural study of ventricular septum obtained at operation from 14 patients with IHSS, Ferrans, Morrow and Roberts found disorganization in the arrangement of muscle cells, myofibrils and myofilaments to be the consistent pathologic abnormality; muscle cells were often extremely large, and demonstrated bizarre irregularities in shape.

We have observed only minimal, focal abnormalities of myofibrillar orientation in right ventricular outflow tract from five to 26 patients with tetralogy of Fallot (unpublished observations). Furthermore, abnormalities in muscle cell and myofibrillar orientation have not been noted in right ventricular anomalous muscle bundles.
Figure 6

Low power electron micrograph of muscle from right ventricular outflow tract in patient R.B. Cardiac muscle cell in the center with bizarre shape and prominent cytoplasmic processes is surrounded by parts of seven other cells. Insert at lower right diagrammatically outlines the cellular boundaries; sarcolemma is shown as solid lines and intercellular junctions as dotted lines. (x7,500.)
Figure 7
Low power electron micrograph of right ventricular outflow tract muscle of patient R.B. shows irregularly shaped cardiac muscle cell surrounded by parts of five other cells. Insert at lower left diagrammatically outlines the cellular boundaries; areas of sarcolemma are shown as solid lines and intercellular junctions as dotted lines. Note T tubules (T). (×8,300.)
Figure 8

Right ventricular outflow tract muscle of patient R.B. Parts of three cardiac muscle cells, two of which are joined by an extensive side-to-side intercellular junction (arrowheads). Note divergence of myofibrillar orientation between cell at the bottom and the two cells above. Thickened Z bands (Z) are present. (×10,500.)
Table 2

Clinical Hemodynamic, and Operative Data in 6 Previously Reported Patients with Spontaneously Closing Ventricular Septal Defect and Developing Infundibular Stenosis

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical diagnosis</th>
<th>Catherization data (pressures in mm Hg)</th>
<th>Operative findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RV PA PSG Qs-Qr</td>
<td></td>
</tr>
<tr>
<td>1*</td>
<td>M</td>
<td>9 wks</td>
<td>VSD, CHF</td>
<td>40/0 40/15 0</td>
<td>VSD only a few mm in diameter;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>moderately severe IS</td>
</tr>
<tr>
<td>2*</td>
<td>M</td>
<td>3½ yrs</td>
<td>IS</td>
<td>180/8</td>
<td>Severe IS, VSD closed by fibrous tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infancy</td>
<td>VSD, CHF</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3*</td>
<td>M</td>
<td>8 months</td>
<td>VSD, CHF</td>
<td>58/6 43/8 15</td>
<td>Massive hypertrophy of CSV;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VSD closed by fibrous tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4*</td>
<td>F</td>
<td>8 yrs</td>
<td>IS, small VSD</td>
<td>92/4 20/8 72*</td>
<td>Fibromuscular ring at level of CSV;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tiny VSD</td>
</tr>
<tr>
<td>5*</td>
<td>F</td>
<td>9 wks</td>
<td>VSD, CHF</td>
<td>55/8 50/8 5</td>
<td>Fibromuscular stenosis at level of CVS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6*</td>
<td>M</td>
<td>3 months</td>
<td>VSD</td>
<td>100/5 18/9 82</td>
<td>VSD 2 mm in diameter</td>
</tr>
<tr>
<td>7*</td>
<td>M</td>
<td>9 yrs</td>
<td>IS, small VSD</td>
<td>55/8 50/8 5</td>
<td>Fibrous obstruction at level of CVS</td>
</tr>
</tbody>
</table>

Abbreviations: RV = right ventricle; PA = pulmonary artery; PSG = peak systolic gradient; Qs-Qr = pulmonary-to-systemic flow ratio; VSD = ventricular septal defect; CHF = congestive heart failure; IS = infundibular stenosis; CVS = crista supraventricular.

*Small left-to-right shunt evident on an indicator dye dilution curve obtained by injection in the left ventricle and sampling in the pulmonary artery.
†Ventricular septal defect demonstrated as a small jet of contrast material on left ventricular angiogram; administration of isoproterenol to this patient caused right ventricular pressure to increase to 180/0 without change in systemic arterial pressure.
‡Pulmonary arterial pressure reported as "close to systemic."

The etiology of malorientation of cardiac muscle cells is not known. It has been postulated that a fundamental error in cardiac morphogenesis is the most probable explanation for the presence of these abnormalities in patients with IHSS and that a manifestation of an advanced stage of cardiac hypertrophy is a less likely possibility.15

Similarities between our two patients with acquired infundibular stenosis and patients with IHSS include: 1) outflow tract obstruction; 2) disproportionate hypertrophy of part of the heart; and 3) alterations in the arrangement of cardiac muscle cells. We believe that these similarities are expressions of the presence of abnormal muscle cells localized in specific parts of the heart. Although definitive proof is lacking, our studies suggest that these abnormal myocardial cells in the right ventricular outflow tract may be responsible for the development of progressive infundibular stenosis in some patients with ventricular septal defects.

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