

Mitral valve prolapse and joint hypermobility: evidence for a systemic connective tissue abnormality?

DAVID PITCHER AND RODNEY GRAHAME

From the Departments of Cardiology and Rheumatology, Guy's Hospital, London SE1 9RT

SUMMARY Clinical evidence for an abnormality of extracardiac connective tissue was sought in 21 patients with idiopathic mitral valve prolapse and was compared to that in 21 matched controls. The incidence of rheumatic and orthopaedic complaints and the prevalence of hypermobile joints, Marfanoid habitus, and skeletal deformity were compared in the 2 groups. Skin thickness and elasticity were measured, and the mean values in the 2 groups were compared. Hypermobile joints were significantly commoner in patients with mitral valve prolapse. Easy bruising was reported significantly more commonly by patients with mitral prolapse; the incidence of other rheumatic complaints was similar in the 2 groups. There was no significant difference in skin thickness, skin elasticity, and the prevalence of either skeletal deformity or Marfanoid habitus between patients with mitral valve prolapse and controls. The results support previous evidence of an association between mitral valve prolapse and benign hypermobility of the joints, but emphasise that many patients with mitral valve prolapse have no clinically apparent connective tissue abnormality outside the heart. It remains uncertain whether the valve lesion in these patients represents a tissue-specific abnormality of mitral valve collagen or the only clinical expression of a minor systemic connective tissue abnormality.

The floppy mitral valve is a common cardiac abnormality^{1,2} in which the mitral leaflets and chordae become stretched and elongated, allowing redundant valve tissue to prolapse into the left atrium in systole. Many patients with mitral valve prolapse (MVP) have no symptoms, but some present with chest pain, palpitation, syncope, or dyspnoea. The characteristic clinical sign is a nonejection systolic click with or without a late systolic murmur. Some patients have only a mitral regurgitant murmur, and in others MVP is clinically silent but may be detected by echocardiography or contrast left ventriculography.

An increased prevalence of MVP, detected clinically and by echocardiography, has been shown in patients with heritable connective tissue disorders—Marfan's syndrome,^{3,4} the Ehlers-Danlos syndrome,^{5,6} and osteogenesis imperfecta.⁷ We recently demonstrated an increased prevalence of MVP in patients with the hypermobility syndrome.⁸ In this communication we report the results of a

further study in which we sought clinical evidence of extracardiac connective tissue abnormalities in a group of patients with idiopathic MVP and in a control group.

Patients and methods

Twenty-one patients with MVP were recruited from the Cardiology Clinic of Guy's Hospital. Nine were male and 12 female; mean age (\pm standard deviation) was 42.6 ± 12.7 years. The clinical diagnosis of MVP was confirmed by echocardiography in all cases. Initial referrals had been either for cardiac symptoms or for assessment of a symptomless cardiac murmur. Twenty-one control patients, matched for age (mean age \pm SD = 43.5 ± 12.5 years), sex, and mode of presentation were recruited from the same clinic. No control patient had clinical or echocardiographic evidence of MVP, and in all controls a clear alternative cause for their cardiac symptoms and signs had been established. Patients with rheumatic heart disease were excluded from the study because of uncertainty concerning the effect of rheumatic fever on subsequent joint mobility.

Accepted for publication 15 July 1981.
Correspondence to Dr D. Pitcher, Plymouth General Hospital, Plymouth, Devon.

All patients were examined by a single observer under blind conditions. Information was sought concerning past and present rheumatic and orthopaedic complaints. Joint mobility was assessed in each case by determining the hypermobility score proposed by Beighton and Horan.⁹ A score of 3 or greater out of a maximum of 9 was considered to indicate widespread hypermobility of the joints. Skinfold thickness was measured on the dorsum of the right hand with the Harpenden caliper.¹⁰ Skin elasticity was measured by the suction cup method.¹¹ In addition measurements were made of the patients' height, arm span, and upper and lower segments. Clinically apparent skeletal deformities were noted.

Statistical analysis of the results was performed with McNemar's test for paired alternatives or the *t* test, as appropriate.

Results

Hypermobility of the joints was significantly more common in patients with MVP than in the control group, being present in 7/21 patients with MVP but in only 1/21 controls ($p < 0.05$).

Mean skin thickness (\pm SD) was the same (0.11 ± 0.02 cm) in patients with MVP and in the control patients. The skin elastic modulus was not significantly different in the 2 groups, mean values (\pm SD) being $0.66 \pm 0.33 \text{ Pa} \times 10^7$ in patients with MVP and $0.86 \pm 0.41 \text{ Pa} \times 10^7$ in controls.

Marfanoid habitus was more common in patients with MVP. A reduced upper segment/lower segment ratio (≤ 0.89) was present in 7/21 patients with MVP and in 3/21 control patients. This difference was not

statistically significant. Span exceeded height in only one patient in each group.

The prevalence of skeletal deformities was similar in patients with MVP and in controls, mild degrees of scoliosis being relatively common (7/21) in both groups.

Back pain was a common symptom in both groups of patients. The incidence of other rheumatic and orthopaedic complaints was low, and similar in both groups (Table 1), except for easy bruising, which was reported significantly more commonly by patients with MVP ($p < 0.05$).

Discussion

The pathogenesis of MVP has not been established. Increasing evidence¹² points to a primary valvular abnormality, most probably defective or deficient collagen in the connective tissue framework of the valve and its supporting structures. It is likely that several different biochemical abnormalities may affect mitral valve collagen and lead to MVP, since MVP occurs with increased prevalence in several distinct disorders of connective tissue.³⁻⁷ However, many patients with MVP do not have the classical features of these disorders, and previous suggestions¹³ that MVP may represent a forme fruste of Marfan's syndrome have not been substantiated.

Abnormal chordal arrangement may provide inadequate support and predispose to the development of a floppy valve.¹⁴ However, this explanation cannot be universal, since it could not account for the occasional association of aortic valve prolapse with MVP.¹⁵ A recent report¹⁶ suggested that thickening of the amorphous zona spongiosa of the mitral valve may be the primary abnormality, but failed to explain how this could weaken the valve unless the supporting collagen tissue (zona fibrosa) is deficient or damaged.

In a recent study⁸ we found MVP in 33% of a group of patients with the hypermobility syndrome (HMS), a significantly increased prevalence over that (7%) in a control group. Patients with HMS had additional evidence of a systemic connective tissue abnormality: reduced skin thickness, spinal anomalies, reduced upper segment/lower segment ratio, and a greater frequency of previous fractures compared with controls.

The results of the present study provide further evidence of an association between MVP and HMS, since hypermobility of the joints was significantly more common in patients with MVP than in controls. Significantly more patients with MVP reported easy bruising than did controls, but other evidence of abnormal connective tissue in skin or skeleton was not found in our patients with MVP.

Table 1 Past and present rheumatic and orthopaedic complaints

Complaint	Patients with MVP (n=21)	Controls (n=21)
'Growing pains'	4	2
Arthralgia	8	5
Arthritis	2	1
Muscle cramps	6	9
Joint effusions	3	4
Calf swelling	0	0
Ligament injuries	7	9
Capsulitis	6	6
Epicondylitis	5	2
Carpal tunnel syndrome	3	2
Torn muscles	1	4
Back pain	15	11
Nerve root pain	5	5
Morning stiffness	4	2
Dislocations	3	2
Raynaud's phenomenon	7	5
Easy bruising*	11	5
Poor skin healing	0	2
Varicose veins	9	5
Fractures	7	7

* $p < 0.05$.

The association is presumably due to one or more defects of connective tissue common to both valve and joints. In patients with idiopathic MVP requiring valve replacement Bonella *et al.*¹⁷ have shown procollagen accumulation and a reduced collagen content in pooled resected valve tissue. These authors postulate a deficiency of the enzyme procollagen peptidase as the underlying cause. It will be important to establish whether other connective tissue from patients with MVP shows the same biochemical abnormality. Certainly procollagen excess and reduced collagen has been shown in extracardiac connective tissue from patients with a form of the Ehlers-Danlos syndrome,¹⁸ and although initially attributed to procollagen peptidase deficiency a structural mutation of procollagen has since been identified in this condition.¹⁹

Thus it is possible that our patients with MVP and hypermobile joints have one of the many forms of the Ehlers-Danlos syndrome. However, our results emphasise that in many patients with idiopathic MVP no other clinical manifestation of a connective tissue abnormality can be identified. It remains to be determined whether these patients have a tissue-specific defect of mitral valve collagen, or whether their MVP is the only clinical expression of a minor systemic collagen abnormality.

We thank Drs Paul Curry and Edgar Sowton for allowing us to study patients under their care.

References

- ¹ Procacci P M, Savaran S V, Schreiter S L, Bryson A L. Prevalence of clinical mitral valve prolapse in 1169 young women. *N Engl J Med* 1976; **294**: 1086-8.
- ² Davies M J, Moore B P, Braimbridge M B. The floppy mitral valve. Study of incidence, pathology and complications in surgical, necropsy and forensic material. *Br Heart J* 1978; **40**: 468-81.
- ³ Pocock W A, Barlow J B. Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome: analysis of a further 130 patients with a late-systolic murmur or non-ejection systolic click. *Am J Med* 1971; **51**: 731-9.
- ⁴ Brown O R, DeMots H, Kloster F F, Roberts A, Menashe V D, Beals R K. Aortic root dilatation and mitral valve prolapse in Marfan's syndrome. *Circulation* 1975; **52**: 651-7.
- ⁵ Brandt K D, Sumner R D, Ryan T J, Cohen A S. Herniation of mitral leaflets in the Ehlers-Danlos syndrome. *Am J Cardiol* 1975; **36**: 524-8.
- ⁶ Cabeen W R, Reza M J, Kovick R B, Stern M S. Mitral valve prolapse and conduction defects in Ehlers-Danlos syndrome. *Arch Intern Med* 1977; **137**: 1227-31.
- ⁷ Woods S J, Thomas J, Braimbridge M V. Mitral valve disease and open heart surgery in osteogenesis imperfecta tarda. *Br Heart J* 1973; **35**: 103-6.
- ⁸ Grahame R, Edwards J C, Pitcher D, Gabell A, Harvey W. A clinical and echocardiographical study of patients with the hypermobility syndrome. *Ann Rheum Dis* 1981; **40**: 541-6.
- ⁹ Beighton P, Horan F. Orthopaedic aspects of the Ehlers-Danlos syndrome. *J Bone Joint Surg* 1969; **51B**: 1444-53.
- ¹⁰ Tanner J M, Whitehouse H H. The Harpenden skinfold caliper. *Am J Phys Anthropol* 1955; **13**: 743-6.
- ¹¹ Grahame R. A method for measuring human skin elasticity in vivo with observations on the effects of age, sex and pregnancy. *Clin Sci* 1970; **39**: 223-36.
- ¹² Jeresaty R M. *Mitral Valve Prolapse*. New York: Raven Press, 1979: 9-37.
- ¹³ Read R C, Thal A P, Wendt B E. Symptomatic valvular myxomatous transformation (the floppy valve syndrome); a possible forme fruste of the Marfan syndrome. *Circulation* 1965; **32**: 897-910.
- ¹⁴ Becker A E, De Wit A P M. Mitral valve apparatus. A spectrum of normality relevant to mitral valve prolapse. *Br Heart J* 1979; **42**: 680-9.
- ¹⁵ Rippe J, Fishbein M C, Carabello B, *et al.* Primary myxomatous degeneration of cardiac valves. Clinical, pathological, haemodynamic and echocardiographic profile. *Br Heart J* 1980; **44**: 621-9.
- ¹⁶ Olsen E G J, Al-Rufaie H K. The floppy mitral valve. Study on pathogenesis. *Br Heart J* 1980; **44**: 674-83.
- ¹⁷ Bonella D, Parker D J, Davies M J. Accumulation of procollagen in human floppy mitral valves. *Lancet* 1980; **i**: 880-1.
- ¹⁸ Lichtenstein J R, Martin G R, Kohn L D, Byers P H, McKusick V A. Defect in conversion of procollagen to collagen in a form of Ehlers-Danlos syndrome. *Science* 1973; **182**: 298-300.
- ¹⁹ Steinmann B, Tuderman L, Martin G R, *et al.* Evidence for a structural mutation of procollagen in a patient with Ehlers-Danlos syndrome type VII. *Eur J Paediatr* 1979; **130**: 203.