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Floppy Aortic Valves Without Aortic Root Dilatation: Clinical, Histologic, and Ultrastructural Studies

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Abstract

Gross anatomic, histologic and ultrastructural studies were made on 32 floppy aortic valves (FAVs) resected at the time of aortic valvular replacement for aortic regurgitation. Patients with the FAVs had relatively long clinical courses and had severe aortic regurgitation with mild symptoms of heart failure. The sizes of the mechanical valves implanted in the patients with FAVs were not large, indicating that the aortic regurgitation in these patients was not worsened by dilatation of the aortic ring. Two types of FAVs were recognized grossly, according to whether they showed abnormal cuspal thickening or thinning. Accumulations of myxoid material in the spongiosa were found in all FAVs, regardless of cuspal gross morphology. Histologically, the collagen fibers were sparse and irregularly arranged and elastic fibers were disrupted and finely granular in the myxomaotus areas of FAVs. Ultrastructurally, the myxomatous material consisted of numerous star-shaped proteoglycan granules associated with spiraling collagen fibrils and abnormal elastic fibers. Numerous spiraling collagen fibrils were observed especially at the border area of myxomatous change that extended from the spongiosa into the fibrosa. Abnormal elastic fibers had either a granular appearance of their amorphous components without microfibrils, or irregularly arranged masses of microfibrils without amorphous components. These abnormalities of connective tissue components, resulting from defective formation and/or increased degradation were similar to those in floppy mitral valves, and were related to the floppiness of cardiac valves.

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Key words: floppy aortic valve, myxomatous change in the cardiac valve, spiraling collagen, connective tissue, pathology

Introduction

Recently, isolated aortic valvular regurgitation with floppy cuspal change (floppy aortic valve) has become a common valvular disorder[1,2]. Myxomatous degeneration of the cusps, similar to that in floppy mitral valves is recognized as a characteristic histologic change in floppy aortic valves[3]. Based on light microscopical observation, alterations in collagen and elastic fibers have been considered to be related to the weakness of the fibrous cores of these floppy valves[4–6]. Although there have been several reports of clinico-pathological studies on patients with floppy

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Table 1 Patients with myxomaouts aortic valve

Myxomatous aortic valve		61
With combined disease (excluded form this study)		29
Ascending aortic disease	16	
Noninflammatory aortic root dilatation	11	
Ascending aortic aneurysm	4	
Aortic dissection (without root dilatation)	1	
Infectious endocarditis	8	
Severe mitral regurgitation	2	
Others	3	
Idiopathic floppy aortic valve		32
Isolated floppy aortic valve	26	
Mild to moderate mitral regurgitation	6	

aortic valves, ultrastructural examination of these floppy aortic valves is not enough to clarify their difference from floppy mitral valves. We previously reported abnormalities in connective tissue components of floppy mitral valves[7,8]. In this study, we investigated histologic and ultrastructural changes of connective tissue components in floppy aortic valves and compared the findings with those in floppy mitral valves.

Patients and Methods

From January 1981 to December 2000, 61 aortic valves, which were surgically excised due to aortic regurgitation, showed myxomatous change as a main pathological finding (**Table 1**). Among these, 16 patients (26.2%) also had aortic disease. Eleven of them had noninflammatory aortic root dilatation, including 3 with Marfan syndrome (2 of which were complicated with aortic dissection), 1 with Ehlers Danlos syndrome, and 1 with syphilis. Another 4 patients had a dilatation or aneurysmal formation of the ascending aorta, and one of these had rheumatic arthritis. One other patient's condition was complicated by dissection of the ascending aorta. Eight patients' (13.1%) conditions were complicated by infective endocarditis on the myxomatous aortic valve. All these patients were excluded from this study. Another 3 patients, 1 with a ventricular septal defect, 1 with a coronary arterial aneurysm, and 1 with rheumatic arthritis were also excluded from the study. Two patients had mitral regurgitation due to floppy mitral valve. An aortic valve with mild regurgitaion was replaced together with a mitral valve in one patient. This patient was excluded from the study because alteration of the aortic valve was mild. An aortic valve with moderate to severe regurgitation was replaced 15 years after the mitral valve replacement in another patient. This patient was excluded from the study to eliminate the effect of cardiac surgery.

Aortic valves obtained from the remaining 32 patients (23 men and 9 women, 16 to 73 years old, mean 58.4 years) were used as the subjects of this study, and all were considered to have idiopathic floppy aortic valves. No evidence of rheumatic heart disease or Marfan syndrome was found in these patients.

For the control, normal aortic valves were obtained at autopsy from 3 men aged 42 to 66 years old (mean 56.3 years), who died of noncardiac diseases. These patients had grossly and histologically normal coronary arteries, heart valves, and myocardium.

These valves were fixed in 10% formalin immediately after excision. Photographs were taken of the inflow and outflow surfaces of the aortic valve cusps, and then the cusps were cut at right angles to the valvular ring. Tissues were processed for light and electron microscopy. For light microscopic study, paraffin embedded sections were stained using hematoxylin-eosin, elastica Masson, and Alcian blue and periodic acid-Shiff methods. For electron microscopic study, small blocks were cut from formalin-fixed tissue and washed with 0.01 M phosphate-buffered saline (PBS), and refixed with 2.5% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4. Tissue blocks were postfixed with 0.1% osmium tetroxide in 0.1 M phosphate buffer, pH 7.4. They were then dehydrated and embedded in Epock 812. Ultrathin sections were stained either with uranyl acetate and lead citrate or according to the method of Kajikawa et al.[9] for elastic fibers.

Results

1. Clinical findings

The patients' age distribution was mainly in the fifties and sixties (five cases in their seventies, 12 cases in their sixties, 10 cases in their fifties, 3 cases in their forties, 1 case in his thirties, and 1 case in his teens).

As an initial sign or symptom, cardiac murmur was an incidental finding on medical examination in 10 patients. Clinical symptoms developed 4 to 7 years later and the time course from the appearance of symptoms to the operation was 0 (non-symptomatic) to 1 year (mean 5 months) in these patients. Dyspnea was an initial symptom in 16 patients. The time course from symptom onset to the operation was 6 months to 10 years (mean, 2.5 years) in these patients. Chest pain was an initial symptom in 2 patients. The time course from symptom onset to the operation was 3 months and 3 years, respectively, and no coronary disease was found in these patients. One patient was pointed out as having arrhythmia and was operated on 5 years later. Another patient was pointed out as having atrial fibrillation and was operated on 10 years later. One patient complained of an increased cardiac impulse felt at the base of the neck and was found to have aortic regurgitation on clinical examination. The time course from the appearance of this symptom to the operation was 2 years. None of the patients had a clinical history of infectious endocarditis.

NYHA classification at the operation was Class I in 13 patients, Class II in 15 patients, and Class III in 4 patients. Sellers' classification of preoperative left ventriculography revealed aortic regurgitation to be Class I to II in one patient, Class II to III in one patient, Class III in 23 patients, Class III to IV in 4 patients, and Class IV in 3 patients.

An indirect measurement of the aortic annulus was given by the diameter of the implanted prosthetic valves. The size of implanted mechanical valves was 21 mm in 1 patient, 23 mm in 14 patients, 25 mm in 14 patients and 27 mm in 3 patients.

Six patients with complications of mild to moderate mitral regurgitation were diagnosed with floppy mitral valve clinically. Mitral valvoplasty was performed together with aortic valve replacement in 2 patients, and the mitral valve was not operated on the other 4 patients. Atrial fibrillation was found in 3 patients, 2 of which had mitral regurgitation. One patient received mitral valvoplasty with a radial procedure as a surgical therapy for atrial fibrillation. Six patients with coronary arterial stenosis received coronary artery bypass grafting together with valve replacement surgery. Five of these had an episode of angina pectoris in their clinical courses. Abdominal aortic aneurysm was found in 3 patients, one of which had received graft implantation 3 years before valve surgery.

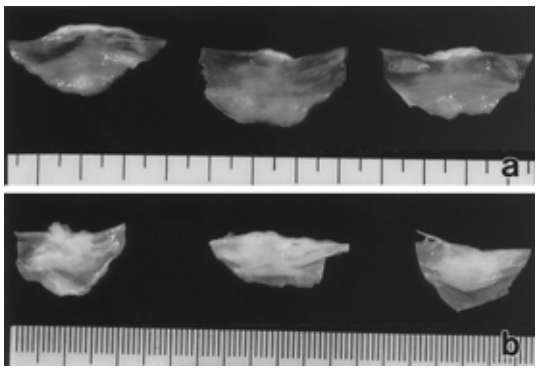

Fig. 1 Gross anatomic finding of floppy aortic valves
Two types of floppy aortic valves are recognized according to the presence of abnormal cuspal thinning (a) and thickening (b).

Hypertension was pointed out in 16 patients, and hyperlipidemia in 4 patients. Diabetes mellitus was pointed out in 2 patients. Adenomatous goiter without thyroid dysfunction was found in 2 patients. Another patient had received an operation for hyperthyroidism 28 years before the valve surgery.

2. Gross anatomic finding

Two types of floppy aortic valves were recognized according to the presence of abnormal cuspal thinning and thickening (**Fig. 1**). Eleven patients showed abnormal cuspal thinning, and 6 of them showed cuspal elongation. These thin, redundant cusps kept translucency and had a mildly gelatinous appearance. Cuspal shortening was found in the other 5 patients. Twenty-one patients showed abnormal cuspal thickening. These cusps were soft and gelatinous, similar to the appearance of a typical floppy mitral valve. Cuspal elongation was found in 8, and cuspal shortening was observed in the other 13 patients. Thickening of cuspal free edges was obvious, especially in cases with longer preoperative time courses. The commissure was not fused in any of these cases.

Cuspal fenestration was found in two cases, in the right coronary cusp of a 48-year-old man and in the non-coronary cusp of a 64-year-old woman, respectively.

3. Light microscopic findings

(1) Normal aortic valve

Normal aortic valve cusps were composed of three main layers of tissue. From the aortic to the ventricular aspects, these layers were the fibrosa, the spongiosa and the ventricularis. The fibrosa formed the structural core of the cusps and was composed of densely packed collagen bundles and a few small elastic fibers. The collagen bundles were oriented parallel to the free edge of the cusp, and blended into the collagen of the commissure. The spongiosa lying between the fibrosa and the ventricularis contained Alcian blue-positive materials. The ventricularis was composed mainly of elastic fibers.

(2) Floppy aortic valve

Accumulations of myxoid material in the spongiosa and fibrosa were found in all floppy aortic valves, regardless of cuspal gross morphology (**Fig. 2**). Histology confirmed the absence of active or inactive bacterial endocarditis in all cases. Myxomatous change was mainly distributed in the spongiosa and the fibrosa (**Fig. 3**), but the ventricularis was also involved in severely damaged cusps. There was no tendency in the distribution of the changes among the three cusps. Collagen fibers in the myxomatous area had an irregular arrangement, with poorly formed bundles. Collagen fibers in the fibrosa were decreased, and the fibrosa was substituted with myxomatous materials in severely disrupted areas. Compared with the spongiosa of a normal valve, elastic fibers were increased in number in the myxomaouts areas. These elastic fibers showed fragmentation and granular appearance (**Fig. 4**).

The free edge of floppy aortic valves showed thickening with reactive fibrosis due to regurgitant blood flow, which was also found on the ventricular surfaces. Rolling of free edges with fibrous thickening sometimes contributed to the shortening of cusps, and a thick layer of reactive fibrosis contributed to the thickening of cusps, especially in cases with longer preoperative time courses. Small calcific deposits were found in thickened, sclerotic fibrosa of the cusp in 8 patients. These patients were aged 51 to 71 years (mean 63.5 years).

In the fenestrated cusp of 2 cases, the edge of the

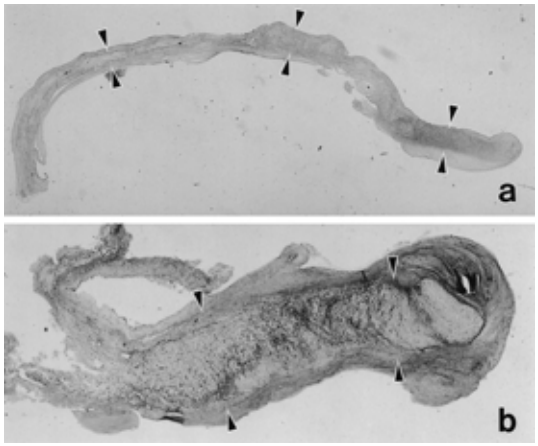

Fig. 2 Histologic finding
Alcian blue positive myxoid materials (arrowheads) in the spongiosa and fibrosa are found in both thin, elongated cusp (a) and thick, shortened cusp (b). (AB-PAS stain)

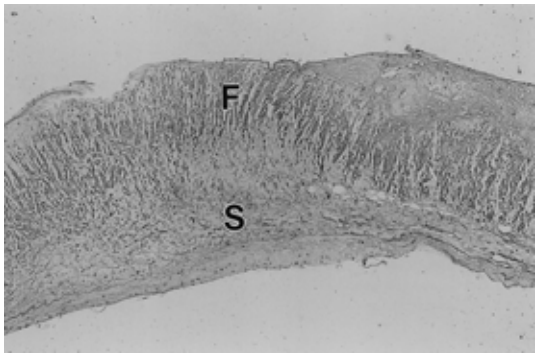

Fig. 3 Typical myxomatous change in floppy aortic valve
Myxomatous change is mainly distributed in the spongiosa (S) and extends into the fibrosa (F). (H-E stain)

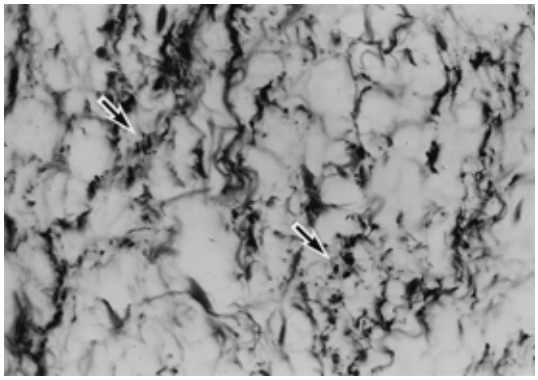

Fig. 4 High magnification view of the myxomatous area
Collagen fibers in myxomatous area have an irregular arrangement with poorly formed bundles. Elastic fibers show fragmentation and granular appearance (arrows).
(elastica Masson stain)

fenestration showed fibrous thickening possibly due to regurgitant jet, and the surrounding area showed marked myxomatous change. Inflammatory change was not found in these cusps.

4. Electron microscopic findings

(1) Normal aortic valve

In the fibrosa, dense collagen fibrils were arranged in an orderly parallel pattern. A few elastic fibers were found between these collagen fibrils. The spongiosa was recognized by the abundance of star-shaped granules of proteoglycan materials. The spongiosa also contained small amounts of elastic fibers and collagen fibrils. The ventricularis was characterized by a profusion of elastic fibers. The elastic fibers of normal aortic valves consisted of amorphous components, which were stained darkly and homogeneously with the method of Kajikawa et al.[9], and small amounts of surrounding microfibrils. The cellular components of the aortic valves, that is, fibroblasts, myofibroblasts, and poorly differentiated mesenchymal cells, were mainly distributed in the spongiosa.

(2) Floppy aortic valves

In the floppy valves, myxomatous material that consisted of star-shaped granules and amorphous clumps of proteoglycans separated the elastic fibers and collagen fibrils in the myxomatous area. The amorphous components of the elastic fibers showed fragmentation and a granular appearance. Microfibrils were found only occasionally in association with finely granular amorphous components (**Fig. 5a**). In contrast, masses of irregularly and compactly arranged microfibrils, which were not associated with amorphous components, were observed (**Fig. 5b**). Some masses of microfibrils were associated with poorly demarcated amorphous components (**Fig. 5c**) or calcific deposits (**Fig. 5d**). Collagen fibrils in the myxomatous area showed a spiraling appearance in longitudinal sections and a flower-like appearance in transverse sections (**Fig. 6a, b**). These spiraling collagen fibrils were extensively observed especially in the fibrosa at the border area of myxomatous change that extending from the spongiosa.

The ultrastructural findings are summarized in **Table 2**.

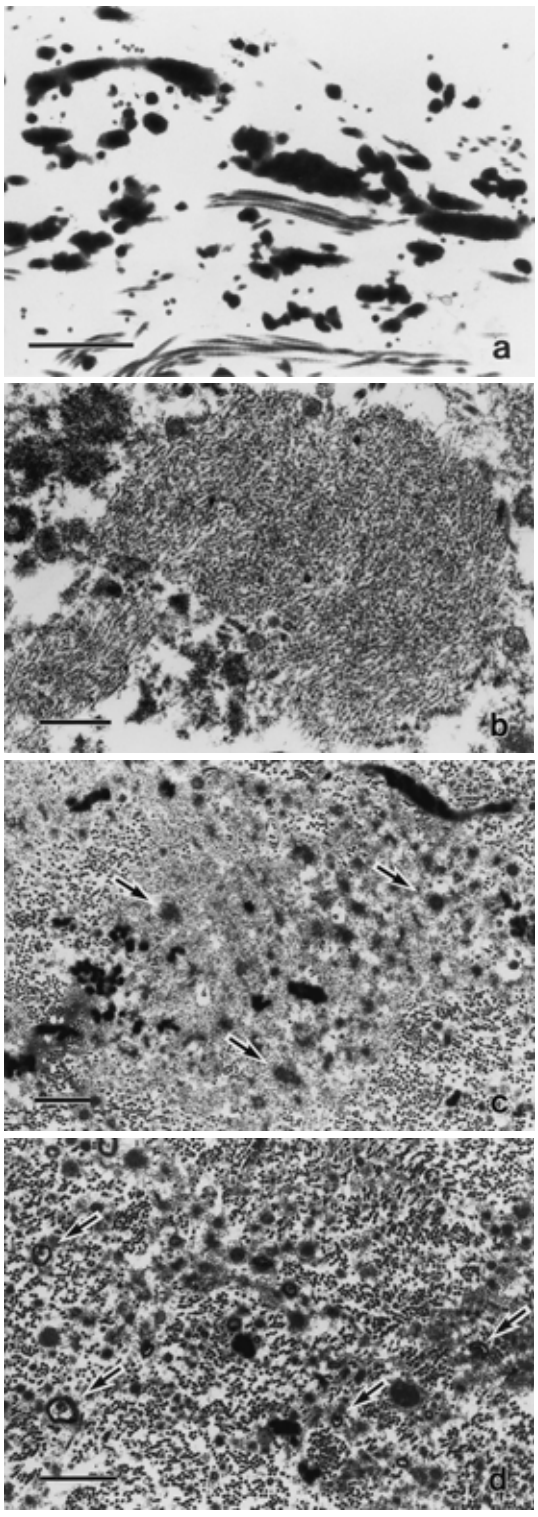

Fig. 5 Electron microscopic findings of elastic fibers a: Amorphous components of elastic fibers show granular appearance. Microfibrils are difficult to find in this area. b: Isolated masses of irregularly and compactly arranged microfibrils are not associated with amorphous components. c: Masses of microfibrils are associated with poorly demarcated amorphous components (arrows). d: Scattered masses of microfibrils are associated with calcific deposits (arrows). (Kajikawa stain, bar = a: 1 μm, b: 500 nm, c: 1 μm, d: 1 μm)

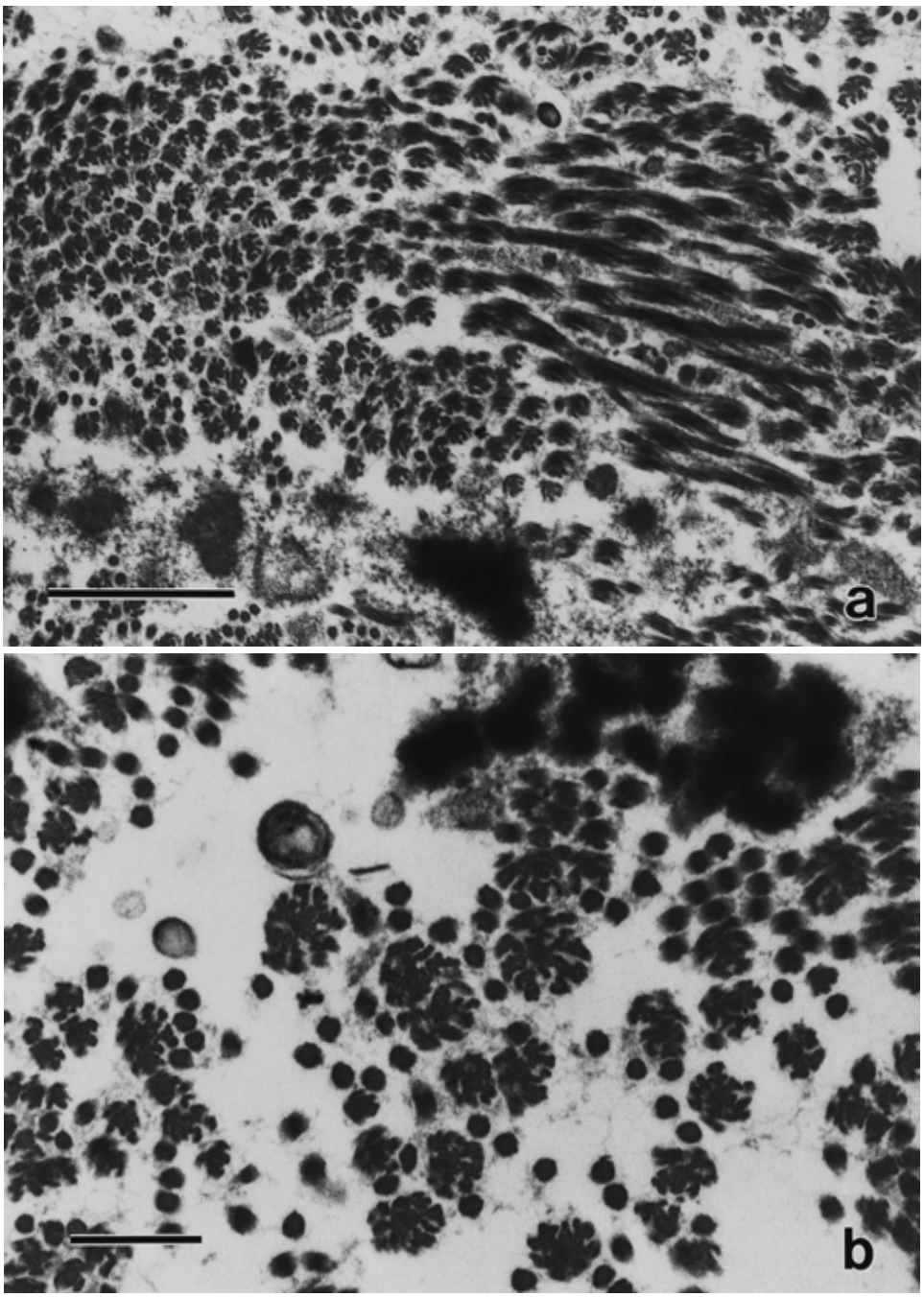

Fig. 6 Electron microscopic finding of collagen fibers
Collagen fibrils in myxomatous area of the fibrosa show a spiraling appearance in longitudinal section (a) and flower-like appearance in trasverse section (b). (Kajikawa stain, bar = a:1μm, b: 300 nm)

Table 2 Summary of Ultrastructural Findings

	Normal Aortic Valve	Floppy Aortic Valve
Elastic Fiber	Parallel Arrangement AC associates MF —	Granular Appearance AC without MF Mass of MF without AC
Collagen Fiber	Compact Arrangement —	Sparse Arrangement Spiraling Collagen Fibrils

AC: amorphous component MF: microfibrils

Discussion

A floppy mitral valve with or without rupture of chordae tendineae is one of the most common cardiac valvular disorders[7]. The same abnormality is pointed out in aortic valves[3] and the number of operations for these cases is increasing in Japan[10].

The patients with floppy aortic valves were divided into two groups, according to whether they had aortic root dilatation or not[11]. Bellitti et al. pointed out that the prolapse of aortic valves was generally associated with noninflammatory aortic root dilatation. However, they also mentioned the presence of the isolated disease with a normal aortic root[5]. Allen et al. reported that dilatation of the aortic annulus was not a significant factor in the pathogenesis of myxoid valve disease[4]. Floppy aortic valve and aortic root dilatation may be based on the same connective tissue disorder. However, some cases with aortic dilatation do not show myxomatous change in the aortic valve. Thus, a secondary change in the aortic valve following aortic regurgitation due to ring enlargement become mixed if the aortic valve with aortic root dilatation is examined together with pure floppy aortic valve without root dilatation. In this paper, we collected the cases without aortic root dilatation in order to study the histopathological changes in pure, isolated floppy aortic valves. The sizes of the mechanical valves implanted in the patients with floppy aortic valves were not large, indicating that aortic regurgitation in these patients was not worsened by dilatation of the aortic ring. Histopathological evaluation of these patients revealed alterations in idiopathic, isolated floppy aortic valves.

Clinical characteristics

Floppy aortic valves are found mainly in patiens in their 50s and 60s, and 23 of the 32 patients (72%) in this study were male. As reported in the literature, the mean age of such patients is distributed from the thirties to the sixties, and males are dominant[4-6,10,11]. Clinical recognition of mitral valve prolapse has been reported to be common in these in their 30s to 50s. More than two-thirds of younger patients were female, but the sex distribution of floppy mitral valve appeared to be more even in middle age and older life[12].

Patients with floppy aortic valves have relatively long clinical courses and have severe aortic regurgitation with mild symptoms of heart failure. Patients with floppy mitral valves also have long clinical courses with cardiac regurgitant murmur caused by prolapse, which is confirmed pathologically with the finding of reactive fibrosis of the surface of leaflets. Acute symptoms of heart failure are usually caused by chordal rupture in patients with floppy mitral valve. Basically, alterations in the valves may have the same time course in floppy mitral and aortic valves, and only the presence of chordal rupture results in different, acute symptoms in patients with floppy mitral valves.

Half of the patients with floppy aortic valves in this study had a clinical history of hypertension. Allen et al. provided the idea that the myxoid degeneration of aortic valves may be secondary to long-standing systemic hypertension[4]. However, hypertension was not commonly observed in patients with floppy aortic valves in other reports[6]. This difference may be related to the patients' age: the mean age in Allen's report is higher than that in other reports. Systemic hypertension is usually not observed in patients with floppy mitral valves. The same abnormalities of connective tissue are observed in floppy aortic valves, so it is difficult to explain that these abnormalities originated from hypertension. Therefore, we think that hypertension is not related to the pathogenesis of floppy aortic valve, but is a secondary, compensatory reaction following aortic regurgitation.

There were 8 patients who suffered infective endocarditis. The aortic valves of these patients showed myxomatous change with inflammation, suggesting infection of the floppy aortic valves, but they were excluded from this study. The surgically excised valves with bacterial endocarditis usually have severely damaged structures. In these cases, it is difficult for pathologists to determine whether the valve basically had a myxomatous change, even if the patient had a clinical history of aortic regurgitation with valvular floppiness before infection[13]. Mitral

valve prolapse with regurgitation is thought to be one of the moderate-risk categories for bacterial endocarditis, and prophylaxis is recommended[14]. Floppy aortic valve with regurgitation must be in the same category, and needs to be evaluated for prophylaxis.

Perforation of the leaflet was observed in 2 cases. As with the mitral valve, spontaneous rupture of floppy aortic valve has also been reported previously[15,16]. Inflammatory change was not found in these cases, and severe myxomatous change with connective tissue degradation was observed in the perforated areas of the cusps. The elastic fibers with unique, round-shaped expansion of the amorphous component were found in the perforated floppy mitral valve[8]. These features resembled those of the elastic fibers in animals treated with β-aminopropionitrile, an inhibitor of lysil oxidase[17]. These findings, not observed in the floppy aortic valves in this study, were not the causative changes of the perforations, but were thought to appear during the synthetic process of elastic fiber after the perforation. It is uncertain how long after a leaflet perforation these abnormal elastic fibers appear. Therefore, the lack of these abnormal elastic fibers in perforated floppy aortic valves does not mean that the basic connective tissue abnormality of a floppy aortic valve is different from that of a floppy mitral valve.

Histologic and ultrastructural characteristics

Tonnemacher, et al.[6] described the histopathological criteria of myxomatous degeneration of the aortic valve: 1) disruption of the fibrosa; 2) expansion of the spongiosa with acid mucopolusaccharides; and 3) >50% of the valve involved with acid mucopoly-saccharide deposition as shown by the colloidal iron stain. All 32 patients in this study cleared these criteria.

Two types of floppy aortic valves were recognized grossly, according to whether they showed abnormal cuspal thickening or thinning. These changes were first described by Lakier et al.[18], but cases with degenerative valvular change due to aging were included in their description. Idiopathic degeneration of an aortic valve is not an appropriate word to describe the pathology of aortic valve disorder, because it includes both aging change and myxomatous change. Aging change in the aortic valve causes stenosis with severe calcification, but it is functionally normal if the change is mild[19]. In the floppy aortic valves in this study, the focal mineralization in the fibrosa observed in elderly patients was thought to be due to aging and not related to the myxomatous change.

Focal myxomatous change is often observed in aged mitral valves. However, abnormalities of connective tissue components, which are characteristic findings of floppy mitral valves, have not been found in aged mitral valves[7]. In the same manner, focal myxomatous change is also found in aged aortic valves, but it is different from the myxomatous change in floppy aortic valves. In floppy valves, collagen fibers in the myxomatous area have an irregular arrangement, with poorly formed bundles. Elastic fibers show fragmentation and a granular appearance. These are typical connective tissue alterations of floppy aortic valves, which are the same in floppy mitral valves. Secondary myxomatous change in cardiac valves is distinguishable light microscopically because it lacks these connective tissue abnormalities. Myxomatous change in the fibrosa accompanied by the disappearance of collagen bundles is another characteristic finding of floppy valves.

Floppy mitral valve leaflets usually show gelatinous thickening, and abnormal thinning has not been reported. It is not clear why two types, cuspal thickening and thinning, were found in floppy aortic valves, but ther is no difference in the basic histological changes between them. Myxomatous change in aortic valves was the same as that in floppy mitral valves, regardless of cuspal gross morphology. In some cases, cuspal thickening caused by reactive fibrosis joined myxomatous change. In cases with a long clinical course, the rolling of the cuspal free edge was concerned in cuspal shortening. But the difference between the clinical courses was not enough to explain the reason why both thickening and thinning was observed in floppy aortic valve.

Another difference from floppy mitral valves was the finding of numerous spiraling collagen fibers in floppy aortic valves. In floppy mitral valves, these altered collagen fibers were also found, but the

distribution was scattered and sometimes hard to find on electron microscopical observation[7]. In floppy aortic valves, spiraling (or flower-shape in transverse section) collagen fibers were easily found in the frontal area of myxomatous change that extended from the spongiosa to the fibrosa. The alteration was diffuse and marked in all cases. According to the finding that there were no obvious difference between floppy aortic and mitral valves in the ultrastructural alterations of other connective tissue components such as elastic fibers and proteoglycan materials, the fundamental abnormalities of the connective tissue must be the same in both valves. Spiraling collagen fibrils are thought to develop as a result of dissociation or fraying of previously normal fibrils[20]. The difference in degree between floppy aortic and mitral valves in the appearance frequency of the spiraling collagen fibril may be explained by the anatomical differences between these valves. Collagen fibers in the fibrosa of aortic valve are aligned circumferentially with the free edge of the leaflet[21]. However, those of mitral valves are irregularly arranged because of the insertion of chordae tendineae. Accumulations of proteoglycans play an important role in the assembly of collagen fibrils[22], and collagen fibers in parallel arrangement may easily be affected by infiltration of proteoglycans. The possible contribution of collagenolytic activity (matrix metalloproteinases) in these valves also needs to be considered[23].

Although damage to collagen fibrils was found more frequently in aortic than mitral floppy valves, enlargement of the leaflets was usually more severe in mitral than aortic valves. This may be explained by the difference in the mechanical forces on the leaflet, that is, the pressure on the mitral valve at the closure is higher than that on the aortic valve. The difference in such an environment may also influence the degree of the alterations, which are caused by not only mechanical forces but also enzymatic destruction of valve tissue[23].

Ultrastructural alterations of elastic fibers in the myxomatous area of the floppy aortic valve were the same as in the floppy mitral valves in the previous report[7]. Irregularly arranged aggregation of microfibrils without amorphous components and amorphous components without microfibrils were indicative of a disorder in the formation of elastic fibers. The granular appearance and fragmentation of amorphous components, and amorphous components and microfibrils associated with calcific deposits were suggestive findings of excessive degradation. So a mixture of degradation and abnormal synthesis of elastic fibers were common characteristic findings in floppy mitral and aortic valves.

The present study demonstrates structural abnormalities in all connective tissue components of floppy aortic valves. The ultrastructural abnormalities in connective tissue components, such as massive spiraling collagen fibrils and altered elastic fibers, have not been reported previously in floppy aortic valves. These abnormalities are similar to those in floppy mitral valves. While the finding of connective tissue abnormalities is the same, the reason why the aortic valve is involved in certain cases and the mitral valve is involved in other cases is unclear. The case classified as idiopathic floppy valve may not actually be a single disease entity, but may include various unknown diseases, even leaving aside Marfan syndrome and other inherited connective tissue diseases. Further investigation is required to evaluate and classify idiopathic floppy valves including cases with aortic root dilatation.

References

1. Rose AG: Etiology of valvular heart disease. Current Opinion in Cardiology 1996; 11: 98–113.
2. Boudoulas H, Vavuranakis M, Wooley CF: Valvular heart disease: the influence of changing etiology on nosology. J Heart Valve Dis 1994; 3 : 516–526.
3. Kern WH, Tucker BL: Myxoid changes in cardiac valves: pathologic, clinical, and ultrastructural studies. Am Heart J 1972; 84: 294–301.
4. Allen WM, Matloff JM, Fishbein MC: Myxoid degeneration of the aortic valve and isolated severe aortic regurgitation. Am J Cardiol 1985; 55: 439–444.
5. Bellitti R, Caruso A, Festa M, Mazzei V, Iesu S, Falco A, Cotrufo M, Agozzino L: Prolapse of the "floppy" aortic valve as a cause of aortic regurgitation. A clinico-morphologic study. Int J Cardiol 1985; 9 : 399–410.
6. Tonnemacher D, Reid C, Kawanishi D, Cummings T, Chandrasoma P, McKay CR, Rahimtoola SH, Chandraratna PAN: Frequency of myxomatous degeneration of the aortic valve as a cause of isolated aortic regurgitation severe enough to warrant aortic valve replacement. Am J Cardiol 1987; 60: 1194–1196.

7. Tamura K, Fukuda Y, Ishizaki M, Masuda Y, Yamanaka N, Ferrans VJ: Abnormalities in elastic fibers and other connective-tissue components of floppy mitral valve. Am Heart J 1995; 129: 1149–1158.
8. Tamura K., Fukuda Y, Ferrans VJ: Elastic fiber abnormalities associated with a leaflet perforation in floppy mitral valve. J Heart Valve Dis 1998; 7 : 460–466.
9. Kajikawa K, Yamaguchi T, Katsuta S, Miwa A: An improved electron stain for elastic fibers using tannic acid. J Electron Microsc (Tokyo) 1975; 24: 287–289.
10. Moriyama Y, Toyohira H, Koga M, Watanabe S, Saigenji H, Shimokawa S, Taira A: Isolated aortic valve regurgitation due to degeneration of the valve leaflet—a clinical study. J Jap Ass Thorac Surg 1995; 43: 951–955.
11. Agozzino L, Vivo F, Falco A, Shinosa LLT, Cotrufo M: Non-inflamatory aortic root disease and floppy aortic valve as cause of isolated regurgitation: a clinico-morphologic study. Int J Cardiol 1994; 45: 129–134.
12. Devereux RB, Perloff JK, Reichek N, Josephson ME: Mitral valve prolapse. Circulation 1976; 54: 3–14.
13. Tamura K: Pathology of infective endocarditis. Kyobu-geka 1996; 49: 606–611.
14. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G, Zuccaro Jr G: Prevention of bacterial endocarditis. Recommendations by American Heart Association. JAMA 1997; 277: 1974–1801.
15. O' Brien KP, Hitchcock GC, Barratt-Boyes BG, Lowe JB: Spontaneous aortic cusp rupture associated with valvular myxomatous transformation. Circulation 1968; 37: 273–278.
16. Esteves CM, Dillon JC, Walker PD, Feigenbaum H, Chang S: Echocardiographic manifestations of aortic cusp rupture in a myxomatous aortic valve. Chest 1976; 69: 685–687.
17. Pasquali-Ronchetti I, Fornieri C, Castellani I, Bressan GM, Volpin D: Alterations of the connective tissue components induced by β-aminopropionitrile. Exp Mol Pathol 1985; 35: 42–56
18. Lakier JB, Copans H, Rosman HS, Lam R, Fine G, Khaja F, Goldstein S: Idiopathic degeneration of the aortic valve: a common cause of isolated aortic regurgitation. J Am Coll Cardiol 1985; 5 : 347–351.
19. Otto CM, Kuusisto J, Reinchenbach DD, Gown AM, O' Brien KD: Characterization of the early lesion of "degenerative" valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994; 90: 844–853.
20. Ghadially FN: Extracellular matrix. "In Ultrastructural pathology of the cell and matrix. 3rd ed. Vol. 2." Ghadially FN, ed. 1988; pp 1215–1289, Butterworths, London.
21. Clark RE, Finke EH: Scanning and light microscopy of human aortic leaflets in stressed and relaxed states. J Thorac Cardiovasc Surg 1974; 67: 792–804.
22. Chandrasekhar S, Kleinman HK, Hassell JR, Martin GR, Termine JD, Trelstad RL: Regulation of type I collagen fibril assembly by link protein and proteoglycans. Coll Relat Res 1984; 4 : 323–338.
23. Tamura K, I-ida T, Ishizaki M, Asano G, Tanaka S, Ferrans VJ: Increased activity of matrix metalloproteinases in floppy aortic valves. J Am Coll Cardiol 2000; 35 (Suppl A) : 525 A-526 A.

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