Canine and Feline Cardiomyopathy (13-Nov-2004)

S. P. Bishop
Department of Pathology, School of Medicine, University of Alabama, Birmingham, AL, USA.

Introduction
Primary or idiopathic cardiomyopathy is a term used for a variety of conditions affecting the heart of both animals and man with no clearly identified cause. Although the term secondary cardiomyopathy has been used with specific causative factors such as ischemic cardiomyopathy, drug induced cardiomyopathy, toxic cardiomyopathy or infectious agent induced cardiomyopathy, recent classifications would restrict the use of cardiomyopathy to those conditions with no clearly defined cause. In dogs, cardiomyopathy is most common in large breed dogs and some familial relationships have been identified. In the cat, some breed relationships have been identified. Transgenic mice with cardiomyopathy have been produced by insertion of a DNA sequence which transmits the single heavy myosin gene abnormality of a human form of familial cardiomyopathy [1]. Clinically, cardiomyopathy may result in sudden death, but more often death is preceded by congestive heart failure.

Pathologic Forms of Cardiomyopathy
Secondary cardiomyopathy due to various known causes such as ischemia, drug reactions such as with daunorubicin, toxic injury, peripartum or infectious agents generally result in a dilated form of cardiomyopathy, usually with hypertrophy as well. Congestive heart failure is the main clinical feature of these secondary cardiomyopathies. Primary or idiopathic cardiomyopathy may have several pathological manifestations, and for classification purposes, they are described as hypertrophic, dilated, restrictive and arrhythmogenic right ventricular fibroadipose dysplasia.

1). Hypertrophic cardiomyopathy involves mainly the left ventricle, but may include the left ventricle and atria as well. In man, this form has variously been referred to idiopathic hypertrophic subaortic stenosis (IHSS), asymmetrical septal hypertrophy (ASH) or hypertrophic obstructive cardiomyopathy (HOCM). More recently this form is referred to as familial hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy in man has been shown to have a genetic basis, appearing in some families for several generations and with several specific gene loci having been identified. The missense mutation usually involves a single nucleotide substitution of a single amino acid in the head region of the myosin heavy chain gene. Other mutations have been identified in the cardiac troponin T and α tropomyosin genes [2-4]. In the dog and the cat, genetic factors have received less study than in man. The main feature is marked increase in the weight of the left ventricle, often with disproportionate thickening of the interventricular septum and left ventricular outflow tract obstruction. Dilation may occur terminally, but sudden death is a common occurrence.

2). Dilated cardiomyopathy is characterized by a large left ventricular lumen, often with thinning of the LV walls, but usually accompanied by increase in left ventricular weight due to cellular hypertrophy. However, cellular atrophy and degeneration may attenuate increase in mass. Congestive heart failure is the usual clinical presentation.

3). Restrictive cardiomyopathy in man is a rare form which may involve infiltration as with amyloid or some forms of endocardial fibrosis, seen mainly in African children or in Loeffler’s endocarditis. This form has only rarely been reported in animals [5]. Extensive endomyocardial fibrosis with focal scar formation in the left ventricle or septum is seen in the cat, resulting in reduced chamber size and diastolic dysfunction [6].
4). Arrhythmogenic right ventricular fibroadipose dysplasia is a rare condition in man [7] and has been reported in a small number of dogs [8-11].

**Histopathology**

**Hypertrophic Cardiomyopathy** - The main feature of hypertrophic cardiomyopathy is increase in cardiac mass due to hypertrophy of individual cardiac myocytes. The left ventricle is most severely affected, but increase in weight of the right ventricle and atria may also occur. Cellular hypertrophy may involve all cells in the left ventricle, or may be limited to or more severe in a segment, most often the basal regions of the interventricular septum. The characteristic feature of hypertrophied myocytes in this form of cardiomyopathy is intracellular myofibrillar disarray and malalignment of cells with each other, first described in human hearts by Maron [12-15]. Subsequently, similar myofibrillar and myofiber disarray was described in both dogs and cats with hypertrophic cardiomyopathy [16-18]. Although the extent of myofiber disarray is usually sufficient to easily diagnose the condition, in some individuals the disarray is less extensive and quantitative analysis has been applied to identify these patients [19].

By electron microscopy, the myofibrillar disarray is visualized as individual fibrils or bundles of fibrils coursing a sharp angles to each other within the cell.

The extent of cellular degeneration and replacement fibrosis is extremely variable, ranging from no fibrosis to extensive replacement of lost myocytes with multifocal areas of connective tissue. Medial and intimal thickening of the left ventricular small intramural coronary arteries with marked lumen reduction is a common feature.

**Dilated Cardiomyopathy** - In dilated cardiomyopathy the cells are also increased in size, but the main change is in cell length, with the cross sectional area remaining normal or even decreased in size. As opposed to the hypertrophic type, sarcomeres are added in series rather than in parallel, and myofiber disarray is not a feature. The extent of fibrosis is variable from none to extensive. Changes in intramyocardial arteries are generally not remarkable.

In many large breed dogs with congestive heart failure and dilated cardiomyopathy, there is extensive left ventricular mid wall myocellular degeneration characterized by central myofibrillar lysis and cellular atrophy. There is extensive interstitial fibrosis around the degenerating myocytes and often, extensive fatty infiltration [20,21]. Another form of histopathological alteration has been described in large breed dogs with dilated cardiomyopathy by Tidholm et al [21-25]. In these animals, the myofibers are attenuated to less than 6 microns diameter and have a wavy form similar to that seen in early ischemic myocardial cell injury.

**Restrictive Cardiomyopathy** - Amyloid infiltration of the myocardium may occur as a primary condition involving only the myocardium or may be part of widespread amyloidosis throughout the body. Amyloid in the heart has the typical congo red birefringent material infiltrating the interstitial tissue between myocytes and resulting in increased myocardial stiffness. This is a rare condition in animals.

Endocardial fibrosis with marked collagen and elastic deposition over the endocardium of the left ventricle is a rare condition in animals. It is most often seen in cats resulting in increased myocardial stiffness and reduced left ventricular chamber size and diastolic dysfunction. It has been reported as a congenital lesion in a young dogs [5,26].

**Arrhythmogenic Right Ventricular Fibroadipose Dysplasia** - Lesions are restricted to the right ventricle, most often involving the outflow tract region. There is focal fibroadipose replacement of the myocardium which is very thin walled in many cases [9-11,27-29].

**Feline Cardiomyopathy**

**Hypertrophic** - Hypertrophic cardiomyopathy is the most commonly occurring of the feline myocardial diseases [30]. Systemic hypertension [31,32] and hyperthyroidism [33] are also well recognized conditions in the cat and must be ruled out in patients with non dilated cardiac enlargement, as well as congenital cardiac lesions which may result in cardiac hypertrophy. Idiopathic hypertrophic cardiomyopathy is most often reported in domestic short hair cats; in Maine coon cats there appears to be a heritable basis [34].

Left ventricular weight to body weight is substantially increased. Left ventricular hypertrophy is usually symmetrical involving all portions of the left ventricle and septum, but segmental hypertrophy also may occur, involving the interventricular septum or other portions of the left ventricle. Histologically there is characteristic myofiber disarray resulting in bizarre disorganized cellular architecture. Increased interstitial fibrosis is commonly present. Intramural small coronary arteries have medial and intimal thickening with narrowed lumens. Perivascular fibrosis is frequently present.

**Dilated** - Dilated congestive cardiomyopathy is characterized by moderate increase in cardiac mass and marked dilation of all
four chambers with thinning of the ventricular walls. Papillary muscles are thin and flattened. Histologically, myocytes are thinner than normal and there is generally only mild interstitial fibrosis. In the cat, dilated cardiomyopathy has been shown to be related to low levels of taurine in the diet. Taurine is an essential amino acid in cats. Cats with dilated cardiomyopathy have plasma taurine levels less than 30 nmol/ml and are responsive to dietary supplementation with taurine [35-38].

Restrictive - Restrictive cardiomyopathy is a condition of uncertain etiology resulting in diastolic dysfunction and myocardial stiffness. Heart weight to body weight is mildly to moderately elevated with thickening most marked in the left ventricular free wall and septum, with the apex less affected. Focal left ventricular or septal scar formation is frequent and fibrous tissue may bridge the ventricular lumen or papillary muscles. The transmural scar tissue may be so extensive as to cause intracavitary diastolic and systolic pressure gradients [6]. Histologically there is myofiber hypertrophy and multiple areas of collagenous scar tissue on the endocardium, often extending through the myocardium. Focal areas of active endomyocarditis with mononuclear cells and occasionally, neutrophils, are sometimes present. Mural thrombi in the left atrium and left ventricle are frequent and very often accompanied by aortic thromboembolism [39-43].

Hypereosinophilia has rarely been reported in cats, but there is little evidence to suggest that this is associated with cardiac disease in the cat as with Loffler’s endocarditis in man. The endomyocarditis present in some cats with restrictive cardiomyopathy or endomyocardial fibrosis suggests that a viral or immunologic mediated mechanism may be responsible. Parvoviral genomic material has been isolated from feline hearts with cardiomyopathy and myocarditis, though definite etiologic relationship has not been established [44].

Canine Cardiomyopathy

Hypertrophic - Hypertrophic cardiomyopathy is a relatively uncommon condition in the dog. It is characterized by marked left ventricular enlargement and asymmetrical thickening of the interventricular septum, with a lateral free wall to septal thickness ratio of greater than 1.3. Histologically, the hypertrophied myocytes have myofiber and myofibrillar disarray as is seen in both the human and feline forms [16,45-47]. Interstitial fibrosis ranges from mild to severe and there is medial and intimal thickening of small intramural coronary arteries.

Dilated - The most common form of idiopathic cardiomyopathy in the dog is the dilated form. The left ventricle and atrium are most severely affected, but the right ventricle and atrium may also be dilated. The left ventricular myocardial wall is thin and the papillary muscles are thinned and flattened. Histologically, at least two forms have been described. Tidholm has reported a series of large breed dogs with dilated cardiomyopathy which at necropsy have a wavy fiber character with myofibers less than 6 microns in diameter [21-25]. Thin wavy fibers have previously been associated with early ischemic lesions, the usual interpretation being that stretched fibers subjected to acute ischemia lack the necessary energy requirements for contraction and are forced into a wavy formation by contraction of surrounding contracting fibers. Whether this explanation is appropriate for the attenuated wavy fiber histopathology described by Tidholm is not clear.

The histologic form most often described for dilated cardiomyopathy does not include wavy fiber formation. Hearts from large breed dogs with dilated cardiomyopathy are often near normal or only moderately increased in weight, in spite of cellular hypertrophy of many left ventricular myocytes. Histologically there is extensive myocyte degeneration and atrophy within the central third of the left ventricular myocardial wall, often extending to both the endocardial and epicardial surfaces. Papillary muscles are only involved when there is extensive mid wall lesion. There is marked disparity in myocyte size, some cells being very large, some normal, and others small due to atrophy. Many cells have central myofibrillar lysis. Interstitial fibrosis in the midwall region is variable, but often extensive. Fatty infiltration in the midwall lesion area is frequently present. Occasional small foci of replacement fibrosis are sometimes present. Vascular lesions are limited to moderate medial thickening of small intramural coronary arteries.

Although there have been few molecular genetic studies in the dog with dilated cardiomyopathy, there is a definite breed disposition. The large breeds are most commonly affected, especially Irish Wolfhounds [48-51], Doberman Pinschers [20,52-54], Newfoundland [22,55], Great Danes [56-58], Boxers [24] and Dalmations [59]. Families of affected individuals have been identified in other breeds as well, including American Cocker Spaniels [22,55,60,61], English Cocker Spaniels [24] Portuguese water dogs [62,63] and Presa canario dogs [64].

The role of taurine in canine dilated cardiomyopathy is less clear than in the cat. Several studies have identified some dogs with dilated cardiomyopathy with very low taurine levels, but many affected dogs have normal plasma taurine. Dogs fed a predominantly lamb meal and rice diet will develop low taurine levels and some will develop dilated cardiomyopathy [55,65,66]. Some breeds, especially American Cocker Spaniels may be particularly susceptible to dietary deficiency of taurine and have some clinical improvement when taurine is supplemented in the diet [60,67].
Restrictive - Restrictive cardiomyopathy is rare in the dog, having been reported only in a few cases of congenital endocardial fibrosis [5,26]. The condition was found in young dogs with extensive fibroelastic thickening of the left ventricular endocardium.

Arrhythmogenic right ventricular fibroadipose dysplasia. This rare condition in dogs is characterized by a large area of focal fibroadipose replacement of the right ventricular myocardium, which may involve the right atrium as well. It has been reported most often in Boxer dogs [9-11,27-29,68].

References

61. Kittleson MD, Keene B, Pion PD, et al. Results of the multicenter spaniel trial (MUST): taurine- and carnitine-


All rights reserved. This document is available on-line at www.ivis.org. Document No. P1221.1104. This manuscript is reproduced in the IVIS website with the permission of the ACVP & ASVCP www.acvp.org