

Age and the clinical profile of idiopathic mitral valve prolapse

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SUMMARY The prevalence of mitral valve prolapse was determined in two independent populations (6887 consecutive adults and children referred for echocardiography during a three year period and 206 non-referred first degree relatives of 65 patients with mitral valve prolapse). In the 118 adults with echocardiographic evidence of prolapse those aged ≥ 50 years were significantly more likely to have pansystolic murmurs and increased echocardiographic dimensions than those aged < 50 years; and patients with complications of mitral valve prolapse were significantly older than those without. In the population referred for echocardiography and in the non-referred relatives there was a significant increase in prevalence in the two decades after adolescence (20-39 years) compared with that in the first two decades. The data suggest that prolapse principally becomes manifest in late adolescence when the growth spurt is complete and that thereafter the severity of prolapse increases with age in an important subset of patients. The latter findings accord with the predictions of the response to injury hypothesis for the pathogenesis of progressive changes.

Although mitral valve prolapse is now one of the most common causes of isolated mitral regurgitation in Western society,^{1,2} its aetiology remains speculative. We have proposed that the underlying pathophysiological mechanism is a continuing process of repeated minor injury and repair occurring during the cardiac cycle in a mitral valve with minor congenital anatomical variations in the valve apparatus.^{3,4} If this hypothesis is correct the development and progression of prolapse should be related to age. Genetic data^{5,6} suggest that the frequency of prolapse does indeed increase with age; however, a recent epidemiological study from Framingham did not support this suggestion.⁷

To explore the hypothesis further we investigated the association between age and the prevalence of idiopathic mitral valve prolapse in two independent populations, 6887 patients referred for echocardiography during a three year period and 206

unreferred first degree relatives of 65 patients with mitral valve prolapse. We also assessed the relation between age and the mode of presentation in 118 consecutive adult patients among the 6887 referred patients who were found to have primary or idiopathic prolapse.

Patients and methods

We determined the prevalence of mitral valve prolapse throughout the age spectrum among 6887 consecutive children, young adults (< 20 years), and adults who came to echocardiography during the period of this study (June 1980-June 1983).

Clinical evidence of mitral valve prolapse was deemed to be present if a mid to late systolic click with or without a systolic murmur was recorded at phonocardiography when either or both were detected on auscultation. The diagnosis was established at M mode echocardiography by the finding of abrupt mid to late systolic displacement of part of the mitral systolic closure line at least 2 mm below the line joining the point of valve closure in systole (C) to the point of valve opening in diastole (D). Mitral valve prolapse was also diagnosed if there was pansystolic prolapse with posterior displacement of

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at least 3 mm below the line joining C and D with the nadir occurring in mid-systole when cross sectional echocardiography also showed bulging of the mitral leaflet above the plane of the mitral annulus into the left atrium during systole on the apical four and two chamber views as described by Morganroth *et al.*⁸ Patients with typical phonocardiographic features in the absence of echocardiographic criteria were excluded as were patients with isolated pansystolic prolapse at M mode echocardiography without evidence of prolapse at cross sectional echocardiography and those with diseases known to be associated with mitral valve prolapse, that is secondary prolapse.⁹

We recorded M mode echocardiograms and phonocardiograms with an Irex mark II echoscope and a 2.25 MHz transducer, and cross sectional echocardiograms from a Toshiba Sonolayergraph

SSH10A with a 2.5 MHz transducer. To assess the effect of age on the severity of prolapse we related cardiac dimensions measured from the M mode echocardiograms, and symptoms, physical signs, and complications to age in the 118 consecutive adult patients. When the left ventricular diastolic dimension was >55 mm or the left atrial dimension was >40 mm cardiac dimensions were considered to be increased.

Results

RELATION BETWEEN AGE AND PREVALENCE

Mitral valve prolapse was detected at echocardiography in 123 (1.8%) of the clinical population of 6887 who had had echocardiograms and 21 (10%) of the 206 first degree relatives that we examined. Among the 123 prolapse patients there were

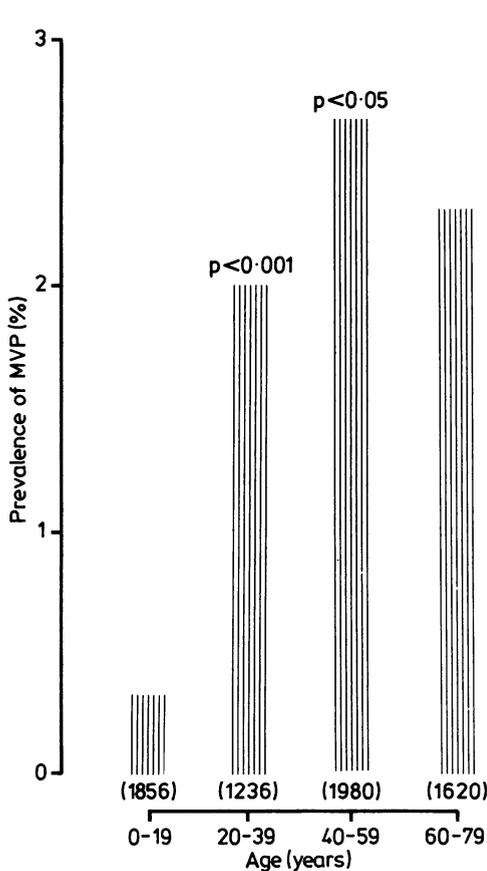


Fig. 1 Prevalence of mitral valve prolapse (MVP) by age in 6887 consecutive patients referred for echocardiography. The numbers studied in each age group are indicated in parentheses. Numbers of male and female cases in each 20 year segment were approximately equal.

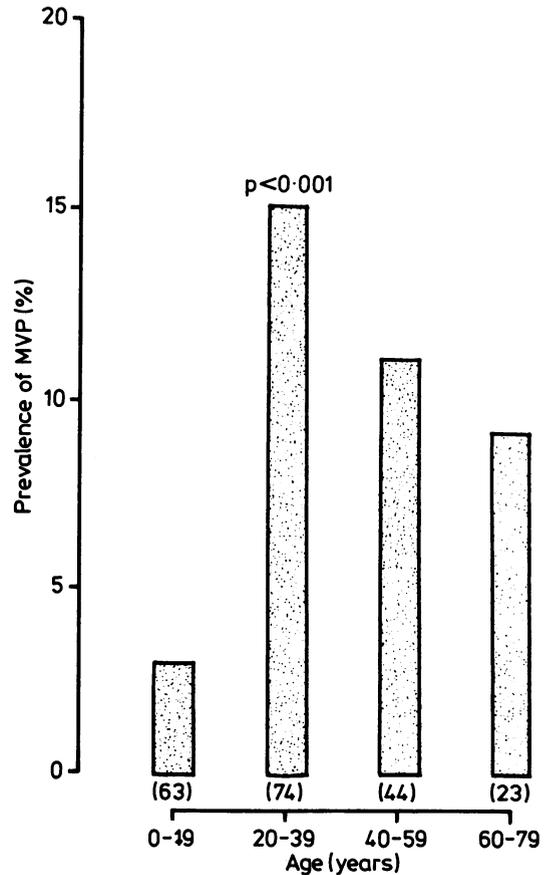


Fig. 2 Prevalence of mitral valve prolapse (MVP) by age in 206 consecutive first degree relatives. The numbers studied in each age group are indicated in parentheses. Numbers of male and female cases in each 20 year segment were approximately equal.

Table 1 Prevalence of mitral valve prolapse by 20 year periods in a referred clinical population and non-referred first degree relatives of patients with prolapse. *p* values refer to comparison of each prevalence in a 20 year period with that in the preceding 20 year period

Age	Clinical population (<i>n</i> = 6887)	<i>p</i> value	First degree relatives (<i>n</i> = 206)	<i>p</i> value
00–19	5/1856 (0.3%)	< 0.001	2/63 (3%)	< 0.001
20–39	25/1236 (2.0%)	< 0.05	11/74 (15%)	NS
40–59	53/1980 (2.7%)	NS	5/44 (11%)	NS
60–79	38/1620 (2.3%)		2/23 (9%)	

Table 2 Relation between physical signs and age in 118 consecutive adult patients with mitral valve prolapse (MVP)

Physical signs	Patients		<i>p</i> value
	< 50 years (<i>n</i> = 45)	≥ 50 years (<i>n</i> = 73)	
Pansystolic murmur	2 (4%)	24 (33%)	< 0.01
Late systolic murmur ± click	17 (36%)	28 (38%)	NS
Silent MVP (5) and systolic click only (42)	26 (58%)	21 (29%)	< 0.01

118 adults and five adolescents and children. Prolapse was rare in all patients and relatives under the age of 10 years; only one of 1385 had mitral valve prolapse (Figs. 1 and 2). During the second decade the prevalence of prolapse increased but the increase was mainly confined to the 15 to 19 year age group; four of the five children and adolescents with prolapse were in the 10–19 year age group (Figs. 1 and 2).

From these results we considered that the growth spurt may have had an effect on the development of prolapse. We therefore divided the patients and first degree relatives into 20 year age groups (Table 1) assuming that growth had ceased by the age of 19. When we compared the prevalence in the 20–39 year age group with that in the first two decades we found a highly significant increase ($p < 0.001$) in both study populations. But when we compared the prevalence in the 40–59 year age group with that in the 20–39 year age group (Table 1) no such dramatic increase was evident. Furthermore, as shown in Figs 1 and 2, the prevalence declined in later life.

SYMPTOM PROFILE IN ADULT PATIENTS WITH MITRAL VALVE PROLAPSE

Of the 118 adults with prolapse (mean age (SD) 51 (15) years, range 20–78 years) there were 67 females and 51 males (ratio 1.3:1). Of these, 17 patients were symptom free and had been referred only because of incidental auscultatory findings. The remaining 101 (86%) patients had symptoms at presentation. Palpitation was the commonest symptom, occurring in 53 patients (palpitation alone 31, and with chest pain and dyspnoea or both 22) of whom 38 (72%) were

≥ 50 years old. Chest pain alone was found in 20 patients and dyspnoea alone also in 20. The remaining eight presented with either syncope, transient ischaemic attacks, or panic attacks.

PHYSICAL SIGNS AND AGE

Table 2 shows the relation between physical signs and age. A significantly higher proportion of patients over 50 years presented with a pansystolic murmur ($p < 0.01$) than those under 50 years. The latter were more likely to have silent prolapse or an isolated click than were those aged ≥ 50 ($p < 0.01$). Pansystolic murmurs were more common in men (27%) than in women (17%) but the difference did not reach statistical significance ($p = 0.15$). In the five patients with silent prolapse no clicks or murmurs were heard or recorded at phonocardiography although there were unequivocal echocardiographic features of prolapse.

ECHOCARDIOGRAPHIC FEATURES

In 92 patients late systolic mitral valve prolapse was identified at M mode echocardiography; in a further 17 there was pansystolic prolapse. All these 17 patients had the auscultatory signs of mitral valve prolapse. In another six patients the diagnosis was confirmed at cross sectional echocardiography as it was not possible to obtain an M mode recording of sufficient quality to be certain of the diagnosis. Chordal rupture was diagnosed at echocardiography in three patients aged 63, 72, and 74 years.

Forty patients had increased cardiac dimensions at echocardiography (left ventricular diastolic dimension > 55 mm, left atrial dimension > 40 mm);

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29 of these were ≥ 50 years, and 11 < 50 years ($p < 0.01$).

COMPLICATIONS AND AGE

Twelve (10%) of the 118 patients presented with complications directly related to mitral valve prolapse. Their mean age (SD) was 59 (10) years. Ten of these 12 patients were ≥ 50 years and the group was older than those patients without complications ($p < 0.05$). Bacterial endocarditis occurred in six, and two of these had ruptured chordae as a result of the infection. Three others presented with syncope due to ventricular tachycardia. Two patients presented with severe mitral regurgitation. One of them had a valve replacement. The other patient had evidence of chordal rupture at echocardiography. The final patient of this group who presented with a complication of mitral valve prolapse had a left hemiplegia of sudden onset. Four vessel intracranial angiography showed no evidence of a localised vascular lesion, and an embolus originating from a prolapsing mitral valve was diagnosed.

Discussion

We undertook this study to determine whether there was clinical evidence to support our hypothesis that the underlying process in the pathogenesis of mitral valve prolapse is a continuing cellular proliferative response to repeated minor injury occurring in the prolapsing valve during the cardiac cycle; this results in increased production of collagen (largely type III collagen) and mucopolysaccharide.^{3,4} If the hypothesis is correct the prevalence of the mitral valve prolapse syndrome and its complications will increase with increasing age and the prevalence among children will be low.

The data reported in this study accord with these predictions. There was a considerable increase in prevalence in late adolescence, after the growth spurt, in both the clinical population and the non-referred population of first degree relatives. The prevalence after the second decade, however, followed a normal distribution pattern with an unexplained decline in later life. While ascertainment bias introduced by the clinical population that we studied may have influenced the findings, this was not a factor in the relatives examined. The likelihood of an association between the growth spurt in the second decade and the onset of echocardiographically detectable prolapse is supported by the finding that the diagnosis of mitral valve prolapse is uncommon in children. We found only one child with prolapse among 1462 children aged < 10 years and none among 23 first degree relatives who were aged < 10 years. Sakamoto reported a preva-

lence of only 0.8% among 26 604 schoolchildren aged < 9 years¹⁰ and the only large reported case series of children contains 119 children who were collected over a 22 year period.¹¹

Our prevalence findings accord with those of Devereux *et al* and Strahan *et al*.^{5,6} In their studies of heritability they found a similar age dependence in that they only detected prolapse at echocardiography after the age of 10–15 years. These investigators also found prevalences of 30% and 40% respectively among first degree relatives of patients with mitral valve prolapse,^{5,6} whereas we detected prolapse in only 10% (12.8% in those aged over 19 years, Table 1). Ascertainment bias may have played a role in the high prevalence reported by Devereux *et al* because almost 40% of the relatives they studied knew they had a murmur before diagnosis and this could have influenced their willingness to participate in the study. No relative in our study was aware of the presence of any cardiac abnormality. We have previously reported a prevalence of 21% of prolapse among relatives of patients with severe mitral regurgitation due to floppy mitral valves.¹² It is possible that those with a floppy mitral valve and pronounced regurgitation are a separate subgroup among persons with mitral valve prolapse who have advanced disease and an inheritance pattern different from those without severe mitral regurgitation.

The reason for the decline in the prevalence in later life that we found is unclear. An increased mortality associated with mitral valve prolapse is possible but unlikely.¹³ The diagnosis at echocardiography may be obscured by a concomitant abnormality of the mitral apparatus in the elderly such as mitral annular calcification.¹⁴ Alternatively there may have been a different pattern of referral in this age group. Our findings were similar to those of Savage *et al* who studied the prevalence of mitral valve prolapse in a free living population.⁷

All patients in our series had idiopathic prolapse. They met strict echocardiographic criteria that were supplemented by phonocardiographic documentation of clinical findings. It was surprising that only 1.8% of our 6887 consecutive referred patients had prolapse. Markiewicz *et al* in a study of the echocardiographic findings in 1000 consecutive patients found a prevalence of 6%.¹⁵ The series, however, included only 86 (9%) children (< 12 years) and they grouped idiopathic and secondary prolapse together. In our study we examined 1462 children (< 10 years) who made up 21% of the study population and included only patients with idiopathic mitral valve prolapse. Even so, the prevalence among adults in our referred population was only 2.4%.

The frequency of isolated clicks declined with age in our series of 118 consecutive adults with prolapse (Table 2) and the findings of Beton *et al* were similar.¹⁶ We also found that a significantly greater proportion of those with pansystolic murmurs were older than 50 years ($p < 0.01$) which is consistent with mitral valve prolapse being a progressive age related condition. We cannot determine whether progression from stage 1, an isolated click, through stage 2, a click and late systolic murmur, to the final stage 3, a pansystolic murmur, occurred in all of these patients. This was indeed the case in one patient who presented 20 years ago for a medical check and was found then to have an isolated click. When he had another routine medical examination 10 years later he had a pansystolic murmur.

Pansystolic murmurs were more common in men (27%) than in women (17%) in our series. This accords with previous reports that the complications of severe regurgitation and chordal rupture of the floppy mitral valve occur predominantly in middle aged and elderly men.^{12,17} Our finding of a significantly greater proportion of patients ≥ 50 with increased echocardiographic dimensions ($p < 0.01$) than those < 50 is also consistent with prolapse being a progressive condition. Patients presenting with complications were also significantly older than those without such complications. The most frequent serious complications in our series were bacterial endocarditis, recurrent ventricular tachycardia, and severe mitral regurgitation. We did not find the high frequency of cerebral emboli reported by Malcolm *et al*.¹⁸ The difference may be explained by different referral patterns. As we have reported elsewhere, our patients were leaner than age- and sex-matched controls¹⁹ as were the patients of Devereux and his associates.¹³

In conclusion we suggest that idiopathic mitral valve prolapse is an age dependent condition that usually becomes clinically evident in early adulthood after the growth spurt; and that in a subset of subjects the severity of leaflet prolapse increases with age. These data accord with the predictions of a "response to repeated injury" hypothesis to explain the pathogenesis of progressive changes. Progressive prolapse due to the effect of intraventricular pressure on a congenitally weakened mitral valve would also accord with these findings, but biochemical studies of excised valves^{3,4} favour the former explanation. Prospective studies of carefully documented cases are required to define which persons with mitral valve prolapse in the general population develop progressive changes and the clinical syndrome of prolapse, and to establish the prognosis in this important subset of patients.

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