Pathology of Chronic Mitral Valvular Disease in the Dog

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Abstract. A total of 64 canine cases of so-called mitral valvular fibrosis were studied morphologically and histologically. They were divided into three groups. Group I had small, discrete lesions with or without large nodules in the rough zone. Group II exhibited extensive thickening all over the rough zone. Group III had remarkably thickened leaflets and ruptured chordae tendineae. Morphologically, as the disease progressed in severity, the leaflets apparently became more and more redundant and the chordae tendineae gradually elongated. Chordal rupture was found in 8 of 12 cases of Group III. The characteristic histological changes were the destruction of collagen bundles and the deposition of acid mucopolysaccharide in the spongiosa and the fibrosa. The destruction of chordal collagen bundles was especially severe in the case of chordal rupture. It is considered that these morphological changes closely resemble those found in the mitral valve prolapse syndrome in human beings.

Chronic mitral valvular disease, which frequently causes congestive heart failure, is one of the most common cardiovascular diseases in the dog. Clinical and pathological studies have been performed on this condition by many researchers [5, 8–11, 17, 21, 22, 28–30]. Pathological studies revealed diffuse thickening of the mitral valve sometimes accompanied with discrete nodular thickening. They also demonstrated that the leaflets and the chordae tendineae were contracted with their free edges rolled up. Affected leaflets were reported to show such histological changes as loose fibroelastic proliferation and mucoid degeneration in the spongiosa and the fibrosa.

Chronic valvular disease has therefore been regarded as valvular fibrosis [9, 13, 15] or endocardiosis [22, 28–30] because of the above-mentioned features. The present study failed, however, to find these features in the cases examined. Instead, it revealed clinical and pathological changes closely resembling those of mitral valve prolapse syndrome [1, 5, 12]. This syndrome has also been described in human beings as floppy valve [7, 27], redundant cusp syndrome [18], billowing mitral valve leaflet [3], and ballooning mitral valve syndrome [2]. The author studied in detail the morphological and histological features of the canine mitral valve with this disorder, by collecting samples randomly from three institutions.

Materials and Methods

Sixty-four samples of the affected mitral valve accompanied with diffuse and sometimes discrete nodular thickening of the leaflets and chordal rupture were used. They were found among 306 canine hearts in the collections of three institutions: the Heart Institute of Japan, Nippon Veterinary and Zootecchnical College, and Tokorozawa Small Animal Hospital. They were derived from 39 males and 25 females. The age varied from 2 to 18 years, showing a median age of 4. The affected valves were divided into three groups according to a modified version of Whitney's classification [29].
Group I: Small discrete and large coalescent nodules were present in the rough zone. No chordal thickening was present. These valves corresponded to Whitney's types 1 and 2.

Group II: Thickening extended all over the rough zone. Some rough zone chordae were thickened in their proximal portion. No chordal rupture was present. These valves were similar to Whitney's type 3.

Group III: The leaflets and rough zone chordae were thickened and an occasional chordal rupture was present. These valves corresponded to Whitney's type 4.

In addition, 50 canine mitral valves which had no valvular changes were compared with the affected valves [16].

The morphology of the mitral leaflets and chordae tendineae was extensively studied. The normal morphology of the leaflets and chordae tendineae was described according to Ranganathan's and Lam's method [20, 28]. The length of each chorda tendinea was measured from its origin at the papillary muscle to its insertion at the leaflet. In order to compare chordal lengths, a chordal ratio (chordal length (L)/distance between the chordal origin at the papillary muscle and the valvular annulus (D)) was obtained, as shown in Fig. 3. The height of the leaflet was measured at the center of each leaflet (Fig. 3). These measurements were made with calipers and a metallic rule graduated to 0.5 mm.

After routine fixation in 10% formalin, affected valves and normal controls were cut into sections, which were stained with hematoxylin and eosin, elastica-van Gieson and Masson's trichrome stains. For the study of mucopolysaccharide deposition in connective tissue, alcian blue stain was employed.

Results

The materials used are summarized in Table 1. Age varied from 2 to 13 years with a median age of 2 years in Group I, from 3 to 11 years with a median age of 4 in Group II, and from 8 to 18 years with a median age of 10 in Group III. The morphological abnormality characteristic of all the groups was a redundancy of the mitral leaflets and chordae tendineae; that is, excessively long and thick valvular apparatuses. Such abnormality occurred in the rough zone of the anterior and posterior leaflets, especially in the posterior half of the anterior leaflet (AL), the posteromedial commissural scallop (PCS) and the middle scallop (MS). This redundancy of the mitral valvular apparatuses can produce localized or generalized ballooning of the mitral valve into the left atrial cavity. The morphological features of each group of the author's classification are as follows.

Group I: The posterior half of AL, PCS, and MS prolapsed slightly into the left atrial cavity (Fig. 4).

Group II: The prolapsing and thickening of the same portions were strikingly apparent.

Group III: Severe redundancy occurred on leaflets, as shown in Figs. 5, 6 and 7. The thickened area extended over the rough zone and into the rough zone chordae tendineae. The AL, PCS and MS were affected most severely. Although a chordal rupture, which was present in 8 of 12 cases, occurred always in the rough zone chordae, no thickened and ruptured chordae tendineae were seen in the cleft and commissural chordae tendineae.

The measurements proved that the rough/clear zone ratio of AL and the chordal ratio of rough zone chordae in affected valves had undoubtedly increased (Figs. 1 and 2). The rough/clear zone ratio of AL in Group I (1.6) and Group II (1.9) with the prolapsing mitral valve was almost equal to that in the normal canine heart valves (1.9) [16].

In Group III, the rough/clear zone ratio of AL with the severely prolapsing mitral
valve (3.1) was clearly higher than that of AL with the valve in Groups 1 and II.

With progressive disease, the chordal ratio of rough zone chordae of the AL progressively increased (83.6% in Group I, 85.5% in Group II and 108.0% in Group III). The chordal ratios in the commissural chordae were 72.6% in Group I, 76.3% in Group II, and 81.4% in Group III, and those in the cleft chordae, 78.3% in Group I, 80.1% in Group II and 82.0% in Group III.

The most prominent microscopic feature was the destruction of collagen bundles with deposition of acid mucopolysaccharide (AMP) readily seen as foci in the spongiosa and fibrosa. Histologic changes in each group were as follows.

Group I: Increased AMP was seen in the spongiosa of the distal half of the valve (Fig. 8). The nodular thickening was due mainly to the deposition of AMP in the fibrosa. The collagen bundles were almost intact.

Group II: The distal half of the valvular spongiosa displayed an increase in loose mucoid substance. A slight degeneration of collagen bundles was found in the fibrosa.

Although the distal half of the valvular architecture was disrupted, a normal structure was preserved in the proximal half.

Group III: Marked increase in AMP and disrupted collagen bundles of the fibrosa were seen in the distal half of the valve (Fig. 9). The components of the fibrosa were completely replaced by AMP material. Fibroelastic proliferation in both atrialis and ventricularis was commonly found. Thickening of the leaflets was due chiefly to increased AMP.

Discussion

Canine mitral valvular disease is characterized by nodular thickening of the leaflets and results in mitral insufficiency. It has generally been regarded as mitral valvular fibrosis [9, 13, 15] or endocardiosis [22, 28–30]. Detweiler et al. [11], Luginbuhl and
Detweiler [21], and Whitney [29] described, from their visual impression, morphological changes in the affected mitral valvular apparatuses as nodular thickening of the leaflets with contraction of the leaflets and shortening of the chordae tendineae. The redundancy of the leaflets and chordae tendineae was proved by the author’s measurements.

With the progress of the disease, the rough zone of the leaflets is apparently elongated and prolapses into the left atrial cavity. The leaflets assume so-called “bilowing sail deformity”. In clinical studies, left ventricular cineangiography in the lateral projection demonstrated both mitral regurgitation and prolapsing of leaflets (Fig. 10). Moreover, the prolapse of the mitral leaflet could be seen directly by M mode and two-dimensional echocardiography (Fig. 11). These morphological and clinical findings closely resemble those of the mitral valve prolapse syndrome in human beings. An anatomical diagnosis should be made on the basis of morphological features. It is reasonable therefore to apply the term mitral valve prolapse syndrome to such chronic mitral valvular disease.

In more advanced cases, both the edge and the surface of the leaflet increase in thickness. The rough zone chordae elongate with the progress of the disease. However, the cleft and the commissural chordae remain intact. These findings suggest that the pressure load may be imposed more markedly on the rough zone chordae than on the other chordae during ventricular systole.

The prolapse is severer in the posterior half of AL, PCS and MS than in the anterior half of AL and ACS. Similar findings have been reported in human beings [7, 19]. The etiology of such imbalance is unknown.

The most characteristic histological finding is the deposition of AMP. In the early stage, or in Group I, the localized deposition of AMP is seen only in the spongiosa. In a more advanced stage, or in Group II, AMP increases and mucoid degeneration extends to the collagen bundles of the fibrosa. In the terminal stage, or in Group III, AMP is visible in the chordae tendineae. On the contrary, Whitney [29] reported that the mucoid degeneration initially occurred in the fibrosa and then extended to the spongiosa and the chordae tendineae. Fibrosis appears to be a secondary change in the atrialis and the ventricularis. It is caused by mechanical friction during ventricular systole. The same change has also been described in human beings [7].

The author agrees with Buchanan [4] who proposed the term “mucoid degeneration”, not valvular fibrosis, for this condition. As to the pathogenesis of prolapsing valve, I suggest that the valve is weakened by the degeneration of collagen bundles, which causes the ballooning deformity. It seems that chordal elongation and rupture are induced by the same cause by which the leaflet has been elongated. Ettinger and Buergelt [14] proposed that chordal rupture should be regarded as an entity distinct from chronic valvular disease. It is believed, however, from the present study that pathologically, chordal rupture is to be included in the same category as chronic valvular disease.

The etiology of the degenerative change in collagen bundles is still unknown. This change is common in advanced age groups of both dogs [22, 28–30] and human beings [7, 23, 24]. This fact may provide a clue to elucidation of the pathogenesis of this unique condition.
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要約

犬の慢性僧帽弁疾患の病理形態学的研究：小暮一雄（東京女子医科大学附属日本心臓血管研究所循環器小児科・心臓本室）——著者が収集した犬の心臓標本306例のなかから僧帽弁線維症の特徴を有する64例の心臓標本の僧帽弁について、形態学的検討と詳細な計測を行なった。形態学的観察の結果、弁はちょうど「ヨットの帆を張ったような変形」を示し、その病変の好発部位は前尖の後半分と後尖の後交連に隣接する弁の rough zone であった。弁および腱索を計測した結果、弁およびその rough zone に過度な伸展が認められ、腱索では rough zone に伸長する腱索に強い伸張が認められた。一方、交連部や cleft に挿入する腱索は伸張は認められなかった。組織学的には、fibrosa における線維組織の粘液変性と非表面の線維性増殖が認められた。そして、病変の進行とともに多量の粘液性粘液多糖類の沈着を認めた。特に腱索の断面を伴なった症例では腱索の線維組織とも粘液変性が認められた。これらの所見から、本症の本質的病変は線維組織の変性であり、その結果、弁の脆弱化が起こって、特徴的な変化をもたらすものと考えた。これらの特徴はヒトにおける僧帽弁脱閉症候群のそれに酷似し、比較心形態学上興味深い。
Explanation of Figures

Fig. 3. Measurement of chordae tendineae and leaflets. The chordal length (L) is a distance from the origin at the papillary muscle to the insertion at the leaflet. D (dotted line) is a distance between the chordal origin and valvular annulus. The height of the leaflet is a distance from the free edge to the center of the base. AL: anterior leaflet of mitral valve. PPM: posteromedial papillary muscle.

Fig. 4. Four-year-old male mongrel dog with mild mitral regurgitation. Arrows show the ballooning deformity of the posteromedial commissural scallop (PCS) and middle scallop (MS). ACS: anterolateral commissural scallop.

Fig. 5. Ten-year-old female Maltese dog with severe mitral regurgitation. Section A: Mitral valve after opening the heart. Myxomatous thickening and ballooning deformity of both anterior and posterior leaflets are present, especially posterior half of AL, PCS and MS. Arrows show jet lesions. Section B: AL viewed from left ventricle. Rough zone of AL is apparently elongated. APM: anterolateral papillary muscle.

Fig. 6. Nine-year-old mongrel dog with severe mitral regurgitation. Large arrows show jet lesions. Small arrows show large left atrial split. Thickening and redundancy of AL, PCS and MS are also present. ACS is almost intact.

Fig. 7. Eleven-year-old male mongrel dog with severe mitral regurgitation. Chordal ruptures are present (arrows).

Fig. 8. Group I lesion. A: Masson's trichrome stain, ×50. B: Alcian blue stain, ×50. Blue-stained foci in spongiosa of B represent acid mucopolysaccharide.

Fig. 9. Group III lesion. A: Masson's trichrome stain, ×10. The fibrosal architecture is completely disrupted. Fibrous proliferation is seen in the atrialis. B: Alcian blue stain, ×10. The thickening is due mainly to the presence of large amounts of blue-stained acid mucopolysaccharide.

Fig. 10. Left ventricular cineangiography. Moderate mitral regurgitation and prolapse of both anterior and posterior leaflets (dotted line) are demonstrated.

Fig. 11. Echocardiographic features. A: M mode echocardiogram demonstrating pansystolic bowing (arrows). B: Two-dimensional echocardiogram. Anterior leaflet (AL) and posterior leaflet (PL) are located above the plane of the mitral ring. IVS: interventricular septum.