The floppy mitral valve

Study on pathogenesis

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SUMMARY The pathogenesis of the floppy valve syndrome is not fully solved. An almost invariable histological finding is the great accumulation of mucinous material in the valve leaflets and constitutes the basis of the valvular theory of the syndrome. The presence of a mucinous layer in normal valves—the zona spongiosa—is not well recognised. To establish the normal range of the extent of this zone, 50 excised mitral valves from patients aged 2 to 89 years and who died as a result of road traffic accidents or non-cardiac causes have been analysed by measuring the thickness of the zone in relation to the valve thickness. A range of 0 to 60 per cent was found and this was not influenced by age.

The findings were compared with 50 patients clinically diagnosed as suffering from the floppy valve syndrome. A value of over 60 per cent (range 62 to 94%) was found in 43 patients. The increase in the extent of the mucinous material was considered to be a secondary change in the thickened fibrosa which normally accompanies the floppy valve syndrome. Measurements of zona spongiosa falling within the normal range were found in seven patients. The clinical features, complications, and accompanying conditions have also been analysed. Chordal rupture had occurred in 20 patients, infective endocarditis in three, and calcification was found in four valves. In four patients the aortic valve was also involved and accompanying aortic root dilatation in an additional patient. It is suggested that these patients should not be included in the group of Marfan's *forme fruste*, nor in the typical floppy mitral valve syndrome.

Apart from the valvular theory, the myocardial theory in the pathogenesis of the syndrome has been discussed and the components ensuring normal mitral valve function have been reviewed.

It is concluded that an inherent, prominent zona spongiosa predisposes to the floppy valve syndrome, particularly if any one of the components of normal valve function is abnormal.

For the past 15 years attention has focused on the floppy valve syndrome, first described by Fernex and Fernex¹ in 1958. It is characterised by protrusion particularly of the posterior valve leaflet into the left atrium and results in recognisable signs²⁻⁵ constituting a specific syndrome.⁶ Other synonyms for the syndrome include prolapse of the mitral valve,⁷ billowing of the mitral valve,³ and ballooning, or the syndrome of mid-late systolic click and late systolic murmur.⁸

Despite many possible suggestions, the pathogenesis of the floppy valve syndrome is still not fully understood. Mitral regurgitation can occur as the result of failure of any of several anatomical components which interact to ensure normal functional integrity of the mitral valve apparatus⁹ but must be distinguished from the syndrome.

Dilatation of the valve ring has been established in the floppy valve syndrome¹⁰ and more recently attention has been drawn to normal variants in the deposition of chordae tendineae.¹¹ Myocardial and haemodynamic alterations, as well as anatomical variations of the circumflex branch of the left coronary artery, have also been suggested as resulting in the syndrome.

There is a considerable body of opinion suggesting that myxomatous degeneration is the underlying mechanism of mitral valve prolapse.^{12 13} In many reports dealing with histological changes, definition of specific location of myxomatous change and "fibrosis" has been omitted.¹⁴ The normal structure of valve leaflets¹⁵ has also not been taken into account and it is the purpose of this study to investigate the variable prominence of the zona spongiosa—a constant component of normal valve

leaflets—and to compare the findings with those valves removed at surgical operation from patients firmly diagnosed as suffering from the floppy valve syndrome.

Material and methods

NORMAL VALVES

Valves removed at necropsy—21 female and 29 male, 2 to 89 years of age—of patients who died as a result of road traffic accidents, or from extracardiac causes, have been available for study. Tissue from the centre of the “scallop” and from the region of strutt chordae¹⁶ was selected from the patient's posterior leaflet, as were samples from the anterior leaflet near the posteromedial commissure of the leaflet. The blocks were paraffin embedded and processed in the conventional manner.

For histological examination five μm thick sections were stained with haematoxylin and eosin and Weigert's elastic van Gieson stain. Histochemical examination included staining with peri-

odic acid Schiff, colloidal iron, toluidine blue at pH 3 and pH 5, and Congo red stains.¹⁷ These investigations were carried out on isolated specimens. Staining with Alcian blue at pH 2.5 was carried out on every block selected.

Isolated specimens were also selected for electron microscopical examination. This material was placed in buffered 3 per cent glutaraldehyde for one hour at 4°C. Subsequently the fixing fluid was replaced by buffered sucrose washing solution (4°C) pH 7.4. Post-fixation in 1 per cent osmium tetroxide was undertaken and the tissue was embedded in epon. Fifty nm thick sections were cut with a Porter Blum MT 1 ultramicrotome and stained with uranyl acetate and lead citrate and viewed on a Phillips 301 electron microscope.

ASSESSMENT OF ZONA SPONGIOSA

Measurement of the thickness of the zona was undertaken on the Alcian blue stained preparation, in the middle third of the valve leaflet (base to free edge), using an eye piece graticule. The thickness

Fig. 1 (a) Photomicrograph of a normal posterior leaflet of the mitral valve, showing a thin zona spongiosa (3%). (Alcian Blue, original magnification $\times 80$.) (b) Posterior leaflet of the normal mitral valve with a prominent zona spongiosa (47.6%). The extent of the thickness of the valve leaflet can just be discerned. (Alcian Blue, original magnification $\times 80$.)

of the zona was expressed as a percentage of the width of the valve leaflet.

FLOPPY MITRAL VALVES

Mitral valves from 50 patients—34 male and 16 female, removed at operation (age range 6 to 70 years)—were processed and measured in exactly the same manner as the tissue from the normal subjects. Other histochemical analyses and electron microscopy were carried out in isolated instances.

Results

NORMAL VALVES

Microscopical changes

No differences between male and female cases were noted. In Table 1 the cases are grouped according to age in decades and the number of valves available for each group are listed. The range of the zona spongiosa, expressed as a percentage of the valve thickness for each group, is detailed. The extreme variability of the prominence of this valvar component is striking. In some cases the zona was represented by a single cell thick streak of Alcian blue positive material (0%), while in others it occupied

Table 1 *Variation of normal zona spongiosa*

Age (y)	No. of valves	Zona spongiosa	
		From (%)	To (%)
0-10	5	0	48.4
11-20	2	10.2	33.6
21-30	3	25.3	50.4
31-40	5	23.2	35.7
41-50	7	0	50.3
51-60	7	8.3	28.2
61-70	9	18.1	60.0
71-80	10	0	13.3
81-90	2	12.3	23.6

60 per cent of valve thickness. Fig. 1a and 1b illustrate a small and prominent zona spongiosa.

Histochemical analysis

This showed a strongly positive reaction to periodic acid Schiff staining, minimally affected by diastase digestion. A strongly positive reaction was also obtained by colloidal iron ablated after testicular hyaluronidase digestion. Faint metachromasia was obtained with toluidine blue staining at pH 3. The Congo red treated tissue showed only very faint

Fig. 2 *Electron micrograph of the zona spongiosa in a normal valve leaflet, showing amorphous material. The adjacent collagen fibrils show normal periodicity. (Lead citrate and Uranyl acetate, original magnification $\times 147\,500$.)*

apple green fluorescence on examination under crossed polaroids.

Electron microscopical changes of the area of the zona spongiosa consisted of amorphous material surrounded by collagen fibrils showing the typical periodicity (Fig. 2).

FLOPPY MITRAL VALVES

Macroscopical examination of these valves showed characteristic features consisting of doming towards the left atrium, principally of the posterior mitral valve leaflets from side to side, and from the free edge of the basal attachment. In 23 out of 50 patients the anterior mitral valve leaflets were also significantly affected. In three patients that leaflet showed the most severe change and in one patient the anterior leaflet alone was affected (case 11, Table 2). Doming was most prominent between chordal insertions and in the middle third of the valve leaflet. These leaflets were usually thin, transparent, and showed a bluish tinge. Along the line of closure in all valves, but also in the region of the clear zone, in several cases thickening was present, altering the appearance to white and opaque. The commissures were widely separated and measurements exceeded the normal range of linear measurement of 90 to 110 mm by up to 20 mm. In four patients the measurements exceeded 160 mm (dilated valve ring, Table 2).

Elongation of the chordae was frequently found and could be accurately assessed when the specimen included attached tips of papillary muscles. Beading of the chordae was a characteristic and frequent finding. In cases of rupture the chordae tapered to a fine point (Fig. 3). The salient features of the macroscopical involvement are listed in Table 2. This table has been arranged according to age. The sex of the patient and the time when a murmur was first heard are also stated. Complications and associated or other conditions are included. In 20 patients rupture of chordae tendineae was found. Evidence of infective endocarditis was observed in three patients. In two patients atrial septal defect was diagnosed and patency of the fossa ovalis was found in another two patients. Calcification was found in four valves examined.

Measurements of the zona spongiosa in Table 2 have been confined to the posterior mitral valve leaflets. In those valves where the anterior mitral valve leaflet showed microscopical dominant features, the posterior leaflet showed similar or more severe histological changes. In 43 cases over 60 per cent of the valve leaflet was occupied by the zona spongiosa. In the remaining seven valves the extent of the zona spongiosa fell within the range observed in normal valves.

Apart from the prominent zona spongiosa and the increased "length" of the posterior mitral valve

Fig. 3 A specimen of a surgically removed mitral valve (ventricular aspect) from a patient with the floppy valve syndrome and rupture of chordae tendineae. The arrow indicates the larger anterior leaflet.

Table 2 Clinical data, macroscopical involvement of valves, complications, and measurements of zona spongiosa (post. leaflet) of patients with floppy valve syndrome

No.	Age (y)	Sex	History of murmur	Gross appearance of mitral valve involvement	Other valves	Complications	Associated condition and other diseases	Zona spongiosa (%)
1	6	M	3 mth	Both leaflets	—	—	—	74.7
2	9	M	5 mth	Both leaflets	—	—	—	65.2
3	14	M	14 y	Both leaflets	—	—	—	66.6
4	17	M	4 y	Posterior leaflet	—	—	—	90.6
5	18	M	25 d	Both leaflets	—	—	Atrial septal defect	94.0
6	27	M	6 mth	Posterior leaflet	—	Calcification	—	87.5
7	44	M	19 y	Both leaflets	—	Ruptured chordae	—	60.0
8	44	F	6 y	Both leaflets	—	—	—	46.4
9	45	F	15 y	Posterior leaflet	Aortic valve	—	—	90.0
10	45	F	28 y	Both leaflets	Aortic valve	—	—	66.6
11	50	M	27 y	Anterior leaflet	—	Ruptured chordae	—	85.7
12	50	M	14 y	Both leaflets	—	—	—	64.4
13	51	M	1 y	Predominantly anterior leaflet	—	—	Patent foramen ovale	52.6
14	52	M	44 y	Posterior leaflet	—	—	Dilated valve ring	64.2
15	52	M	8 y	Posterior leaflet	Aortic valve and root dilatation	—	Dilated valve ring	85.7
16	52	M	8 y	Both leaflets	—	—	—	87.8
17	53	F	10 y	Posterior leaflet	—	—	—	91.0
18	54	M	1 y	Both leaflets	Aortic valve	—	—	78.0
19	54	M	8 y	Both leaflets	—	Calcification	—	62.3
20	55	F	1 mth	Predominantly anterior leaflet	—	—	Ischaemic heart disease	87.8
21	55	M	8 y	Both leaflets	—	—	Dilated valve ring	72.1
22	55	M	8 y	Both leaflets	—	—	Ischaemic heart disease	82.9
23	56	M	7 y	Posterior leaflet	Aortic valve	Ruptured chordae	—	47.1
24	57	M	34 y	Posterior leaflet	—	—	—	68.0
25	57	F	1 mth	Both leaflets	—	—	—	54.1
26	58	M	10 y	Posterior leaflet	—	Ruptured chordae	—	89.5
27	58	F	Many years	Both leaflets	—	Ruptured chordae	Calcification of annulus	75.5
28	59	M	4 mth	Predominantly anterior leaflet	—	—	—	85.0
29	59	F	28 y	Both leaflets	—	—	—	74.0
30	59	M	2 y	Both leaflets	—	Ruptured chordae	—	65.2
31	60	F	10 y	Both leaflets	—	Calcification	—	66.6
32	60	F	5 y	Posterior leaflet	—	Ruptured chordae	—	68.7
33	61	M	4 y	Posterior leaflet	—	—	—	67.6
34	62	M	29 y	Posterior leaflet	—	Ruptured chordae	Patent foramen ovale	60.0
35	62	M	2 mth	Posterior leaflet	—	Ruptured chordae	Ischaemic heart disease	74.1
36	63	M	8 y	Posterior leaflet	—	Ruptured chordae	—	76.2
37	63	M	2.5 y	Both leaflets	—	Ruptured chordae	Atrial septal defect	76.9
38	64	M	26 y	Posterior leaflet	—	Ruptured chordae	—	70.0
39	64	M	31 y	Both leaflets	—	Ruptured chordae	—	83.3
40	64	M	49 y	Both leaflets	—	Infective endocarditis	—	87.8
41	64	M	8 y	Posterior leaflet	—	Ruptured chordae	Ischaemic heart disease	66.6
42	65	M	22 y	Both leaflets	—	Infective endocarditis	—	74.0
43	65	M	4 y	Posterior leaflet	—	Ruptured chordae	—	85.0
44	67	F	5 y	Both leaflets	—	Ruptured chordae	Dilated valve ring	89.0
45	69	F	13 y	Posterior leaflet	—	Ruptured chordae, infective endocarditis	—	84.2
46	69	F	5 y	Posterior leaflet	—	Calcification	—	68.0
47	69	F	14 y	Posterior leaflet	—	Ruptured chordae,	—	58.3
48	70	M	22 y	Posterior leaflet	—	—	Ischaemic heart disease	69.2
49	70	F	8 y	Posterior leaflet	—	Ruptured chordae	—	87.5
50	70	F	8 y	Posterior leaflet	—	Ruptured chordae	—	70.0

leaflet, the histological appearances did not differ from those observed in the normal valve tissue. The architecture was preserved and vascularity was not increased. Superimposition of predominantly collagen tissue on the line of closure, and along the atrial aspect of the valve leaflets, indicated that regurgitation had been present for some time (Fig. 4). The myxomatous tissue extended into the chordae tendineae and was particularly prominent in the areas noted as beading macroscopically. Thickening of the chordae by superimposition of collagen tissue was also found.

Histochemical analyses did not differ from those of the normal valves.

Electron microscopical examination showed similar amorphous material to that observed in normal valves, but the collagen tissue surrounding these areas frequently showed loss of periodicity of collagen fibrils.

Discussion

For assessment of the extent of the myxomatous zone occupied in the valve leaflets, the middle third (free edge to basal attachment) was chosen because of frequent thickening and often even more prominent myxomatous tissue being present in the area of the line of closure in the diseased valves. Though

invariably some diffuseness of the adjacent collagen tissue was found, examination at low magnification showed a fairly clear separation between myxomatous tissue and the adjacent unaffected collagen.

Histochemical examination confirmed the changes previously reported,¹⁷ suggesting that the mucinous area was predominantly composed of uronic acid mucopolysaccharides. A similar conclusion was reached by Torii *et al.*,¹⁸ by determining the carbazol/orcinol ratio of uronic acid in acid mucopolysaccharides. Apple green fluorescence by examination under crossed polaroids, after staining with Congo red, was only very faint in our study though a somewhat stronger reaction has been noted.¹⁷

Electron microscopical changes only showed evidence of degeneration of the adjacent collagen fibrils, having resulted in loss of periodicity. In all other respect no differences between affected and normal valves could be identified.

The normal function of the mitral valve apparatus is dependent on six components: the left atrial wall; the annulus; valve leaflets; chordae tendineae; papillary muscles and left ventricular wall.⁹ Abnormalities of any of these components—such as deficiency or excess of valvar tissue, abnormally long or short chordae, papillary muscle dysfunction, and alteration of the left ventricular shape—

Fig. 4 Photomicrograph of the posterior mitral valve leaflet from a patient with the floppy valve syndrome. Superimposition of predominantly collagen tissue on the "auricularis" is present (arrowed) indicating valvular regurgitation. The pale central area is the zona spongiosa. (Weigert's elastic van Gieson, original magnification $\times 80$.)

can result in abnormal mitral valve function. Distinction must be made, however, between abnormal closure, for example resulting from papillary muscle dysfunction, and true mitral valve prolapse. In the syndrome characteristic doming towards the left atrium and elongation of the chordae tendineae (often showing beading) are found, together with expansion of the valve area. Nevertheless, dilatation of the mitral valve annulus of sufficient severity, so as to cause mitral regurgitation, has been established in patients with the floppy valve syndrome.¹⁰ In the present study measurement of the excised valves exceeded 160 mm in four of the 50 cases, confirming that annular dilatation can significantly contribute to regurgitation. In all other cases some increase was found above the normal range of mitral valve dimensions (normal: 90 to 110 mm), most probably from dilatation subsequent to mitral regurgitation.

The aetiology of the "floppy valve syndrome" is not solved but two major theories have been suggested: the valvular and the myocardial.⁶ The former suggestion explains the clinical manifestations, chest pain being caused by excessive stretching of the papillary muscles.¹⁹⁻²⁰ Sudden tensing of the everted valve leaflets is responsible for the characteristic click.²¹ The mid-late systolic murmur is attributed to increasing regurgitation of valve leaflets as prolapse develops.²¹⁻²²

The other major theory, the myocardial theory, has included a variety of angiographic and haemodynamic findings such as abnormal protrusion of the inferior aspect of the left ventricle²³ and non-contraction or late systolic expansion of the inflow tract of the left ventricle.²⁴ Absence of the atrioventricular groove branch of the circumflex of the left coronary artery has been the suggested explanation for segmental myocardial dysfunction²⁵; its absence is frequently compensated by a large posterolateral branch of the right coronary artery.²⁴ Left ventricular asynergy²⁶⁻²⁷ and haemodynamic disturbance—such as a constrictive pattern²⁰ and an increase in left ventricular end-diastolic pressure, low resting cardiac index, or an inappropriate rise during exercise²⁷—concludes the myogenic cardiac theory. To explain the various changes, an underlying cardiomyopathy has also been suggested.²⁷ The association of the "floppy valve syndrome" with coronary arterial disease, resulting in papillary muscle involvement (dysfunction), has been suggested.²⁸⁻²⁹

Although in the present study five patients had clinical manifestations of ischaemic heart disease and mitral regurgitation, which may occur in association with papillary muscle dysfunction, we agree with Jeresaty and Liss¹⁰⁻²⁸⁻²⁹ that this combination is likely to be coincidental in the "floppy

valve syndrome". An incidence of only 2 to 3 per cent of coronary arterial disease has been shown to exist in these patients by selective coronary arteriography.⁶

The anatomy of the normal mitral valve has been meticulously studied.¹⁶⁻³¹ Variation in the chordal arrangement and atypical chordae were encountered in 37 of the 50 hearts examined. In a more recent study¹¹ abnormalities were noted in the deposition of chordae tendineae in 36 out of 40 valves obtained from patients with prolapse, particularly those inserting into the commisural area and rough zone areas and preferentially involving the posteromedial commissural area and the middle scallop of the posterior leaflet. Associated finger-like papillary muscle, single long chordae, or haphazard arrangement were encountered, resulting in insufficient valvar support. Weakness of the central area of the valve leaflet was found to be an essential lesion.³²

Our findings at macroscopical examination confirm the presence of the severest doming around the posteromedial commissure, with involvement of the middle scallop of the posterior leaflet. When the anterior leaflet was involved, the area adjacent to the commissure showed the severest changes. In severely affected valves the entire posterior leaflet, and not infrequently the anterior leaflet, showed evidence of doming. Similar findings have been reported.¹¹⁻³²

Regarding complications and associated conditions in our series, 20 of the 50 patients suffered rupture of the chordae tendineae close to a point where secondary fibrous thickening and myxomatous tissue were prominent. Early surgical intervention was achieved. In three patients morphological evidence of infective endocarditis was present; in two patients an atrial septal defect in the region of the fossa ovalis was found (secundum type) and in another two probe patency of the fossa ovalis was noted. A 5 per cent incidence of atrial septal defect has been reported.⁶

Returning once more to the valvar theory, histologically, myxomatous degeneration has consistently been documented.³³⁻³⁶ With the exception of three contributions,¹⁴⁻³⁷⁻³⁸ the normal histological structure has either not been mentioned or not taken into account and has led to the suggestion that the process of degeneration of the fibrosa is present.³⁹

As early as 1931, Gross and Kugel¹⁵ described the normal histology in detail. Between the auricularis (a thin layer composed of collagen and elastic tissue covering the atrial aspect of valve leaflet) and the fibrosa (a thick layer composed of collagen tissue which affords the main support of the

valve) is the zona spongiosa. This present study is the first account of measurement of this structure. The results have shown that variability is great, ranging from just a cell thick streak, expressed as 0 per cent, to occupying 60 per cent of the thickness of the valve leaflet. The extent is not affected by increasing age. By contrast, 43 of the 50 valves removed surgically for prolapse from patients showed values above 60 per cent (range 62 to 94%). In seven valves examined the measurement of the extent of the zona fell within the range encountered in the normal subjects. Nevertheless, clinical and macroscopical findings typical of the "floppy valve syndrome" were present in the tissue. This finding emphasises that though myxomatous tissue is consistently present in "floppy valves", histological examination alone may overdiagnose the condition. It further emphasises the fact that other mechanisms, such as abnormal chordal arrangement, may play a role culminating in the clinically recognisable syndrome.

As a result of our study we suggest that an individual is born either with a thin or a thick zona spongiosa. Family studies⁴⁰⁻⁴² support such a suggestion. Those patients with a prominent zona, inherently weakening the valve, are liable to develop the syndrome, particularly if one or the other factor discussed above is additionally present.

Degeneration of the fibrosa may occur to some extent but in view of the values of up to 60 per cent found in normal valves, it seems reasonable to suggest that only minor, secondary degeneration is necessary to account for the higher values obtained in abnormal valves. It is likely that this secondary degeneration is caused by lysis, which can occur in the accompanying thickening of the fibrosa. Support for such a supposition is provided by examining valves in patients with acquired heart disease, such as rheumatic fever. Towards the free margin of these valves extensive thickening is usually present in which an excess of myxomatous tissue is often found. Elsewhere in the valves the zona is frequently not conspicuous. This prominence of myxomatous tissue in the distal portion of the valves may have led to difficulty in distinguishing the two conditions.⁴³ Other changes usually make distinction easy. In the floppy valve the architecture is preserved and no increase in vascularity is evident. Thickening, when present, consists of a well-defined layer of predominantly collagen tissue superimposed on the surface of the auricularis. Thickening of the fibrosa is frequently present. In valves affected by the rheumatic process, severe thickening, distortion or destruction of the normal architecture, increased vascularity and calcification, together with a variable chronic inflammatory infiltrate, are found.

Calcification of the floppy valve may occur,¹⁴ though this is rare. It was found in four cases in our series.

Changes similar to those described for the mitral valve have been observed in the aortic valve in four patients and in one additional patient aortic valvar changes were accompanied by dilatation of the aortic root. Accompanying aortic valve involvement is well recognised,^{44 45} and the question arises whether the combination of aortic and mitral valve changes constitutes a *forme fruste* of Marfan's disease. Indeed it has been suggested that isolated floppy mitral valve could be considered a form of this disease. This concept is supported to some extent by a report on three patients who developed dissecting aneurysms of the aorta after clamping of the aorta during operation for mitral valve replacement.⁴⁶ Despite the overlapping features there is, however, no firm evidence that isolated mitral valve prolapse forms part of the spectrum of Marfan's disease. When the aortic valve is affected as well, it should also not be classified under Marfan's disease or typical mitral valve prolapse.⁴⁷

We conclude that an inherent prominent zona spongiosa, in otherwise normal valves, predisposes to the floppy valve syndrome. Once doming has taken place, secondary thickening of the valve leaflet occurs, with extension of the myxomatous tissue into the fibrosa. Functional or anatomical abnormalities of any components, ensuring normal mitral valve function, are important contributory factors in the development of this syndrome, particularly in cases with less prominent zona spongiosa.

For the supply of normal mitral valves we acknowledge the co-operation of Dr U Baandrup, University of Aarhus, Denmark, and the Homograft Department of the National Heart Hospital.

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