The Familial Occurrence of the Syndrome of Mid-Late Systolic Click and Late Systolic Murmur

By William E. Shell, M.D., Joseph A. Walton, M.D., Mary E. Clifford, M.D., and Park W. Willis, III, M.D.

SUMMARY

Patients with late systolic murmurs, with and without mid-late systolic extra sounds, have recently been shown to have mitral regurgitation. This syndrome has been found to be familial in each of the four families we have studied. These families were found to have a high prevalence of mid-late systolic extra sounds, late systolic murmurs, pansystolic murmurs, abnormal electrocardiograms, and unexplained premature sudden death.

The prognosis for these patients is unknown but is generally considered good. Periodic medical observation of these patients and their families seems warranted, however, in view of the current lack of knowledge concerning the cause of the chest pain, the rate of progression of the mitral regurgitation, the significance of the electrocardiographic abnormalities, the frequency of important arrhythmias, and the mechanism of sudden death. In addition, antibiotic prophylaxis to attempt to prevent bacterial endocarditis seems clearly indicated.

Additional Indexing Words:

Familial heart disease  Congenital heart disease  Mitral insufficiency
Systolic extra sound

The apical late systolic murmur, with or without an associated systolic extra sound, and the isolated mid-late systolic extra sound have, in the past, been considered extracardiac in origin and the result of pleuropericardial adhesions.1-5 This concept of an extracardiac origin for the mid-late systolic extra sound and the late systolic murmur was based on a number of observations. Among these were: (1) the frequent association of mid-systolic extra sounds with late systolic murmurs1-8; (2) Gallavardin’s reports6,7 of patients with mid-systolic extra sounds who had pleuropericardial adhesions at necropsy; (3) Johnston’s observation8 that mid-systolic extra sounds and the associated murmurs varied with position and respiration, and thus seemed unrelated to any known event in the cardiac cycle; and (4) the observation1 that mid-systolic extra sounds and late systolic murmurs followed episodes of acute pericarditis.

Humphries and McKusick9 coined the term “auscultatory-electrocardiographic syndrome” to describe patients with mid-systolic extra sounds, late systolic murmurs, and T-wave inversion in leads II, III, aVF, V5, and V6, which they attributed to residual pericardial disease following acute pericarditis.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

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Address for reprints: Dr. W. E. Shell, University Hospital, Ann Arbor, Michigan 48104.
Table 1

The Reported Familial Occurrence of Mid-systolic Extra Sounds and Late Systolic Murmurs, Including One Pedigree Reported Previously by Barlow and Bosman

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Number of related individuals examined</th>
<th>Number affected (including propositus)</th>
<th>Relationship</th>
</tr>
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<tbody>
<tr>
<td>Barlow and Bosman(11)</td>
<td>1) 19</td>
<td>6</td>
<td>Three generations including</td>
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<td></td>
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<td>mother-son and</td>
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<td>grandmother-mother-daughter</td>
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<td></td>
<td>2) 6</td>
<td>2</td>
<td>Father-daughter</td>
</tr>
<tr>
<td></td>
<td>1) 3</td>
<td>3</td>
<td>Three sisters</td>
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<tr>
<td></td>
<td>2) 6</td>
<td>2</td>
<td>Two sisters</td>
</tr>
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<td></td>
<td>3) 5</td>
<td>1</td>
<td>Only propositus</td>
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<tr>
<td>Stannard et al.(19)</td>
<td></td>
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<tr>
<td></td>
<td>2) 6</td>
<td>2</td>
<td>Mother-daughter</td>
</tr>
<tr>
<td>Hancock and Cohn(13)</td>
<td>2) 6</td>
<td>2</td>
<td>Mother-daughter</td>
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<tr>
<td>Lenhardt and Taylor(17)</td>
<td>2) 6</td>
<td>2</td>
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</tbody>
</table>

In 1963 Barlow and associates\(^{10}\) effectively challenged the concept that the late systolic murmur was extracardiac in origin by showing with angiocardiography that mitral regurgitation was present in each of the five patients they studied. In 1966 Barlow and Bosman\(^{11}\) reported that, in patients with the distinctive “auscultatory-electrocardiographic syndrome,” left ventricular cineangiocardiograms demonstrated peculiar retroversion or billowing of the posterior leaflet of the mitral valve into the left atrium during ventricular systole. A number of subsequent studies\(^{12-19}\) have confirmed that late systolic murmurs with or without systolic extra sounds, are associated with mitral regurgitation and with

Figure 1

The phonocardiogram of G.C. (family 1), demonstrating a variable mid-systolic extra sound and a late systolic murmur. Abbreviations in this and other phonocardiograms presented: \(S_1\) = first heart sound; SC = systolic click; \(S_2\) = second heart sound; \(sm\) = systolic murmur; ICP = indirect carotid pulse tracing; Log = logarithmic.
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billowing of a large posterior mitral valve leaflet into the left atrium.

There have been six reported instances (table 1) of the familial association of mid-systolic extra sounds and late systolic murmurs, including the one pedigree reported by Barlow and Bosman.11 We are reporting the the pedigrees of four additional families in which there was a high prevalence of systolic clicks, late systolic murmurs, pansystolic murmurs, abnormal electrocardiograms, or sudden death at an early age.

Methods

The propositi were drawn from a group of 41 patients seen in a 6-month period with either a mid-late systolic extra sound or a late systolic murmur, or both.

The four families studied were selected only on the basis of their place of residence and their willingness to be examined. As yet, only these four families have been studied in detail. Each propositus had a complete history, a physical examination, a chest x-ray, an electrocardiogram, and a phonocardiogram. Twenty-three additional family members were studied by physical examination, electrocardiography, and phonocardiography. One propositus was studied by cardiac catheterization, including left ventricular cineangiography.

Results

Family 1

G. C., the propositus, a 37-year-old white woman, presented with substernal chest pain, poorly related to exertion and incompletely relieved by nitroglycerin. She had a history of palpitations and both paroxysmal atrial tachycardia and multiple ventricular premature beats had been noted in the past.

She had a variable mid-systolic extra sound followed by a high-pitched, apical late systolic murmur (fig. 1). Her electrocardiogram showed flat or slightly inverted T waves in leads II, III, and aV\(_3\), and she had an abnormal post-exercise electrocardiogram.

Nine additional family members were examined (fig. 2). G. C.'s 18-year-old son, E. C., had a late systolic murmur introduced by a mid-systolic extra sound (fig. 3); he also had flat T waves in leads II, III, aV\(_3\), V\(_6\), and V\(_7\). Her 30-year-old brother, B. G., had a pansystolic murmur interrupted by a mid-systolic extra sound and had similar electrocardiographic findings. Her 27-year-old brother, R. G., had a pansystolic murmur. Two of her six children had pansystolic murmurs without extra sounds and each had flat T waves in leads II, III, aV\(_3\), and V\(_6\).

Family 2

V. G., the second propositus, a 27-year-old white woman, presented with dyspnea on exertion and intermittent substernal chest pain unrelated to exertion and influenced to a variable degree by position. A mid-systolic extra sound followed by a peculiar, high-pitched, late systolic murmur was heard at the apex. Each of the five family members examined (fig. 4) had a mid-systolic extra sound, a late systolic murmur, a pansystolic murmur, an abnormal electro-
The phonocardiogram of E.C. (family 1), showing a mid-systolic extra sound that varies with respiration and is followed by a late systolic murmur. Rapid deflections retouched for clarity.

Figure 3

The pedigree of the V.G. family (family 2), showing that all five of the individuals examined had a mid-systolic extra sound, a late systolic murmur, a pansystolic murmur, an abnormal electrocardiogram, or some combination of these findings. Two family members died suddenly before age 30. T. G., the 7-year-old daughter of V. G., had a mid-systolic extra sound without a murmur (fig. 5). G. J., the 21-year-old brother of V. G., had a late systolic extra sound occurring in the middle of a late systolic murmur. B. J., the 48-year-old mother of V. G., had a pansystolic murmur interrupted by a late systolic extra sound. Her 47-year-old aunt, A. C., had a pansystolic murmur.

The electrocardiograms of V. G. and her brother were similar to those reported by Barlow and Bosman as typical of this syndrome. V. G.'s electrocardiogram (fig. 6) showed slight T-wave inversion in leads I, II, III, aVF, V4, V5, and V6. The electrocardiogram of her 21-year-old brother demonstrated the same changes (fig. 7).

Family 3

W. Z., Jr., a 23-year-old asymptomatic white male, was rejected by the Peace Corps because of a heart murmur. Examination of his heart showed an early to mid-systolic extra sound, some combination of these findings. In addition, two unexamined members of the family had died suddenly before age 30. See figure 2 for abbreviations.
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followed by a late systolic murmur (fig. 8). He also had a persistently split second heart sound and a pulmonic ejection murmur. Cardiac catheterization showed the presence of the expected atrial septal defect. Left ventricular cineangiography displayed retroversion of the posterior leaflet of the mitral valve into the left atrium without mitral regurgitation. His murmur was markedly dependent on position, and in the right lateral decubitus position, the position in which the left anterior oblique cineangiograms were recorded, there was no audible murmur, and the extra sound was decreased in intensity.

Twelve family members were examined (fig. 9). W. Z., Sr., also had a late systolic murmur introduced by a mid-systolic extra sound, and three siblings had apical pansystolic murmurs. The 12-year-old brother, P. Z., had coarctation of the aorta.

Family 4

The propositus of the fourth family, E. T., a 40-year-old white woman, had a history consistent with angina pectoris. She had a late systolic extra sound followed by a late systolic murmur (fig. 10) and a normal resting electrocardiogram. The exercise electrocardiogram, however, was abnormal. The 71-year-old mother of F. T. had a loud pansystolic murmur at the apex, and a 27-year-old brother died suddenly (fig. 11).

Discussion

The mid-systolic extra sound has long been considered extracardiac in origin and of no clinical significance.1-3, 5 This concept evolved from the observations that (1) affected individuals were usually asymptomatic1, 2 (2) the sounds varied, often markedly, with respiration and position6; (3) pleuropericardial adhesions were observed in three cases at necropsy6, 7; and (4) the sounds occasionally were observed in patients who had acute pericarditis.1 Similarly, the late systolic murmur has been considered extracardiac because of (1) its association with mid-systolic extra sounds1-3; (2) the lack of symptomatic, roentgenologic or electrocardiographic evidence of organic heart disease; and (3) the occurrence of the murmur in late systole when the pressure gradient between left ventricle and left atrium is rapidly decreasing so that mitral regurgitation cannot be explained on the basis of an increasing gradient.20

In 1961, Reid21 proposed the term "chordal snap" for the mid-late systolic extra sound. He felt that the association of this sound with the late systolic murmur was evidence for the intracardiac origin of both phenomena and postulated that mitral regurgitation might occur only in late systole. Since Barlow and associates’ report in 1963,10 a number of studies11-19 have cast further doubt on the presumed extracardiac origin of the late systolic murmur and the mid-late systolic extra sound. Mitral regurgitation has been found, by angiographic studies, in all but one of over 63 patients with unexplained late apical systolic murmurs, with or without systolic extra sounds.11-19 As mentioned before, mitral insufficiency was not demonstrated in our patient W.Z., Jr. (family 3), but his murmur varied greatly with position, and mitral regurgitation might have been found if the cineangiogram had been taken when
he was in the left lateral position. In addition, a high percentage of patients with late systolic murmurs apparently have pronounced ballooning of the posterior leaflet of the mitral valve into the left atrium during ventricular systole.\(^\text{11, 13, 14, 19}\)

Patients with isolated mid-late systolic extra sounds, studied by cineangiography, have been reported to have the same peculiar ballooning of the posterior mitral leaflet without mitral regurgitation.\(^\text{19}\) In addition, Criley and associates\(^\text{14}\) have shown that the mid-late systolic extra sound occurs at the height of the excursion of the ballooning leaflet into the left atrium.

It would, therefore, seem that the affected members of the families presented here have familial mitral valve dysfunction. The high prevalence of mid-systolic extra sounds, late systolic murmurs, pansystolic murmurs, abnormal electrocardiograms, and premature sudden death in these families suggests a familial defect in cardiac structure or function, or both, involving the mitral valve, the chordae tendineae, and ventricular repolarization. There have been six reported instances of the familial association of mid-systolic extra sounds and late systolic murmurs (table 1), including one pedigree reported by Barlow and Bosman.\(^\text{11}\) It would appear that if this is a heritable trait it is of the autosomal dominant type.

The insufficient data do not allow an estimate of the prevalence of familial mitral valve dysfunction in patients with systolic clicks, late systolic murmurs, or the combination of the two. To date we have only examined in detail four families in which the...
propositi had either a systolic extra sound or a late systolic murmur. We do not know whether this high aggregation of extra sounds and late systolic murmurs will be encountered in other families.

Barlow and associates\(^\text{22}\) stated that the syndrome of mid-systolic extra sound and late systolic murmur results from diverse causes. Based on an analysis of 53 patients, they felt that 20 had rheumatic disease (because of a history of rheumatic fever or the presence of mitral or aortic diastolic murmurs, or both); three had the Marfan syndrome; seven had a familial association; four had papillary muscle dysfunction; three had mid-systolic extra sounds secondary to operative manipulation of the mitral valve; one had idiopathic hypertrophic subaortic stenosis; and 17 had no apparent cause for the syndrome.

The nature of the familial defect is obscure. These patients are believed to have large, voluminous posterior mitral valve leaflets with abnormal chordae tendineae.\(^\text{22}\) Barlow and associates reported the case of a 39-year-old patient with a mid-systolic extra sound followed by a late systolic murmur who died suddenly while mowing a lawn.\(^\text{22}\) Necropsy revealed normal coronary arteries, a voluminous posterior leaflet, and thin, elongated chordae tendineae.

Patients with the Marfan syndrome frequently have mitral valve disease with systolic clicks, late systolic murmurs, or pansystolic murmurs.\(^\text{23, 24}\) In a number of reports\(^\text{25, 26}\) on patients with so-called “floppy” mitral valves

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**Figure 7**

The electrocardiogram of G.J. (family 2), with flat T waves in leads I, II, III, aV\(_L\), aV\(_P\), and V\(_{4-6}\).
The phonocardiogram of W.Z., Jr. (family 3), demonstrating a mid-systolic extra sound and a late systolic murmur.

The pedigree of the W.Z. family (family 3), with five individuals, of the 12 examined, having a mid-systolic extra sound, a late systolic murmur, a pansystolic murmur, an abnormal electrocardiogram or a combination of these findings.

with voluminous leaflets repair of the valve is said to be difficult because of "poor connective tissue." There would appear to be some relationship between the mitral valve abnormality of the Marfan syndrome, the floppy mitral valve, and the mid-late systolic click-late systolic murmur syndrome. This possible relationship leads to the speculation that the histological defect may be fibromyxomatous degeneration of the connective tissue of the valve.

This syndrome presents a number of clinical problems. The prognosis for these patients is unknown, but has generally been assumed to be good. However, the unresolved problems of the progression of the
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APEX

Figure 10
The phonocardiogram of E. T. (family 4), with a late systolic murmur introduced by a mid-systolic extra sound.

Figure 11
The pedigree of the E.T. family (family 4). The propositus had a mid-systolic extra sound, a late systolic murmur, and an abnormal electrocardiogram; her mother had a loud apical pansystolic murmur. In addition, E.T.'s brother had died suddenly at 27 years of age while playing basketball.

mitral regurgitation, the pathogenesis of the chest pain, the mechanism of premature sudden death, the implications of frequently observed arrhythmias, and the incidence of bacterial endocarditis in these patients require caution in estimating the prognosis for any individual patient.

Patients with mid-systolic extra sounds with or without late systolic murmurs appear to have minimal functional impairment. The factors determining progression of the mitral regurgitation, however, remain unknown. Levy and Edwards27 have suggested that mitral regurgitation produces left ventricular dilatation which further distorts the mitral valve apparatus, resulting in additional regurgitation; that is, mitral regurgitation begets mitral regurgitation. Barlow and associates22 have observed progression of a late systolic murmur to a pansystolic murmur in one patient with Marfan's syndrome. Examination of the four families presented here shows that the only isolated mid-systolic extra sound occurred in a 7-year-old, while pansystolic murmurs predominated in the older members of the families. The combination of
the click and late systolic murmur occurred only in the middle generation of each family. This circumstantial evidence suggests that minimal regurgitation denoted by a late systolic murmur may progress to significant regurgitation. The determination of the frequency of this occurrence must await long-term observation of larger groups of these patients.

Chest pain is common among these patients\textsuperscript{11, 13, 19} and is often bizarre. It is frequently sharp, is left precordial and substernal in location, and is not related to position or respiration. It is poorly related to exertion and may last minutes or hours. It is of the type often described as "pain of noncardiac origin." Many of these patients, however, have T-wave abnormalities in the resting electrocardiogram, and abnormal exercise electrocardiograms were observed in two of our patients. Selective coronary angiograms of two patients with severe anterior chest pain studied by Stannard and co-workers\textsuperscript{19} were normal, and one of Hancock and Cohn's patients\textsuperscript{13} with chest pain had normal coronary cineangiograms. A good explanation for the chest pain and the electrocardiographic abnormality is not available as yet. Iatrogenic psychoneurosis seems unlikely in the three propositae with significant chest pain, since each of the three had pain before she had knowledge of a heart murmur or an extra sound.

In three of four families studied, one or more individuals died suddenly before the age of 30 years. The cause of these sudden deaths is unknown, but the prevalence in these families seems high.

In other reports,\textsuperscript{13, 14, 19} arrhythmias (ventricular tachycardia, ventricular premature beats, paroxysmal atrial tachycardia, and atrial fibrillation) have been encountered more frequently than in this one, and the sudden death of a young female patient of Hancock and Cohn's\textsuperscript{13} was probably due to a ventricular arrhythmia.

Prophylaxis for bacterial endocarditis seems indicated. During the last year five instances\textsuperscript{4, 17, 28, 29} of bacterial endocarditis have been reported in patients with a late systolic murmur, with or without a systolic extra sound. In two of our patients with a late systolic murmur bacterial endocarditis developed. During the course of the infection one developed a pansystolic murmur and severe congestive heart failure. Le Bauer and associates\textsuperscript{26} have reported bacterial endocarditis in a patient with only a mid-systolic extra sound prior to the infection, but with a late systolic murmur after successful treatment.

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