Cardiac Manifestations of Marfan Syndrome in Infancy and Childhood

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SUMMARY

The clinical profile and course of 36 infants and children with Marfan syndrome is reviewed. Cardiac abnormalities were present in 61% of the patients and were the major cause of death. Mitral regurgitation, the most frequently encountered cardiac lesion (47%), occurred in both males and females, while aortic regurgitation was present only in males. Arrhythmias were observed in four patients, and congenital heart disease (atrial septal defect) was observed in one. A distinguishing auscultatory feature was an apical mid or late systolic murmur preceded by single or multiple clicks. A characteristic electrocardiographic pattern of S-T segment and T-wave changes in leads II, III, aVF, and left precordial leads was noted in 11 patients. The prognosis of children with Marfan syndrome and isolated mitral regurgitation was usually good, whereas patients with combined mitral and aortic regurgitation had a rapidly deteriorating clinical course. The overall mortality in the group was 14%.

Additional Indexing Words:
Mitril regurgitation
Aortic regurgitation
Electrocardiographic patterns
Mid–late systolic murmur

CARDIAC abnormalities, especially aneurysms of the ascending aorta and aortic regurgitation, have been recognized for decades as cardinal manifestations of Marfan syndrome in the adult. Associated congenital heart disease, lesions of the mitral valve, and pulmonary artery, and arrhythmias have been less frequently reported. The clinical and hemodynamic cardiac findings in childhood Marfan syndrome have been limited to selected case reports of the more severe complications resulting from the disease.

This paper reviews our entire experience with Marfan syndrome at The Children’s Hospital Medical Center, Boston, between 1945 and 1970. The cardiac manifestations, course, and prognosis of the syndrome in childhood are presented.

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Supported in part by the U.S. Public Health Service Grant HE 10436-04 from the National Institutes of Health, Bethesda, Maryland, and a Grant-in-Aid from the American Heart Association, New York, New York.

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Received August 22, 1972; revision accepted for publication November 9, 1972.
Results

Diagnosis of Marfan Syndrome

The diagnosis of Marfan syndrome was established in 36 patients (20 females and 16 males). The median age at the initial diagnosis was 6 8/12 years (range: birth–15 10/12 years). The diagnosis was made twice in infancy; once at birth (because of congenital dislocation of the hips) and in the other at 3 months of age (because of a dislocated lens). Twenty-six cases (72%) were diagnosed before the age of 10 years (fig. 1).

Eye defects (subluxation of the lens, myopia) were present in 27 patients (75%) and severe kyphoscoliosis in 19 (53%). The extracardiac features resulted in the initial diagnosis of Marfan syndrome in 31 (86%) of the patients. In only five patients (14%) did the cardiac evaluation lead to the initial diagnosis of Marfan syndrome; of these, two had mitral regurgitation, one paroxysmal atrial tachycardia, and two no significant heart disease (NSHD).

Diagnosis and Distribution of Cardiac Lesions

Fourteen patients (39%) of the total group had no significant heart disease; they had only a grade 1–2/6 physiologic systolic ejection murmur with normal chest X-ray and electrocardiogram when last examined. Valvar lesions were present in 21 patients and included mitral regurgitation (MR) in 17, pure aortic regurgitation (AR) in one, and combined MR and AR in three. One patient had attacks of paroxysmal atrial tachycardia without other clinical evidence of cardiovascular disease.

The distribution of valvar lesions, according to sex, revealed that of the 20 females, 12 had MR and none had AR. Of the 16 male patients, five had MR, one AR, and three both AR and MR (fig. 2).

Dilatation of the ascending aorta was recognized on plain chest X-rays or angiograms in all three patients with combined MR and AR, four of the patients with pure MR, and in three patients without significant valvar lesions. In the patient with isolated AR, the aortic dilatation could not be appreciated on plain chest X-ray. A dissecting aneurysm of the ascending aorta occurred in one patient with MR and AR. None of the patients had a history of rheumatic fever and only one had congenital heart disease (atrial septal defect).

Cardiac involvement was noted on the initial visit in 15 patients. Six patients developed cardiovascular lesions during the follow-up period. The age at which the initial diagnosis of MR was made ranged from 3 months to 15 8/12 years with a median of 6% years. The patient with isolated AR was diagnosed at 2 8/12 years. Of the three patients with combined MR and AR, one developed AR at 6 6/12 years and MR at 9 8/12; a second patient developed AR and MR between 11 and 16 years of age; the third developed MR at 4 7/12 years and AR associated with a dissecting aortic aneurysm at 19 6/12 years.

Symptoms and Physical Findings

Most patients were asymptomatic throughout the follow-up period. Symptoms and cardiac abnormalities noted on physical examination were related to the type and severity of the cardiac lesion.

Mitral Regurgitation. There were only three (18%) symptomatic patients among 17 with pure MR. One, with severe MR, developed congestive cardiac failure at the age of 9 months and died with severe pulmonary infection. Another, also with moderately severe MR, developed atrial fibrillation at 14 5/12 years and the third patient had recurrent palpitation for 2 years, but no arrhythmia could be documented.

All the patients had a grade 2/6 or louder, apical, mid-to-late systolic murmur. An apical pansystolic regurgitant murmur with late systolic accentuation was noted in three patients. Single or multiple mid-systolic clicks often preceding the apical systolic murmur occurred in 12 patients. A third heart

Figure 1
Cumulative distribution by age at initial diagnosis of Marfan syndrome (A) and heart disease (B) in 36 patients.
Figure 2

Distribution of cardiac valvar lesions by sex in 36 patients with Marfan syndrome. Note the absence of aortic regurgitation in girls with Marfan syndrome.

sound was heard in four patients. An apical middiastolic rumble was audible in one patient with severe MR. The auscultatory findings were confirmed by phonocardiography in 14 patients (fig. 3).

Figure 3

Phonocardiogram in a patient with mild mitral regurgitation. Note the late systolic murmur (SM) and clicks (X).

Circulation, Volume XLVII, March 1973
Aortic Regurgitation. Isolated aortic regurgitation was diagnosed in only one child. He was asymptomatic when seen at 2 8/12 years and did not return for follow-up. On examination the heart sounds were normal but he had a grade 3/6 blowing diastolic murmur at the lower left sternal border.

Combined Mitral and Aortic Regurgitation. All three patients with combined AR and MR were symptomatic with progressive exercise intolerance and fatigue. The cardiac auscultatory findings were those of moderate-to-severe MR and AR. A third heart sound was present in all three patients and one had a fourth heart sound as well.

One patient eventually developed acute pulmonary edema at 16 5/12 years and died immediately after mitral and aortic valve replacement. Another patient died suddenly at home at the age of 11 years. The cause of death could not be established. The third patient developed dissection of an aortic aneurysm at age 19 6/12 years and died in the immediate postoperative period.

Abnormalities of the Great Arteries. Dilatation of the ascending aorta was noted in all patients with combined MR and AR, four patients with pure MR, and three patients with NSHD. In the only patient with pure AR, dilatation of the aorta could not be appreciated on plain chest X-rays.

The pulmonary artery appeared prominent in three asymptomatic patients in the absence of clinical evidence of pulmonary artery hypertension, regurgitation, or a left-to-right shunt.

Arrhythmias. There were four patients with arrhythmias. Two had atrial arrhythmias, one had paroxysmal atrial tachycardia with NSHD, and in the other atrial fibrillation complicated moderately severe mitral regurgitation. Two patients had multifocal premature ventricular beats. Symptoms were related to the severity of the associated heart disease or the arrhythmia.

Congenital Heart Disease. The diagnosis of an atrial septal defect was confirmed by cardiac catheterization in one patient. The lesion was associated with mild MR. This patient was asymptomatic during the follow-up period. Pertinent cardiovascular physical findings included a widely split fixed second sound, a grade 2/6 systolic ejection murmur at the left upper sternal border, and a mid systolic murmur of mitral regurgitation at the apex.

Growth Pattern. The growth pattern of children with Marfan syndrome is often that of accelerated rate of maturation for height and average or retarded maturation for weight.10 In four of 16 males and two of 17 females, there was a delay (>1 sp from the mean) in height maturation; all of these had associated severe valvar heart disease, severe scoliosis, or both. Among the seven patients with the poorest weight gain (>2 sp), six had severe heart disease and one severe scoliosis. In the absence of severe scoliosis the presence of retarded growth in children or adolescents with Marfan syndrome should therefore strongly suggest extensive or severe cardiac involvement.

Cerebrovascular Accidents. Two patients recovered from a moderately severe stroke. The cerebrovascular accident was due to a subarachnoid hemorrhage in one case, and probably due to thrombosis of a middle cerebral artery in the second case.

Electrocardiogram

One hundred twenty-four electrocardiograms from 32 patients were available for analysis. The findings are summarized in table 1.

Mean electrical QRS axis in the frontal plane was normal in most patients. Right-axis deviation was present in the patient with an atrial septal defect. Three patients, two with MR and one with combined AR and MR, had an indeterminate QRS axis, and one patient with AR had a superior frontal plane axis. All the patients with abnormal axes had very severe scoliosis and/or pectus deformities (pectus excavatum).

Conduction abnormalities were common. Six patients had first-degree atrioventricular block. Of these, three had MR, one MR and AR, and two NSHD. In addition to these, one patient had paroxysmal atrial tachycardia, and another had intermittent atrial fibrillation complicating severe MR. The Q-Tc interval was prolonged (>0.45 sec) in only three patients.

Left atrial hypertrophy was present in five patients with MR (isolated or in association with AR) and in the patient with paroxysmal atrial tachycardia. Left ventricular hypertrophy was present in four of the 21 patients with valvar lesions. Right atrial or right ventricular hypertrophy was not present in any of the patients.

Inverted T waves, frequently associated with depression of the S-T segment, were noted in leads II, III, aVF, and across the left precordium in 11 patients. Mitral regurgitation was present in eight of the 11 patients. The ST-T wave changes in the left precordial leads were intermittent in two patients with MR (one of whom also showed changes in the standard leads) (fig. 4).
Table 1

Electrocardiographic Data

<table>
<thead>
<tr>
<th>Data</th>
<th>NSHD (N = 11)</th>
<th>AR (N = 1)</th>
<th>MR (N = 17)</th>
<th>MR + AR (N = 3)</th>
<th>Total (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS axis:</td>
<td></td>
<td></td>
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<tr>
<td>0 to 90°</td>
<td>11</td>
<td>—</td>
<td>14</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Right-axis deviation</td>
<td>—</td>
<td>—</td>
<td>1 (ASD)</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Superior axis</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Perpendicular to frontal plane</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>1° A-V block</td>
<td>2</td>
<td>—</td>
<td>3</td>
<td>1</td>
<td>6</td>
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<td>—</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Paroxysmal atrial tachycardia</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Multifocal ventricular extrasystoles</td>
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<td>—</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>LAH</td>
<td>1</td>
<td>—</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>LVH</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>ST-T wave changes in II, III, aVF</td>
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<td>1</td>
<td>8</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Prolonged Q-Tc interval (&gt; 0.45 sec)</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: NSHD = no significant heart disease; AR = aortic regurgitation; MR = mitral regurgitation; LAH = left atrial hypertrophy; LVH = left ventricular hypertrophy.

Chest X-ray

Skeletal abnormalities such as kyphoscoliosis and/or pectus deformity were noted in the plain chest X-ray in most patients. Cardiac size and individual chamber enlargement were difficult to assess due to distortion of the cardiac silhouette from its usual position by the chest or spine deformity. Dilatation of the ascending aorta was noted in all the patients with MR and associated AR, four patients with MR, and three patients with no significant valvar disease. The pulmonary artery appeared prominent (in the absence of clinical evidence of pulmonary artery hypertension, regurgitation, or a left-to-right shunt) in three patients.

Figure 4

Electrocardiogram in a patient with Marfan syndrome and mild mitral regurgitation. Note the intermittent nature of the T-wave changes in leads II, III, aVF, and V5.
Cardiac Catheterization

Eleven cardiac catheterizations were performed in nine patients. Five patients had MR, three MR and AR, and one MR associated with an atrial septal defect. There were no fatalities associated with the catheterization nor were there any vascular complications in the vessels involved. One patient with MR, AR, and dissecting aneurysm of the aorta developed ventricular fibrillation during the aortic angiogram and was successfully countershocked.

Right atrial pressures were normal and none of the patients had tricuspid regurgitation. A left-to-right intracardiac shunt was detected in the patient with an ASD. In patients with angiographic evidence of mitral regurgitation, an elevated mean left atrial or pulmonary artery wedge pressure with a prominent v wave was observed in two, and mild pulmonary artery hypertension in one patient. An increase in LVED (>12 mm Hg) was present in all the patients with significant MR and/or AR. The mean cardiac index was normal, 4.2 liters/min/m² (range 2.5-6.2 liters/min/m²). Selective angiography revealed mild MR in two, severe MR in two, and combined MR and AR in three. Marked dilatation of the sinuses of Valsalva and dilatation of the ascending aorta were present in five patients (fig. 5).

Prognosis

Cardiovascular complications were the cause of death in four cases. One patient died at 9 months of age with severe MR, congestive heart failure, and pneumonia. An 11-year-old boy with moderate MR and AR died suddenly at home. Three patients died in the immediate postoperative period; one following aortic and mitral valve replacement, the second after aortic valve replacement and plication of a dissecting aortic aneurysm, and the third, a patient with NSHD, of cardiac arrest during a spinal fusion for severe scoliosis.

Pathology

Autopsy was performed in two patients. In the infant with severe MR, examination of the heart showed marked left atrial and ventricular hypertrophy. The mitral valve was thickened, its edges rolled, and there was redundant mitral valve tissue. The chordae tendineae were elongated and the posterior papillary muscle arose low in the left ventricular apex. Redundant tricuspid valve leaflets were present. The pulmonary and aortic valves as well as the aorta were normal.

In the patient who died following plication of a dissecting aneurysm, examination of the heart showed a massively dilated left atrium and left

Figure 5
Aortic angiogram (anteroposterior and lateral projections) in a patient with Marfan syndrome showing moderately dilated sinuses of Valsalva. The dilatation cannot be appreciated on the plain chest X-rays since the structures are within the cardiac silhouette.
ventricle. Jet lesions were noted in the left atrium. The mitral valve was thickened and rolled but the attachments were normal. The tricuspid and pulmonic valves were normal. The aortic valve leaflets were thickened, the sinuses of Valsalva were markedly dilated, and dissecting ascending and proximal descending aortic aneurysms were present.

Discussion

Marfan syndrome is a heritable disorder of connective tissue affecting predominantly the musculoskeletal, cardiovascular, and ocular systems. The general clinical features of the syndrome and the cardiovascular manifestations in adults have been extensively reviewed. The cardiac manifestations of the syndrome during childhood are usually more subtle and less severe than those in adults, yet they represent the major cause of death from the disease in this age group. Five of our patients (14%) died, and four of these deaths were directly attributed to cardiovascular disease.

The perinatal period in children with Marfan syndrome is usually uneventful and the diagnosis, except in cases with known family history, is uncommonly made during infancy (fig. 1). The diagnosis of Marfan syndrome should be suspected in infants with isolated mitral regurgitation, congenital dislocation of the hips, ocular or orthopedic deformities.

During childhood most patients exhibit an accelerated rate of maturation for height and an average maturation for weight. Patients with delayed height maturation and very poor weight gain usually had severe cardiac disease and/or kyphoscoliosis. This suggests that severe cardiac or musculoskeletal deformities significantly interfere with the growth and development of these children. The absence of an accelerated growth pattern in a child with mitral regurgitation should also, therefore, not exclude the diagnosis of Marfan syndrome if this is supported by other clinical evidence.

Careful evaluation revealed that 61% of children with Marfan syndrome in our series had an associated cardiac abnormality (fig. 1). The incidence of cardiovascular complications in large groups of patients with Marfan syndrome has previously been reported to be 32%, 40%, and in one series 30–60%. The incidence of cardiovascular complications will depend on the age at the initial examination and will be greater in older children and adults. In a recent review of the life expectancy and causes of death in Marfan syndrome, cardiac problems led to 52 of 56 deaths of known causes. The most common cardiac lesion in the pediatric age group is mitral regurgitation and, in contrast to adults with this syndrome, saccular and dissecting aneurysms of the ascending aorta are rare. Mitral regurgitation was present in 47% of our cases, aortic regurgitation in 11%, and an aneurysm of the ascending aorta in only one patient (3%).

Girls with Marfan syndrome developed mitral regurgitation but no aortic regurgitation. By contrast, mitral regurgitation, aortic regurgitation, or combined lesions were present in boys (fig. 2). The reasons for this distribution of valvar lesions according to sex remain unexplained except for the known predilection of males to aortic diseases (aortic stenosis, coarctation of the aorta, etc.).

Mitral regurgitation usually is an isolated, mild lesion which does not result in any symptoms. It may, rarely however, be severe and lead to congestive heart failure, saccular aneurysm of the anterior leaflet, atrial arrhythmias, or become the focus for bacterial endocarditis. The development of aortic regurgitation, however, is usually indicative of more severe cardiac involvement and subsequent progressive clinical deterioration. Aortic regurgitation may occur as an isolated lesion or in association with dissecting aneurysm of the ascending aorta, or sometimes in combination with MR. The prevalence of left heart lesions in Marfan syndrome suggests that although the abiotrophic changes in the elastic tissue fibers are genetically determined, the severity of the cardiovascular lesion may in part result from mechanical factors.

The aortic regurgitant lesion probably develops secondary to dilatation of the aortic ring and valve cusps or in association with a dissecting aortic aneurysm. We frequently looked for rheumatic valvulitis, but it was not documented in any of our cases.

The murmurs of MR in Marfan syndrome is usually an apical, late systolic murmur accompanied by mild or late systolic clicks (fig. 3). When pansystolic in nature it tends to have a late systolic accentuation. It is very similar to the mitral regurgitation murmur in the “prolapsed mitral valve syndrome” and “papillary muscle dysfunction syndrome.” Barlow et al. and Ronan et al. have clearly demonstrated that apical late systolic murmurs or pansystolic murmurs with late accentuation, associated with mid–late systolic clicks are due to mild mitral incompetence. The regurgitant mitral murmur in patients with Marfan syndrome has been attributed to prolapse of the mitral valve leaflet into the left atrium due to unusually long or
redundant chordae tendineae or a very dilated mitral valve ring. The insufficiency results from the elongated chordae which allow one leaflet to overshoot the other or, rarely, it may be secondary to rupture of the chordae. Mitral incompetence may also be due to deformity of the valve margin by nodularity and fibromyxomatous excrescences. The mid-systolic clicks have been postulated to result from snapping of the elongated or fibrous chordae but may also be related to the sudden distension of the prolapsed mitral leaflet. The high left ventricular pressure could snap redundant or loose chordae taut and produce a click. Midsystolic clicks were not heard in the absence of an apical systolic murmur suggesting that they are of intracardiac origin.

The electrocardiographic tracings in seven of our patients with isolated mitral regurgitation, mid-to-late systolic murmur, and clicks, reveal myocardial ischemic changes in the posterior-inferior cardiac region (fig. 4), supporting the hypothesis that the apical systolic murmur and clicks may in some patients be secondary to papillary muscle dysfunction. Similar observations have been made in patients with coronary artery disease.

Although mitral and aortic regurgitation are the dominant cardiac abnormalities seen in pediatric patients with Marfan syndrome, our group included one patient with dissecting aortic aneurysm, three with a solitary dilated main pulmonary artery, and one with paroxysmal atrial tachycardia. Dissecting aneurysms and rupture of the pulmonary artery and/or aorta have also been reported in childhood. Contrary to other published reports which suggest a strong association between Marfan syndrome and congenital cardiovascular malformations, we encountered only one patient with an atrial septal defect. In a review of 28 autopsied cases, an atrial septal defect was said to be present in six (21%), aortic stenosis or coartation in two (7%), and a patent ductus arteriosus in one (3.5%). The necropsy descriptions on individual patients, however, suggest that most of the interatrial communications were due to an incompetent foramen ovale rather than an atrial septal defect. Fifteen percent of patients with an atrial septal defect, 1.5% of patients with coarctation of the aorta, and 12% of patients with pulmonic stenosis were reported by Paul Wood to have Marfan syndrome. While the prevalence of congenital cardiovascular malformations in Marfan syndrome is probably less than previously suspected, there are numerous case reports of the syndrome associated with coarctation of the aorta or atrial septal defect suggesting a definite relationship between these malformations and Marfan syndrome. A variety of other lesions such as a patent ductus arteriosus, ventricular septal defect, tetralogy of Fallot, and pulmonary stenosis have been reported.

The chest roentgenogram is usually not helpful in detecting mild increase in cardiac size and great vessel enlargement because the severe sternal and spine deformities frequently result in cardiac displacement and rotation. Since the sinuses of Valsalva are within the cardiac silhouette, dilatation or aneurysms of these structures are usually not recognized in the plain chest X-ray unless they are very large.

The classical electrocardiographic finding of a first-degree atrioventricular block and S-T and T-wave changes in leads II, III, and AVF were observed in 19% and 34% of our patients, respectively. The occurrence of first-degree atrioventricular block does not appear to be related to the presence of aortic regurgitation as suggested by McKusick. The S-T and T-wave changes in the standard leads are often accompanied by similar changes in the left precordial leads and are usually, but not always, associated with clinically apparent mitral regurgitation. In two of our patients these changes were intermittent (fig. 4). Prolongation of the Q-Tc interval has also been reported but this was noted in only two of our patients with MR and one patient with MR and AR. QRS-axis abnormalities may be secondary to cardiac malrotation induced by the skeletal deformities. The development of ventricular and atrial hypertrophy is related to the severity of the cardiac lesion. Increased magnitude of left ventricular voltages, however, may occur in the absence of any left ventricular hypertrophy in some patients with a very thin chest wall.

Cardiac catheterization and selective angiography are useful in assessing the severity of the cardiac involvement. Dilatation of the aortic annulus and sinuses of Valsalva has been demonstrated by angiography to occur at a very early age. Catheterization is indicated in patients with hemodynamically significant lesions. It should be undertaken in all preoperative patients to quantitate the severity of the regurgitant lesion, outline the anatomy of the great arteries, and detect the possible coexistence of a congenital cardiovascular malformation. Complications resulting from cardiac catheterization are rare.
Surgical experience with cardiac abnormalities in Marfan syndrome has been limited and the results of treatment have been generally poor. There have been few successful attempts of mitral and/or aortic valve replacement. Two of our patients died in the immediate postoperative period following valve replacement. In view of the primary connective tissue defect in this syndrome, replacement of the mitral and aortic valve is preferable to plication. Postoperative death is usually the result of arrhythmia, pulmonary complications, or dissections in the aortic wall.

The care and treatment of a child with Marfan syndrome require a cooperative effort between a large number of medical specialties frequently available only in a medical center. Particularly important is the care provided by the pediatrician, orthopedic surgeon, physiotherapist, ophthalmologist, cardiologist, and genetic counselor. Death in childhood is usually due to congestive heart failure, intercurrent infection, or rupture of a vascular structure. Early recognition of this syndrome in childhood may improve the prognosis. Patients with mitral incompetence, even if hemodynamically insignificant, should be regarded as susceptible to bacterial endocarditis. The development of an aortic regurgitant murmur in the patient with mitral regurgitation may be regarded as a poor prognostic sign and the patient should be followed more closely. The use of beta-blocking agents such as propranolol has been suggested in these patients. Further clinical investigation and surgical experience, however, will be necessary to determine whether the basic connective tissue defect precludes successful long-term medical and/or surgical results.

References

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Circulation. 1973;47:587-596
doi: 10.1161/01.CIR.47.3.587
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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