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Familial syndrome of midsystolic click and late systolic murmur

Paolo Rizzon, Giuseppina Biasco, Giuseppe Brindicci, and Fernando Mauro
From The Division of Cardiology, Department of Internal Medicine, University of Bari, Italy

Evidence has recently been produced to show that patients with a midsystolic click and late systolic murmur have a peculiar abnormality of the mitral valve: the systolic ballooning of the leaflets, particularly the posterior one, usually associated with mild mitral insufficiency. Occurrence of similar clinical, phonocardiographic, and electrocardiographic findings in more than one member of each of eight families studied strongly supports the hypothesis of a genetic basis. The frequent association with findings indicating myocardial involvement is pointed out. Its potential aetiological implications are discussed. The possible links with the forme fruste *of the Marfan syndrome are also considered. Some distinctive clinical, phonocardiographic, and electrocardiographic features are described.*

Associated midsystolic clicks and late systolic murmurs or honks have been regarded in the past as 'innocent' and considered extracardiac in origin. However, since 1961, there has been evidence to show that these auscultatory findings are almost invariably intracardiac in origin, and are associated with a peculiar abnormality of the mitral valve in which there is systolic ballooning of the leaflets, particularly the posterior one, usually associated with slight mitral incompetence (Reid, 1961; Segal and Likoff, 1964; Ronan, Perloff, and Harvey, 1965; Tavel, Campbell, and Zimmer, 1965; Kesteloot and Van Houte, 1965; Leon *et al.*, 1966; Linhart and Taylor, 1966; Criley *et al.*, 1966; Lucardie and Durrer, 1967; Behar, Whalen, and McIntosh, 1967; Stannard *et al.*, 1967; Barlow *et al.*, 1968; Bittar and Sosa, 1968; Grossman *et al.*, 1968; Leachman, De Francheschi, and Zamalloa, 1969; Willems *et al.*, 1969; Fontana *et al.*, 1970; Dillon *et al.*, 1971).

Because of the cineangiocardiographic appearances this condition has been described as ballooning of the posterior leaflet (Linhart and Taylor, 1966; Behar *et al.*, 1967), prolapse of the posterior leaflet (Criley *et al.*, 1966; Stannard *et al.*, 1967), and aneurysmal protrusion or billowing of the posterior leaflet (Barlow *et al.*, 1968).

The main features of this syndrome include: familial occurrence; association with fossa ovalis atrial septal defect, and with Marfan's syndrome; predominant female incidence; conspicuous increase of the auscultatory findings with changes in posture, particularly in the upright position; atrial and ventricular extrasystoles, and, in some cases, paroxysmal atrial and ventricular arrhythmias; low or inverted T waves in leads II, III, aVF, and sometimes in V5 and V6; normal or slightly enlarged left atrium and ventricle; and normal haemodynamic findings at right heart catheterization (Reid, 1961; Ronan *et al.*, 1965; Kesteloot and Van Houte, 1965; Tavel *et al.*, 1965; Linhart and Taylor, 1966; Hancock and Cohn, 1966; Criley *et al.*, 1966; Rackley *et al.*, 1966; Stannard *et al.*, 1967; Behar *et al.*, 1967; Barlow *et al.*, 1968; Grossman *et al.*, 1968; Bittar and Sosa, 1968; Leachman *et al.*, 1969; Hunt and Sloman, 1969; Shell *et al.*, 1969; Willems *et al.*, 1969; Fontana *et al.*, 1970; Pocock and Barlow, 1970; Fantini and Morace, 1970; McDonald *et al.*, 1971; Rizzon, Biasco, and Maselli-Campagna, 1971).

In a screening study we carried out among 1009 female students aged between 14 and 18 years the prevalence rate for associated midsystolic click and late systolic murmur was 0·33 per cent (Biasco *et al.*, 1972).

Knowledge of the pathology in this syndrome is not adequate, since the opportunity for necropsy (Hancock and Cohn, 1966; Barlow *et al.*, 1968) or the need for surgical repair (Barlow *et al.*, 1968; Bittar and Sosa, 1968; Hunt and Sloman, 1969; Leachman *et al.*, 1969; Rizzon *et al.*, 1971) are rare.

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The main abnormalities are represented by myxomatous degeneration of the cusps (Bittar and Sosa, 1968) which are voluminous and thin (Barlow *et al.*, 1968; Bittar and Sosa, 1968; Wigle, 1968; Hunt and Sloman, 1969; Rizzon *et al.*, 1971), thin elongated chordae tendineae (Bittar and Sosa, 1968; Hancock and Cohn, 1966), ruptured chordae tendineae (Barlow *et al.*, 1968; Hunt and Sloman, 1969), and large annulus without morphological changes of the leaflets, chordae, or papillary muscles (Leachman *et al.*, 1969).

The aetiology of the mitral valve dysfunction has not been clarified. The occurrence in some families of more than one affected member suggests perhaps a genetic basis. Two mechanisms have been held responsible for the ballooning deformity: (1) abnormalities of the mitral annulus or leaflets or chordae tendineae, a mechanism that is supported by the above-mentioned anatomical findings; (2) abnormal systolic contraction ring in the posteroinferior wall of the left ventricle, with lifting of the posterior papillary muscle and consequent prolapse of the posterior mitral leaflet, a mechanism suggested by selective left ventricle cineangiocardiography (Grossman *et al.*, 1968; Engle, 1969; Fontana *et al.*, 1970; Garello and Ribaldone, 1971).

The prognosis appears to be favourable in general, but sudden death (Hancock and Cohn, 1966; Barlow *et al.*, 1968; Shell *et al.*, 1969) or development of bacterial endocarditis (Linhart and Taylor, 1966; LeBauer, Perloff, and Keliher, 1967; Facquet, Alhomme, and Raharison, 1964) has been reported.

This paper intends to focus the attention on some particular and lesser known features of this syndrome.

Subjects and methods

Nine patients with midsystolic click and late systolic murmur were studied in our department between April 1969 and February 1972. Five of them were referred to this clinic because of alleged cardiac symptoms. Four of them were women and one was a man. The other 4 were selected through a screening study carried out among 1009 female students. Their ages ranged from 14 to 24 years. All patients had a complete history, physical examination, electrocardiogram in recumbent and upright position, posteroanterior and lateral chest *x*-rays, and phonocardiogram. Auscultation and phono-

TABLE I *Clinical and electrocardiographic findings in*

Case No.	*Age*	*Sex*	*Symptoms*	*Physical signs*
1	18	F	Atypical praecordial pain; syncope, one occurring after effort, preceded by sudden anginal pain and lasted 10 min; mild exertional dyspnoea; intermittent squeaking noise in chest	Normal stature; red hair and fair complexion; high arched palate; short anteroposterior diameter of the chest; moderate kyphoscoliosis; hollow feet; normal ocular findings
2	23	F	No symptoms	Normal stature; incurved little fingers; normal ocular findings
3	18	F	Atypical praecordial pain; moderate exertional dyspnoea	Tall thin stature, but without Marfan's type abnormalities; high arched palate; slight kyphoscoliosis; slight hollow feet; normal ocular findings
4	14	F	Atypical praecordial pain; slight dyspnoea and palpitation on effort	Tall, thin stature; long extremities and fingers; red hair and fair complexion; high arched palate; kyphoscoliosis; slight flat feet; normal ocular findings
5	18	F	Palpitation and lightheadedness when assuming upright position; slight dyspnoea on effort	Normal stature, red hair, and fair complexion; slight scoliosis; normal ocular findings
6	15	F	No symptoms	Short stature; red hair and fair complexion; very short hands and feet; normal ocular findings
7	18	F	No symptoms	Normal stature; slight high arched palate; normal ocular findings
8	21	F	No symptoms	Normal stature; slight high arched palate; slight flat feet; normal ocular findings
9	24	M	Atypical praecordial pain; slight dyspnoea and palpitation on effort	Normal stature; gracile appearance with thin, long extremities; slight dolicocephaly; slight pectus excavatum; kyphoscoliosis; flat feet; normal ocular findings

cardiograms were done in the recumbent and upright position, during inspiration, expiration, Valsalva's manoeuvre, and after amyl nitrite inhalation. Phonocardiograms were obtained on a four-channel Md R. 108 r. Galileo Direct Recorder with a frequency range of 20 – to 600 Hz at a speed of 50 to 100 mm/sec. Right heart catheterization and left ventricular cineangiography were performed in 3 cases. All patients but one had been followed up clinically, electrocardiographically, and phonocardiographically every 3 months for a period of 6 to 30 months. The available members of the patients' families were similarly studied clinically, electrocardiographically, and phonocardiographically.

Results

The pertinent clinical findings are presented in Table 1, and the auscultatory and phonocardiographic features of the late systolic murmur and honk in Table 2.

History

No patients gave a history consistent with acute rheumatic fever, or of an illness which could have been pleurisy and pericarditis. Two patients had tonsillectomy at the ages of 6 and 7, because of recurrent tonsillitis. Abnormal cardiac findings had been known previously in only one (Case 3 with atrial septal defect).

Symptoms

Four patients were asymptomatic. Among the other 5 the main complaints were slight exertional dyspnoea, vague pain over the anterior chest not typical of angina, and palpitations; only one had syncope, preceded on one occasion by typical anginal pain.

Clinical features

None of the patients had a typical Marfan syndrome with tall stature, long extremities and fingers, dislocated lenses, and prominent aorta. All of them, however, presented minor skeletal abnormalities, such as high arched palate, kyphoscoliosis, incurved little fingers, and hollow or flat foot. Four of them had red hair and fair complexion.

Cardiac findings and phonocardiography

Two patients (Cases 1 and 3) had an intermittent

9 patients with midsystolic click and late systolic murmur

Auscultation	*Electrocardiogram*
Late systolic apical murmur; intermittent loud late systolic honk	Flat T wave in lead aVF, negative T wave in lead III in recumbent position; negative T waves in leads II, III, and aVF in upright position
Midsystolic clicks; late systolic apical murmur; intermittent late systolic honk	Negative T waves in leads III in recumbent position; frequent ventricular extrasystoles with periods of bigeminal rhythm, negative T wave in lead III, flat T waves in leads II and aVF in upright position
Midsystolic clicks; late systolic apical murmur; intermittent loud late systolic honk; pulmonary ejection murmur with fixed splitting of second sound	Multifocal ventricular extrasystoles with periods of bigeminal rhythm, more frequent in upright position; right atrial and ventricular hypertrophy; incomplete right bundle-branch block
Intermittent midsystolic click; late systolic apical murmur; late systolic honk in upright position	Sporadic ventricular extrasystoles in supine position, more frequent in upright position; right axis deviation of QRS in frontal plane (+110°)
Intermittent midsyrtolic click; late systolic apical murmur; late systolic honk in upright position, heard only during first examination	Sporadic ventricular extrasystoles, flat T wave in lead aVF and negative T wave in lead III in recumbent position; transient multifocal ventricular extrasystoles, negative T waves in leads II, III, aVF, and flat T wave in lead V6 in upright position
Intermittent midsystolic click; late systolic apical murmur	Flat T wave in lead III in recumbent position; negative T waves in leads II, III, and aVF in upright position
Intermittent midsystolic click; late systolic apical murmur	Low voltage of QRS; low voltage of T wave in leads II, III, and aVF in recumbent position; flat T waves in leads II, III, aVF, and V6 in upright position
Midsystolic clicks; late systolic apical murmur	Flat T wave in lead II, negative T waves in leads III and aVF in upright position
Intermittent midsystolic clicks; late systolic apical murmur	Frequent atrial extrasystoles; flat T waves in leads III and aVF in upright position

prominent systolic thrill over the praecordium simultaneously with the honk. All patients had an apical late systolic murmur (Fig. 1 and 5) preceded in 8 patients by one or more clicks (Fig. 2 and 5). The murmur could be also heard over the midpraecordium, but there was no transmission elsewhere. Occasionally it was midsystolic, mid-late systolic, or holosystolic (Fig. 5). The murmur was

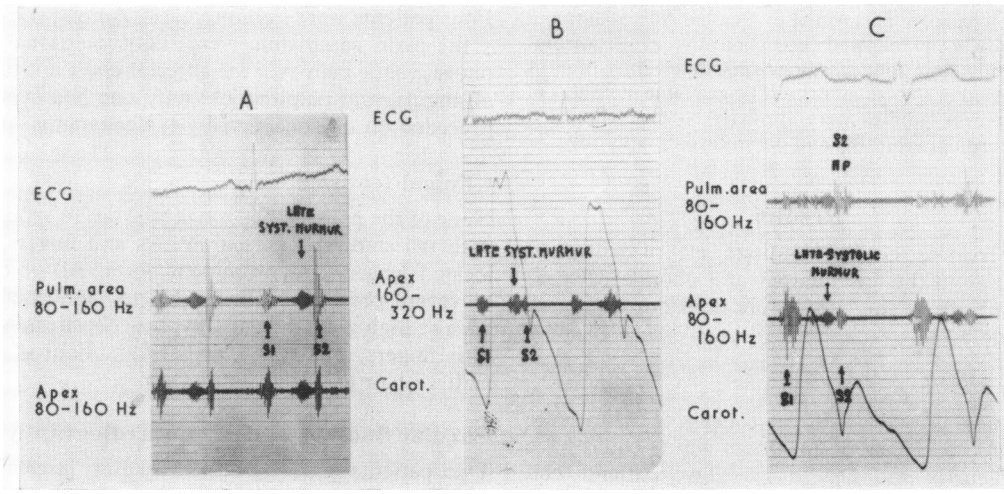

FIG. 1 *Phonocardiograms of (A) Case 1, (B) Case 2, and (C) Case 3, showing a crescendo-decrescendo late systolic murmur.*

TABLE 2 *Auscultatory and phonocardiographic*

Case No.	*Findings*	*Point of maximum intensity*	*Timing*	*Shape*	*Intensity*
1	Murmur	Apex and midpraecordium	Late systolic	Crescendo–decrescendo	Variable (gradc 1–2/6)
	Honk	,, ,, ,,	,, ,,	Fast crescendo–fast decrescendo	Variable (grade 3–6/6)
2	Murmur	Apex and midpraecordium	Late systolic	Crescendo–decrescendo	Variable (grade 1–2/6)
	Honk	,, ,, ,,	,, ,,	Fast crescendo–fast decrescendo	Variable (grade 3–4/6)
3	Murmur	Apex and midpraecordium	Late systolic, sometimes mid-late systolic or holosystolic	Crescendo–decrescendo	Variable (grade 1–2/6)
	Honk	,, ,, ,,	Late systolic	Fast crescendo–fast decrescendo	Variable (grade 3–5/6)
4	Murmur	Apex and midpraecordium	Late systolic, sometimes mid-late systolic or holosystolic	Crescendo–decrescendo	Variable (grade 1–3/6)
	Honk	,, ,, ,,	Late systolic	Fast crescendo–fast decrescendo	Grade 3/6
5	Murmur	Apex and midpraecordium	Late systolic, sometimes mid-late systolic or holosystolic	Crescendo–decrescendo	Variable (grade 1–2/6)
	Honk	,, ,, ,,	Late systolic	Fast crescendo–fast decrescendo	Grade 3/6
6	Murmur	Apex and midpraecordium	Late systolic, sometimes mid-late systolic or holosystolic	Crescendo–decrescendo	Variable (grade 1–2/6); sometimes absent
7	Murmur	Apex and midpraecordium	Mid-late systolic	Crescendo–decrescendo	Variable (grade 1–2/6)
8	Murmur	Apex and midpraecordium	Late systolic	Crescendo–decrescendo	Variable (grade 1–2/6); sometimes absent
9	Murmur	Apex and midpraecordium	Late systolic, sometimes mid-late systolic or holosystolic	Crescendo–decrescendo	Variable (grade 1–3/6)

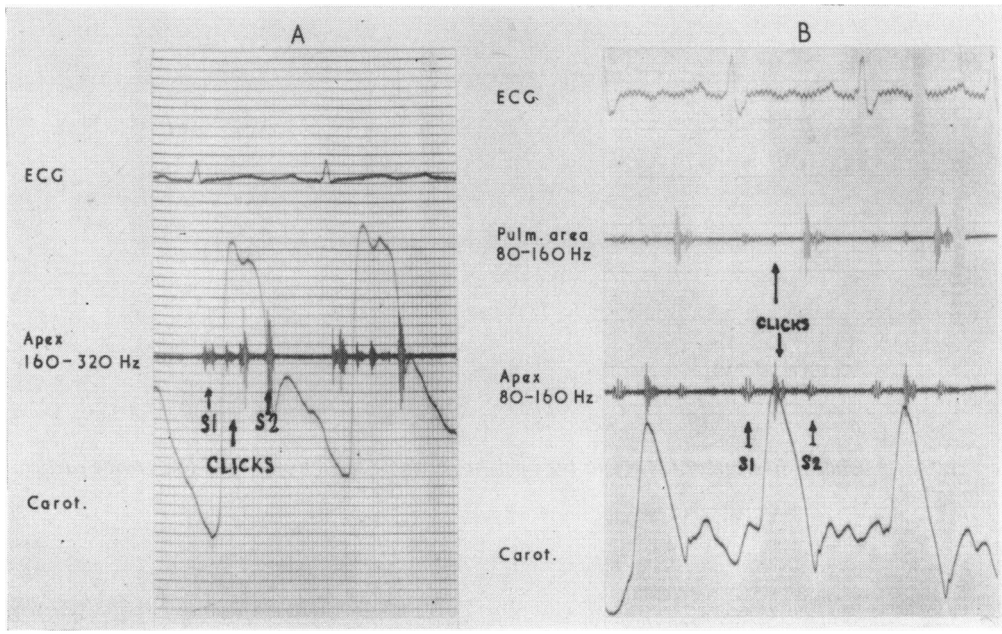

FIG. 2 *Phonocardiograms of (A) Case 2, and (B) Case 3 showing midsystolic clicks.*

features of systolic murmurs and honks

Transmission	*Respiratory changes and body position*	*Valsalva's manoeuvre*	*Amyl nitrite*
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased or eliminated	—
Whole chest	,, ,, ,, ,, ,,	,, ,, ,,	Eliminated
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased or eliminated	—
Whole chest	,, ,, ,, ,, ,,	,, ,, ,,	Decreased
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased or eliminated	—
Whole chest	,, ,, ,, ,, ,,	,, ,, ,,	Decreased
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased or eliminated	Increased; recorded earlier in systole
Whole praecordium	Present for few seconds only in upright position	—	—
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased or eliminated	Increased; recorded earlier in systole
Whole praecordium	Present for few seconds only in upright position	—	—
Absent	Accentuated by expiration and upright position, reduced by inspiration	—	Increased; recorded earlier in systole
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased or eliminated	Increased; recorded earlier in systole
Absent	Accentuated by expiration and upright position, reduced by inspiration	Eliminated	Not modified
Absent	Accentuated by expiration and upright position, reduced by inspiration	Decreased	Increased; recorded earlier in systole

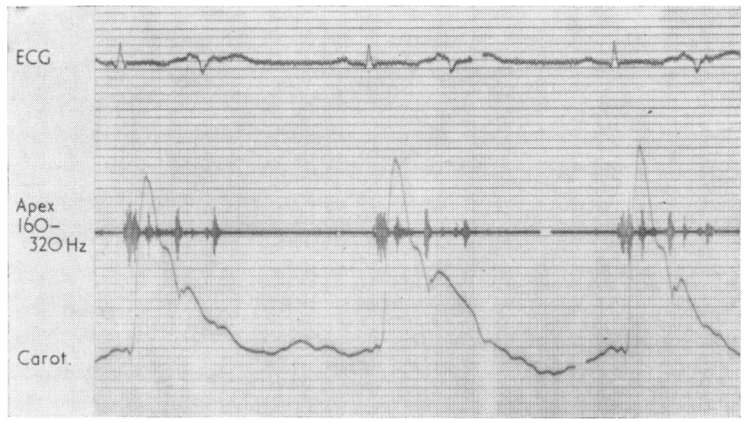

FIG. 3 *Phonocardiogram of Case 5 in the upright position: the murmur and click move earlier in systole.*

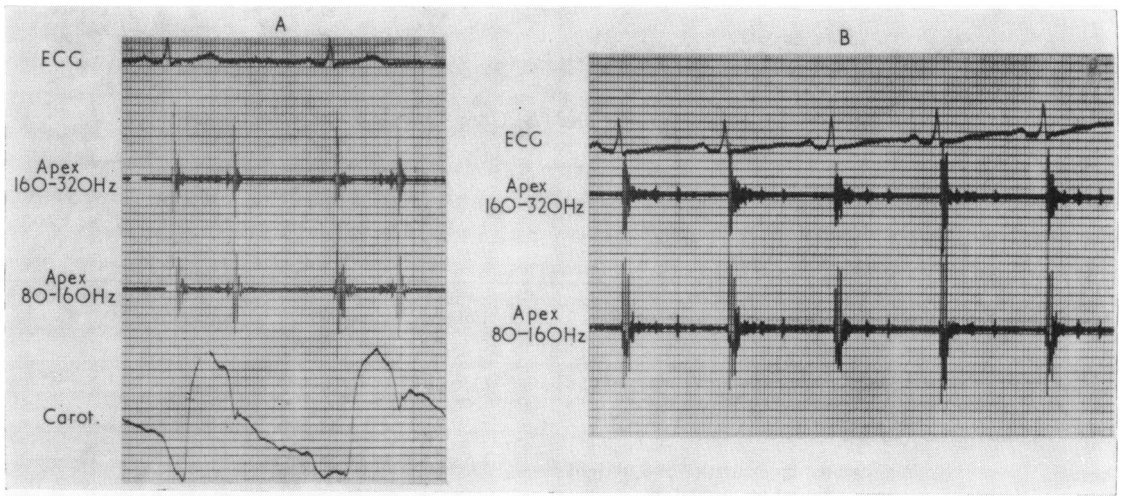

FIG. 4 *Phonocardiograms of Case 6 showing (A) the systolic murmur and (B) that, after amyl nitrite inhalation, the murmur becomes louder and moves earlier in systole.*

generally soft, grade 2/6; spontaneous changes in intensity were frequently observed. The shape was almost constantly of crescendo-decrescendo type (Fig. 1 and 5). The murmur was invariably louder during expiration and especially when the patients assumed the upright position (Fig. 3 and 6); the murmur was reduced by inspiration, and reduced or eliminated by Valsalva's manoeuvre. The amyl nitrite test was performed in 6 patients: the murmur increased in 5 (Fig. 4) and remained unmodified in one. In the upright position as well as after amyl nitrite inhalation, the murmur and the click generally moved earlier in systole (Fig. 3, 4, and 6). A systolic honk was present in the recumbent position in 3 patients; its main characteristics were: its appearance in the second half of systole, at times ending just before the second sound, or extending into it; fast crescendo-decrescendo in shape; intermittent with long periods of absence; variable in intensity, at times becoming very loud or extremely loud to be heard all over the chest; almost constantly accentuated or initiated during expiration and in the upright position (Fig. 7); reduced or eliminated by inspiration, Valsalva's manoeuvre, and amyl nitrite inhalation. In 2 patients the honk was audible only in the upright position; its features were similar to the above-mentioned except for a lesser intensity and transmission.

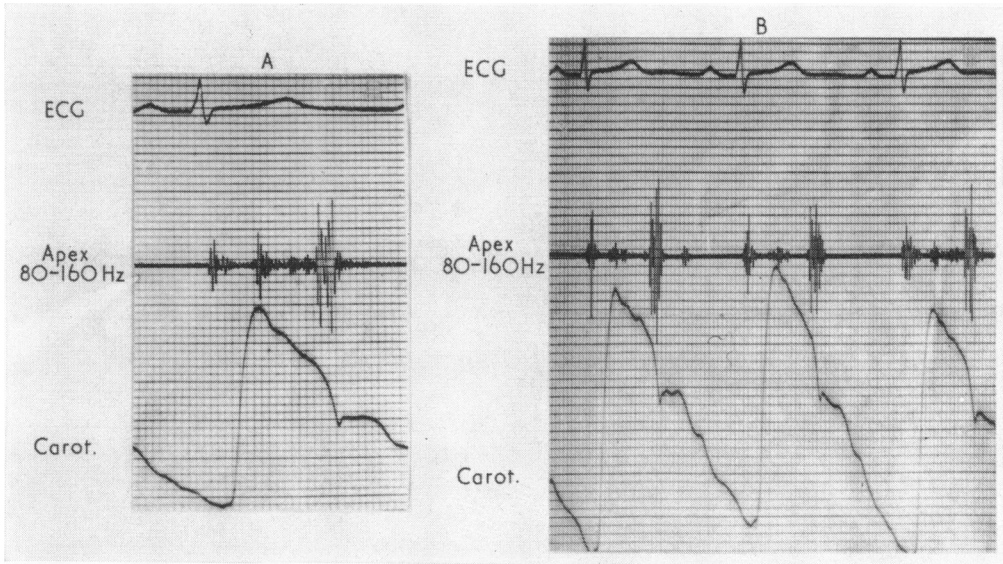

FIG. 5 *Phonocardiograms of Case 7 showing (A) midsystolic clicks and a late systolic murmur, and (B) variations in timing of the murmur which is midsystolic in the first two beats, and late systolic and crescendo-decrescendo in shape in the third beat.*

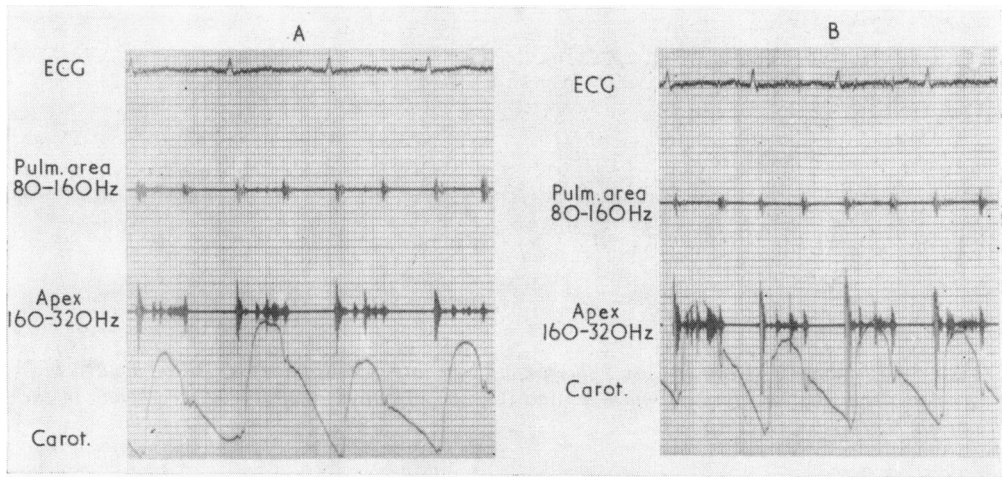

FIG. 6 *Phonocardiograms of Case 8 showing (A) midsystolic clicks and a late systolic murmur which presents spontaneous variation in intensity from beat to beat, and (B) the earlier appearance of the clicks and the increased intensity of the murmur in the upright position.*

Electrocardiogram One patient had supraventricular extrasystoles; 4 had ventricular extrasystoles; in 2 the extrasystoles were multifocal (Fig. 8). In 3 cases the extrasystoles were recorded in the recumbent position and became more frequent when assuming the upright position. In one case extrasystoles were present only in the upright position. Four patients had low, flat, or negative T waves in leads III, or in leads III and aVF, or in leads II, III, and aVF (Fig. 9). The T wave abnormalities were constantly increased by the upright position (Fig. 9). The upright position was respon-

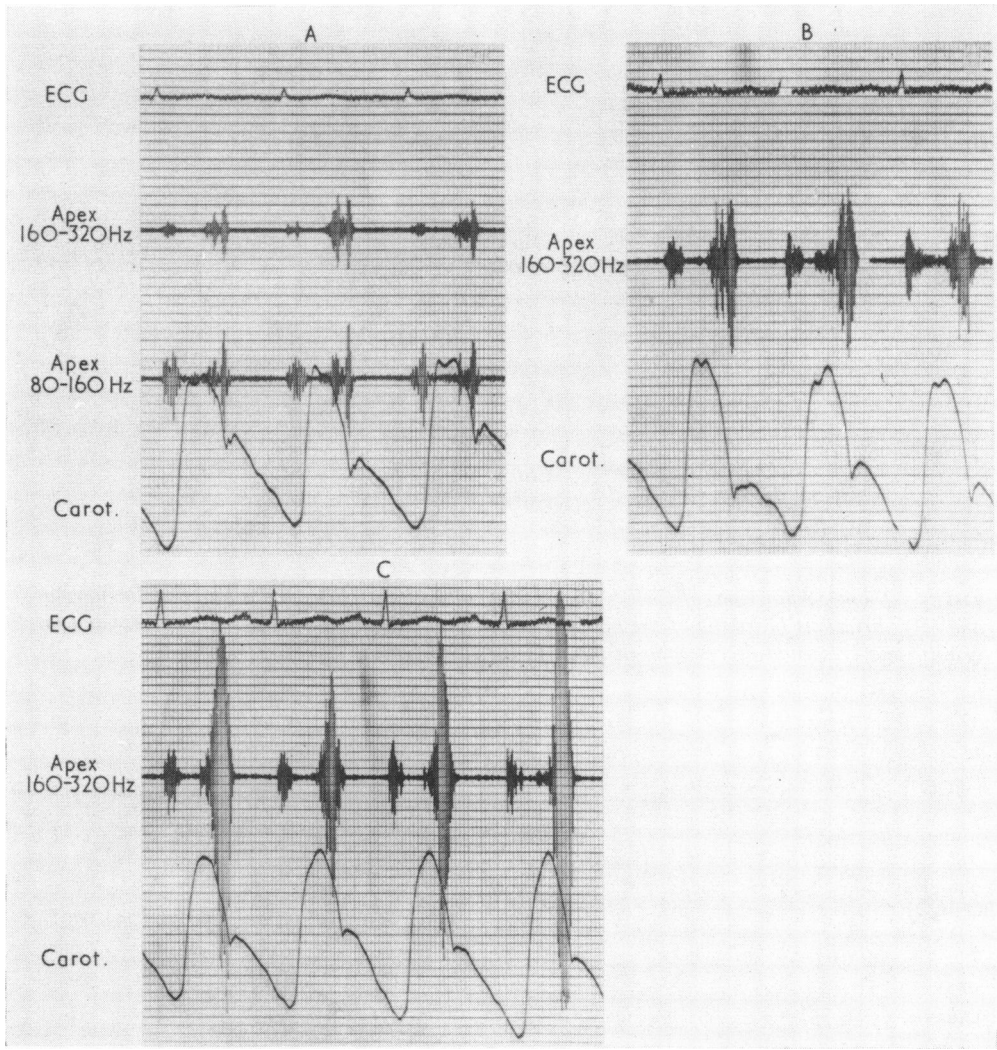

FIG. 7 *Phonocardiograms of Case 2 showing (A) the late systolic murmur, (B) a 'honk' which develops from the late systolic murmur, and (C) the increased intensity of the 'honk' in the upright position.*

sible for the appearance of similar T wave abnormalities in 3 other patients who had normal T waves in the recumbent position.

Chest x-ray

No cardiac abnormalities were observed in 5 patients. The left atrium was of normal size in all patients. Questionable left ventricular hypertrophy was present in 3 patients, and slight prominence of the pulmonary artery in 3 patients. The patient with associated atrial septal defect (Case 3) had obvious right ventricular enlargement and prominent pulmonary arteries.

Haemodynamic studies

The 3 patients who had cardiac catheterization (Cases 1–3) presented normal pressures in the right heart, pulmonary artery, and left ventricle; the pulmonary capillary pulse showed no abnormalities. In Case 3 the clinical diagnosis of secundum atrial defect was confirmed. Left ventricular cineangiocardiograms showed in all cases a systolic ballooning

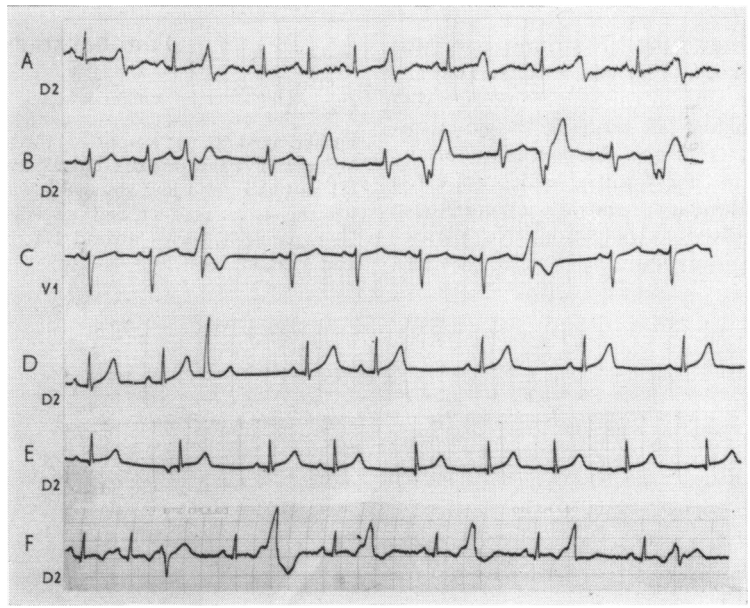

FIG. 8 *Electrocardiogram in the upright position of Cases 2 (A), 3 (B), 4 (C), and 5 (F), showing frequent and sometimes multifocal ventricular extrasystoles, and the electrocardiogram of a brother of Case 4 (D, E) showing sinus bradyarrhythmia, wandering pacemaker, and extrasystoles.*

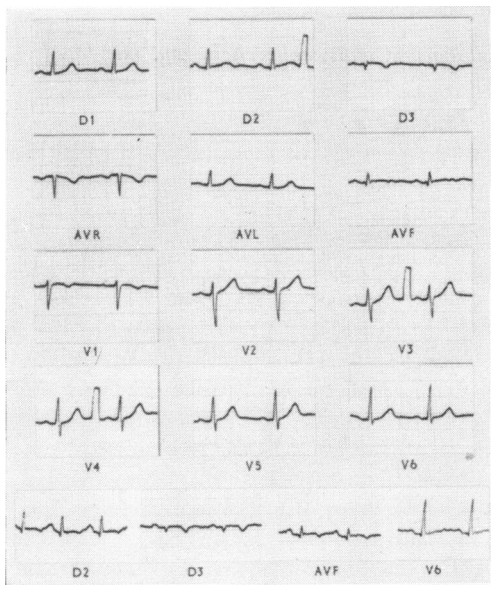

FIG. 9 *Electrocardiogram of Case 5 showing flat T waves in lead aVF and negative T wave in lead III in the recumbent position;* lower strip: *negative T waves in leads II, III, and aVF, and flat T wave in lead V6 in upright position.*

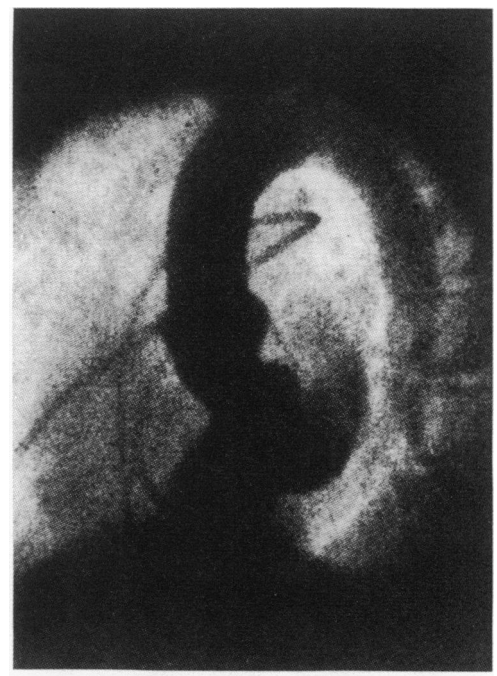

FIG. 10 *Selective left ventricular cineangiocardiography of Case 1 showing the systolic ballooning of the mitral leaflets into the atrium, mild mitral regurgitation, and an abnormal contraction ring of the inferior wall with partitioning of the cavity in two chambers.*

of the mitral valve into the left atrium, associated with mild regurgitation (Fig. 10). In Case 1 an abnormal contraction ring in the posteroinferior wall with partitioning of the left ventricle in two chambers was observed (Fig. 10). At operation for the atrial septal defect in Case 3, mitral leaflets appeared conspicuously redundant; mitral incompetence could not be assessed at palpation. No pleuropericardial adhesion was found.

Familial study

Case 1

Father, aged 50, not examined; the mother, aged 46, had biphasic T waves in lead II, negative T waves in leads III and aVF, and low voltage T waves in leads V5 and V6; the sister, aged 23, had low voltage T waves in lead II, negative T waves in lead III, biphasic T waves in lead aVF.

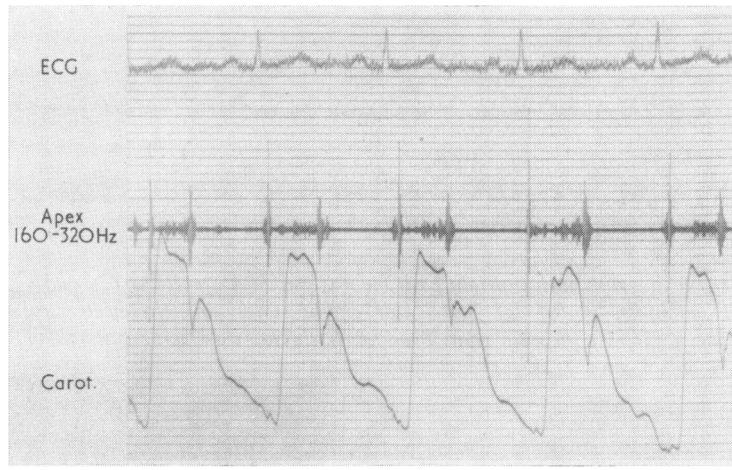

FIG. 11 *Phonocardiogram of a brother of Case 2 showing midsystolic clicks and mid-late systolic murmur.*

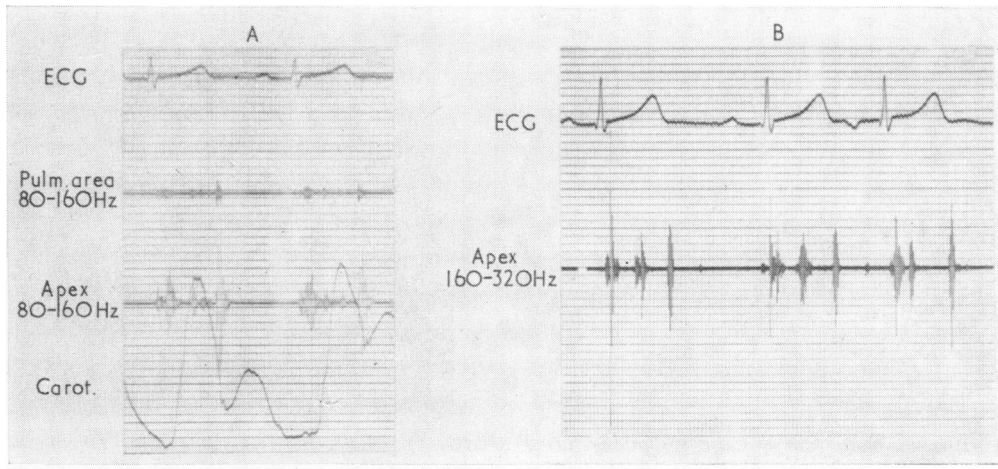

FIG. 12 *Phonocardiograms of a brother of Case 4 showing (A) midsystolic clicks and a late systolic murmur, and (B) midsystolic clicks; the midsystolic click moves earlier in systole in the third beat (extrasystole).*

Case 2

The father, aged 59, had no abnormal findings; the mother, aged 53, had slight pectus excavatum; a brother, aged 27, had pectus excavatum, slight kyphoscoliosis, slight flat foot, midsystolic click, apical late systolic murmur grade 2/6 (Fig. 11) which became louder and sometimes holosystolic in upright position; a brother, aged 20, had sinus arrhythmia and wandering pacemaker.

Case 3

The father, aged 49, a brother, aged 15, and a sister, aged 11, had no abnormal findings; the mother, aged 45, had supraventricular extrasystoles; a sister, aged 21, had a slightly high arching of the palate, slight hollow foot, and sinus arrhythmia; a sister, aged 13, had sinus bradyarrhythmia; a brother, aged 8, had left axis deviation of the QRS on the frontal plane (−15°); a brother, aged 3, had incomplete right bundle-branch block with left axis deviation of the initial vector of QRS on the frontal plane (−10°).

Case 4

The father, aged 35, the mother aged 29, a brother aged 12, and a sister aged 5, had no abnormal findings; a brother, aged 10, had a midsystolic click, late systolic apical murmur grade 2/6 (Fig. 12), transient late systolic honk in the upright position, sinus bradyarrhythmia, wandering pacemaker, and supraventricular and ventricular extrasystoles (Fig. 8), more frequent in the upright position.

Case 5

No member of the family could be examined.

Case 6

The father, aged 59, has not been examined; the mother, aged 55, had intermittent midsystolic click; the sister, aged 17, had a high arched palate, very short hands and feet, intermittent midsystolic click, late systolic apical murmur grade 2/6, flat T wave in lead aVF, and negative T wave in lead III in the recumbent position, and negative T waves in leads II, III, and aVF in upright position.

Case 7

The father, aged 51, had right axis deviation of QRS on the frontal plane (+10°); the mother, aged 41, had flat T waves in leads III and aVF in the upright position; a sister, aged 26, had sinus bradyarrhythmia and left anterior hemiblock; a sister, aged 18 (twin of the patient), had intermittent midsystolic click, short PQ (0·09 sec), right axis deviation of the QRS on the frontal plane (+100°), flat T wave in lead III in the recumbent position, negative T wave in lead III and flat T waves in leads II and aVF in the upright position (Fig. 13); a sister, aged 17, had a slight high arched palate, kyphoscoliosis, and left anterior hemiblock; a brother, aged 6, had left anterior hemiblock (Fig. 14).

Case 8

The father, aged 52, had flat feet; the mother, aged 47,

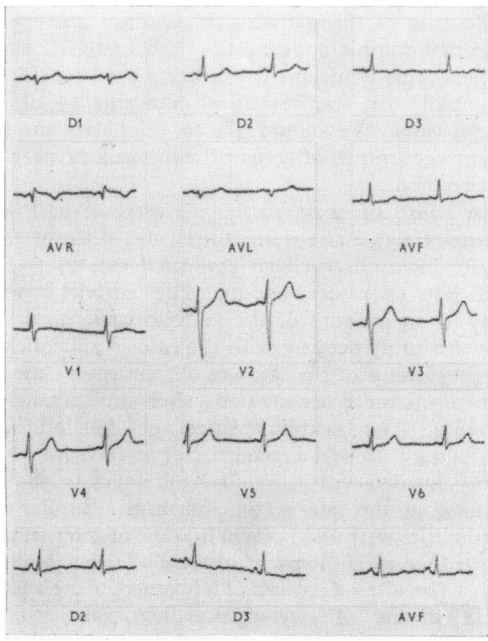

FIG. 13 *Electrocardiogram of a sister (twin) of Case 7, showing short PQ interval, right axis deviation of the QRS on the frontal plane, flat T wave in lead III in the recumbent position;* lower strip: *flat T waves in leads II and aVF, and negative T waves in lead III in the upright position.*

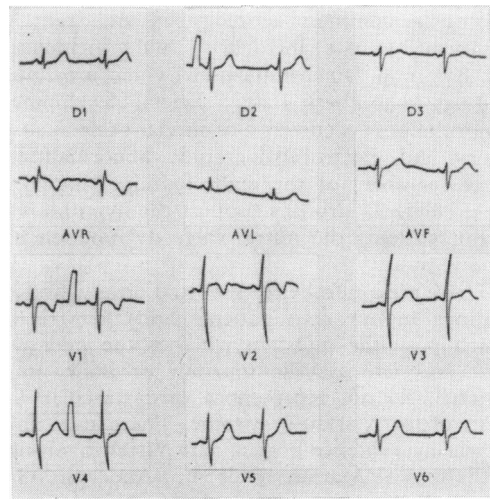

FIG. 14 *Electrocardiogram of a brother of Case 7 showing left anterior hemiblock.*

had incurved little fingers, a midsystolic click in the upright position, biphasic T wave in leads II and aVF, and negative T waves in lead III in the upright position; a brother, aged 18, had a slight high arched palate, long extremities, and slight hollow feet; a sister, aged 9, had incurved little fingers, slight flat feet, and left anterior hemiblock.

Case 9

The father died at the age of 40 of bronchopneumonia; the mother, aged 40, and a sister, aged 17, had no abnormal findings; a sister, aged 21, had slight arched palate, kyphoscoliosis, incurved little fingers, flat T waves in leads II, III, and aVF in the upright position; a brother, aged 18, had a high arched palate and kyphoscoliosis.

Discussion

Many previous reports dealing with the ballooning deformity of the mitral valve and with the related syndrome of midsystolic click and late systolic murmur included patients with cardiac diseases of different aetiology: developmental abnormalities of the mitral apparatus, idiopathic rupture of the chordae tendineae, rheumatic endocarditis, mitral valve operation, cardiomyopathy, ischaemic papillary muscle dysfunction (Tavel *et al.*, 1965; Hancock and Cohn, 1966; Leon *et al.*, 1966; Rackley *et al.*, 1966; Criley *et al.*, 1966; Behar *et al.*, 1967; Lucardie and Durrer, 1967; Stannard *et al.*, 1967; Barlow *et al.*, 1968; Bittar and Sosa, 1968; Leachman *et al.*, 1969; Pomerance, 1969; Fontana *et al.*, 1970; Mercer, Frye, and Giuliani, 1970; Dillon *et al.*, 1971). Our patients presented many features suggesting a common aetiology: young age; predominant female incidence; high incidence of red hair and fair complexion (which are unusual findings in southern Italy); skeletal developmental abnormalities; occurrence of similar skeletal auscultatory and electrocardiographic abnormalities in other members of the eight families studied. All these elements strongly support the hypothesis that in our patients the mitral valve dysfunction has a genetic basis.

There are a number of reported observations and findings in our own patients and their relatives which pose the question whether the midsystolic click and late systolic murmur or honk, in our patients, do not represent a cardiovascular *forme fruste* of the Marfan syndrome. These are: (a) The increasing evidence of frequent mitral involvement in the typical Marfan syndrome (Anderson, Grondin, and Amplatz, 1968). (b) The possibility that mitral insufficiency may appear as an isolated cardiovascular manifestation of the Marfan syndrome (McKusick, 1960; Segal, Kasparian, and Likoff, 1962; Read, Thal, and Wendt, 1965). (c) The finding of myxomatous transformation of the mitral leaflets (a frequent finding in the Marfan syndrome) observed in some cases with ballooning mitral valve deformity and mitral insufficiency (McKusick, 1960; Berenson and Geer, 1963). (d) The occurrence of midsystolic clicks and late systolic murmurs in patients with atypical Marfan syndrome (Hancock and Cohn, 1966; Barlow *et al.*, 1968). (e) The finding in some patients with the Marfan syndrome of an electrocardiographic pattern similar to that found in patients with a midsystolic click and late systolic murmur (Bowers, 1961; Segal *et al.*, 1962). (f) The high incidence among our patients and their relatives of some skeletal stigmata, like kyphoscoliosis, high arched palate, pectus excavatum, incurved little fingers, and flat and hollow feet, which are known to be also associated with the Marfan syndrome. However, not one of our patients or their relatives presented the association of the typical muscular, skeletal (dolicostenomelia, dolicocephaly), ocular (dislocated lenses, megalocornea, microcornea, keratoconus, interstitial keratitis), and cardiovascular stigmata (aortic dilatation, aortic regurgitation) of the Marfan syndrome.

Because of the pathological findings and of the cineangiographic appearances (ballooning of mitral leaflets), this syndrome has hitherto been considered essentially the expression of abnormality of the mitral valve. We should like to emphasize the frequent occurrence of signs of associated myocardial involvement.

In some of their patients Kesteloot and Van Houte (1965), Lane *et al.* (1968), and Willems *et al.* (1969) have observed an abnormal carotid tracing and left apex cardiogram. The carotid tracing showed an incisure of the systolic wave occurring almost simultaneously with the midsystolic click or the beginning of the late systolic murmur; the incisure was more conspicuous after amyl nitrite inhalation. The systolic plateau of the left apex cardiogram showed a retraction or an incisure which also coincided with the midsystolic click or the beginning of the late systolic murmur. Similar abnormalities were also present in some of our patients. According to Willems *et al.* (1969) these findings suggest an altered pattern of left ventricular ejection.

By means of cineangiocardiographic studies, Grossman *et al.* (1968) showed an abnormal contraction ring of the posteroinferior wall of the left ventricle with partitioning of the left ventricle in two chambers. Garello and Ribaldone (1971) showed the existence of a pressure gradient between the two chambers. This pattern was present in one of our 3 patients (Case 1) in whom left ventricular

cineangiocardiography had been performed (Fig. 10).

The frequent occurrence of ventricular extrasystoles and of abnormal T wave in leads II, III, and aVF and sometimes in the left praecordial leads, has been widely reported. In our patients we made additional observations: extrasystoles and T wave abnormalities are frequently influenced by changes in posture, being accentuated by the upright position; in some of our patients with a normal electrocardiogram, the upright position was an easy way to provoke these abnormalities, together with the auscultatory findings.

Myocardial involvement is also suggested by another hitherto undescribed electrocardiographic pattern: 4 of our patients' relatives, 3 of them belonging to the same family (Case 7), had a typical pattern of left anterior hemiblock; others had abnormal left or right axis deviation of the QRS in the frontal plane. A high incidence of abnormal left axis deviation of the QRS was also reported by Willems *et al.* (1969).

These findings, indicating the existence of myocardial involvement, support the hypothesis of Grossman *et al.* (1968) that the midsystolic click and late systolic murmur or honk may be principally due, at least in some cases, to a disturbance of myocardial contractility rather than to a valvular abnormality. According to Engle (1969), the abnormal systolic contraction ring of the posteroinferior wall of the left ventricle could lift the posterior papillary muscle into the cavity of the ventricle and therefore allow the chordae tendineae to slacken, the posterior leaflet to balloon, and some regurgitation to occur. The possibility that a systolic honk may be recorded in spite of normal mitral leaflets and chordae tendineae has been proved at the necropsy of a patient with nonobstructive cardiomyopathy and mitral insufficiency due to papillary muscle dysfunction (unpublished data). This hypothesis receives further support with the localization of the T wave abnormalities, which suggests a disturbed repolarization of the area which is contracting abnormally, that is the posteroinferior wall of the left ventricle, and by the observation that both T wave abnormalities and auscultatory findings are accentuated by the upright position. The hypothesis that a primary defect of the posterior mitral leaflet can succeed in producing a distortion of the circumflex artery, and therefore a posterolateral ischaemia (Barlow and Bosman, 1966) seems unlikely. The possibility that the contraction abnormality of the wall results in the constriction of a coronary artery has been suggested by Grossman *et al.* (1968). One of our patients (Case 1) who presented angiographic evidence of an abnormal contraction ring experienced on one occasion true anginal pain. However, no coronary abnormalities have been demonstrated in some patients who had arteriography (Stannard *et al.*, 1967). Since in many previous reports, as well as in our patients, the T wave abnormalities had a nonspecific rather than an ischaemic pattern, we are inclined to accept the hypothesis that these changes express the abnormal repolarization of the fibres in the hypercontracted area (Garello and Ribaldone, 1971).

In spite of the above-mentioned data in favour of a myocardial mechanism responsible for the ballooning of the mitral valve, the problem remains controversial. Many more cineangiocardiographic and pathological studies are needed to prove this hypothesis.

Some auscultatory features of the familial midsystolic click and late systolic murmur syndrome deserve comment. First of all we must emphasize the frequent association with a late systolic honk (more than 50%). The main auscultatory and phonocardiographic features of the honk were represented by its late systolic timing and by its peculiar modifications with upright position, respiration, and respiratory manoeuvres. These features have diagnostic importance because they are quite different from those of the systolic honk in patients with mitral insufficiency of rheumatic origin, or due to ischaemic papillary muscle dysfunction, described in a previous report (Rizzon *et al.*, 1971). The late systolic murmur also presented some distinctive features: a crescendo-decrescendo shape and behaviour pattern in the upright position with respiration, and during respiratory manoeuvres similar to that of the honk; amyl nitrite inhalation generally increased the murmur producing it earlier in systole.

Among previous reports there is a certain degree of disagreement about the modifications of the murmur with respiration, respiratory manoeuvres, and amyl nitrite inhalation, while it is widely accepted that the murmur increases on upright position. Barlow *et al.* (1968) stated that the murmur was unpredictably modified by respiration and sometimes could increase on inspiration. According to the same authors, the Valsalva manoeuvre decreases the intensity of the murmur, while Kesteloot and Van Houte (1965) stated that its intensity increased. Amyl nitrite inhalation is reported to decrease the intensity of the murmur (Tavel *et al.*, 1965; Barlow *et al.*, 1968) which moves earlier in systole (Barlow *et al.*, 1968), to decrease the intensity in some cases, to increase it in others (Bittar and Sosa, 1968), to eliminate it with the appearance of an early systolic component (Leighton *et al.*, 1966), and to increase the intensity (Kesteloot and Van Houte, 1965;

Willems *et al.*, 1969; Fontana *et al.*, 1970). The reason for these contrasting results is probably the different aetiology of the patients investigated.

Factors responsible for the modification of the murmur on respiration, during respiratory manoeuvres with postural changes, and after amyl nitrite inhalation were thought to be variations of left ventricular end-diastolic volume (Kesteloot and Van Houte, 1965; Barlow *et al.*, 1968; Fontana *et al.*, 1970), and of the heart position in the chest (Leighton *et al.*, 1966; Fontana *et al.*, 1970). The conditions that decrease the end-diastolic volume and consequently reduce the left ventricular volume (upright position) are supposed to exaggerate the prolapse of the mitral leaflets and therefore increase the murmur. A modified position of the heart (respiration, respiratory manoeuvres) can change the direction and the proximity of the jet to the chest wall and hence its transmission. Amyl nitrite inhalation is known to decrease the murmur of mitral insufficiency because of the fall in systemic peripheral resistance. However, in cases with mitral insufficiency due to a ballooning mitral valve, these changes are probably exaggerated by the conspicuous reduction of left ventricular volume, which increases the prolapse of the leaflets, and hence increases the murmur.

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Requests for reprints to Professor Paolo Rizzon, Clinica Medica, Universita, 70124 Bari, Italy.