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Abstract

A novel dilated cardiomyopathy (DCM) in 12 related Portuguese Water Dogs was identified by retrospective analysis of postmortem and biopsy case records. Male and female puppies born to clinically healthy parents typically died at 13 (\pm 7.3) weeks of age (range, 2–32 weeks) because of congestive heart failure. Puppies died suddenly without previous signs or with mild depression followed by clinical signs of congestive heart failure 1–5 days before death. There was no sex predilection. The hearts were enlarged and rounded, with marked left ventricular and atrial dilation. No other significant structural cardiac defects were noted. The histologic changes in the myocardium were diffuse and characterized by myofibers of irregular sizes separated by an edematous interstitium. The myofibers had multifocal swollen, cleared segments often involving perinuclear areas that contained granular, phosphotungstic-acid-hematoxylin-positive material consistent with mitochondria. There was loss of the cross-striation pattern, and intercalated discs were difficult to identify. There was no evidence of concurrent myocardial fibrosis; rare chronic inflammatory infiltrates were noted in one dog. Noncardiac skeletal muscles were not affected. The underlying cause is unknown. From the pedigree analysis, an autosomal recessive pattern of inheritance is suspected. Based on the histologic findings, this DCM is most likely due to an underlying molecular (biochemical or structural) defect. The early onset and rapid progression of the disease makes this a clinically distinctive form of canine DCM.

Keywords

Dog, Idiopathic dilated cardiomyopathy

Disciplines

Animal Diseases | Cardiology | Cardiovascular Diseases | Congenital, Hereditary, and Neonatal Diseases and Abnormalities | Veterinary Infectious Diseases

Familial Dilated Cardiomyopathy of Young Portuguese Water Dogs

Donna M. Dambach, Anne Lannon, Meg M. Sleeper, and James Buchanan

A novel dilated cardiomyopathy (DCM) in 12 related Portuguese Water Dogs was identified by retrospective analysis of postmortem and biopsy case records. Male and female puppies born to clinically healthy parents typically died at 13 (\pm 7.3) weeks of age (range, 2–32 weeks) because of congestive heart failure. Puppies died suddenly without previous signs or with mild depression followed by clinical signs of congestive heart failure 1–5 days before death. There was no sex predilection. The hearts were enlarged and rounded, with marked left ventricular and atrial dilation. No other significant structural cardiac defects were noted. The histologic changes in the myocardium were diffuse and characterized by myofibers of irregular sizes separated by an edematous interstitium. The myofibers had multifocal swollen, cleared segments often involving perinuclear areas that contained granular, phosphotungstic-acid-hematoxylin-positive material consistent with mitochondria. There was loss of the cross-striation pattern, and intercalated discs were difficult to identify. There was no evidence of concurrent myocardial fibrosis; rare chronic inflammatory infiltrates were noted in one dog. Noncardiac skeletal muscles were not affected. The underlying cause is unknown. From the pedigree analysis, an autosomal recessive pattern of inheritance is suspected. Based on the histologic findings, this DCM is most likely due to an underlying molecular (biochemical or structural) defect. The early onset and rapid progression of the disease makes this a clinically distinctive form of canine DCM.

Key words: Dog; Idiopathic dilated cardiomyopathy.

Dilated cardiomyopathy (DCM) is the most commonly reported form of canine cardiomyopathy.^{1,2} DCM is most often associated with large and giant breed dogs and the Doberman Pinscher, Boxer, and English and American Cocker Spaniel breeds.^{3–7} In all breeds, the age range of affected dogs is wide (6 months to 15 years), although the typical age range of clinical presentation is 4–8 years.¹ For the Boxer, Doberman Pinscher, and Great Dane breeds, less than 1% of cases are made up of dogs younger than 1 year of age.⁸ There is a 2:1 male predilection reported in the affected breeds.⁸ Survival is poor after onset of signs ranging from 6 weeks to 2 years, and death is due to congestive heart failure or fatal arrhythmias. The predisposition of specific breeds for DCM suggests a heritable basis for the disease, but the exact underlying molecular or biochemical mechanism(s) for canine DCM in all cases is unknown. Many of the structural and biochemical changes noted may be secondary manifestations of the failing heart. This is the first report of DCM in the Portuguese Water Dog breed. This disease appears to be familial, but it has features that distinguish it from other canine dilated cardiomyopathies.

Materials and Methods

The 12 cases of DCM in Portuguese Water Dogs (POWD) were identified by review of the records of the Necropsy and Surgical Pathology Services of the School of Veterinary Medicine, University of

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Pennsylvania, for the period 1987–1996. Postmortem examinations were performed on 5 pups, and heart weight and heart:body weight ratio were recorded in 3 pups. Heart weight was determined after removal of the pericardium and great vessels and after all heart chambers were opened and blood clots were removed. Body weight and condition were recorded at postmortem to allow calculation of heart:body weight ratios. Tissues and information from the remaining 7 cases of DCM were obtained through submissions to the Surgical Pathology Service. Hearts from clinically normal age- and breed-matched pups were also examined histologically. All tissues were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, and sectioned at 3–5 μ m for light microscopy. Tissue sections were stained with hematoxylin and eosin, Masson's trichrome for collagen, alcian blue (pH 2.7) for mucopolysaccharides, phosphotungstic acid-hematoxylin for mitochondria, and periodic acid-Schiff for glycogen. Formalin-fixed, frozen tissue from 1 pup (10) was stained with oil red O for lipid. When whole hearts were submitted for evaluation, the following were examined histologically: sections through the entire left and right free walls (atria, atrioventricular valves, and ventricles) and sections through the entire interventricular septum, including right atrioventricular valve and aortic valve.

Clinical and historical data were obtained either by examination of the clinical records from affected pups at the Veterinary Hospital, University of Pennsylvania, or from the referring veterinarians. Two pups (4, 10) were clinically evaluated with radiographs, EKG, and echocardiography prior to death. Results of serum clinicopathologic analysis and CBCs were available for 1 pup (10). Urinary metabolic screening was performed on pup 10 using spot tests and 1-dimensional paper chromatography to analyze the types of amino acids, organic acids, and carbohydrates in urine.⁹ Pedigree analysis was performed using 4–6-generation pedigree information from affected pups provided by owners and breeders.

Results

Clinical Findings

The clinical courses of the 12 pups were similar. The affected pups were 13 \pm 7.3 (SD) weeks of age (range, 2–32 weeks) at the time of death. The longest clinical course was 5 days and was characterized by depression and decreased appetite, collapse, and death. The remainder of the pups presented with either an acute onset of respiratory distress leading to death within hours or sudden unexpected collapse and death (Table 1). There was no evidence of protracted disease, even in the 32-week-old male. Because

Table 1. Characteristics of Portuguese Water Dog pups with dilated cardiomyopathy.

Pup No.	Age (weeks)	Gender	Heart Weight (g) (% body weight)	Clinical History
1 ^a	12	Female		Several days depression, anorexia; sudden collapse, death
2 ^a	12	Female		24-hour respiratory distress, death; cardiomegaly, pulmonary edema
3	32	Male	174 (1.06%)	Acute onset respiratory distress; enlarged heart, pulmonary edema
4	14	Female	73 (1.3%)	Few hours of weakness, then respiratory distress, cyanosis, death; pup from previous litter from same parents died with similar signs
5	2	Male		Respiratory distress; failure to thrive
6	7	Male		Sudden, unexpected death
7 ^b	9	Male		Not available
8 ^b	11	Female	44	Respiratory distress; severe interstitial pattern
9	8	Female	32	Lethargic, decreased appetite on day of death; died suddenly while playing; breeder reported another littermate died
10 ^c	14	Female	67 (1.09%)	Quiet pup; echocardiography showed dilated heart; all other clinical data normal; euthanized
11 ^c	13	Male	73	Sudden onset respiratory distress; exercise intolerance; died 4 hours later
12 ^c	17	Female	83	Sudden onset respiratory distress; died 30 minutes later

Pups with same superscript are littermates.

of the unexpected onset of the clinical signs and the rapid decline, 10 of 12 pups lacked clinicopathologic data. Two pups (4, 10) were evaluated and followed clinically from the onset of clinical signs to death. Pup 4 was presented because of respiratory distress. Physical examination revealed a grade III/VI soft systolic murmur at the left cardiac

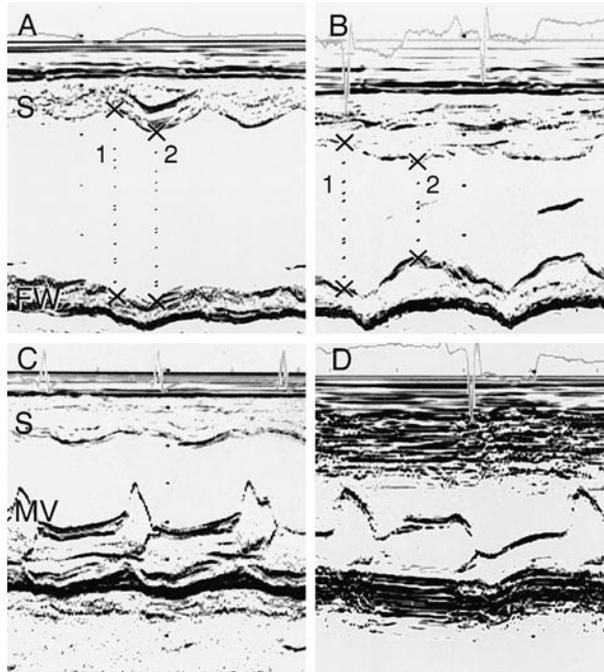


Fig 1. M-mode echocardiographs from affected pup 10 (A, C) and a normal age-, breed-, and weight-matched pup (B, D). The affected pup had increased left ventricular end-diastolic diameter (1) (3.7 cm) and increased end-systolic diameter (2) (3.4 cm), yielding a shortening fraction of 10%. Respective values in the normal pup (B) were 2.3 cm, 1.5 cm, and a shortening fraction of 35%. An echocardiogram of the affected pup (C) showed mitral valve (MV) motion and increased E-point septal separation (EPSS) of 1.1 cm. EPSS in the normal pup (D) was 0.5 cm. S = interventricular septum, FW = left ventricular free wall.

apex. The cardiac rhythm was regular; however, weak pulses and pale mucous membranes were detected. Crackles were auscultatable over all lung fields, and the pup was markedly dyspneic. Radiographs revealed left-sided cardiomegaly and a hilar alveolar pattern consistent with pulmonary edema. The vertebra: heart ratio measurement was 11.9 (normal = 8.6–10.6).¹⁰ Echocardiography revealed a severely dilated left ventricle with a shortening fraction of 10% (normal = 27–48%)¹¹ (Fig 1). The pup was treated with furosemide (2 mg/kg IV q8h), nitroglycerine (0.6mL sc q6h), digoxin (0.04 mg PO q12h), and increased inspired oxygen tension via an oxygen cage. The pup underwent cardiac arrest later that day, and resuscitation attempts were not successful.

Pup 10 was presented because a littermate (pup 11) died suddenly, and cardiomyopathy was diagnosed at postmortem. Physical examination of pup 10 at the time of presentation revealed a slightly muffled 1st heart sound; however, no murmur was detected. Normal bronchovesicular lung sounds were auscultated over all lung fields. Radiographs revealed a heart size at the upper limit of normal, with a vertebra: heart ratio of 10.7. The right cranial pulmonary arteries and veins were enlarged. All variables on an EKG examination were within normal limits (PR = 80 ms; QRS = 40 ms; QT = 200 ms; RII = 1.7 mV; mean electrical axis = normal), although a sinus tachycardia was present (heart rate [HR] = 180beats/minute). An echocardiogram revealed cardiomegaly, with a left ventricular end diastolic diameter of 3.7 cm and a left ventricular systolic diameter of 3.4 cm (respective normal values from an age-, breed-, and size-matched control animal: 2.3 and 1.5 cm). The shortening fraction was 10%. E-point septal separation was 1.1 cm (normal, 0.3 cm), and the aortic ejection time was 0.135 seconds (normal, 0.185 seconds) (Sleeper, unpublished data). Mild mitral regurgitation was detected with Doppler investigation.

The following day, the pup remained tachycardic, and a faint, intermittent diastolic gallop was occasionally auscultatable. By that evening, the pup was slightly weak and had a decreased appetite. Bronchovesicular sounds were in-

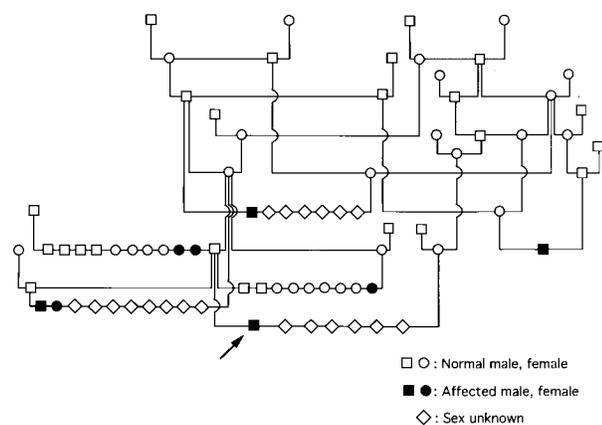


Fig 2. Pedigree analysis of 8 pups affected with dilated cardiomyopathy (DCM). The arrow indicates the propositus (pup 10). Pedigree analysis reveals common ancestry of the 8 POWD affected with DCM. Both genders are affected and were produced by phenotypically normal parents. In another family of POWD sharing no common ancestor with the propositus within 6 generations, there are 4 affected dogs (1 male, 3 females). These results are highly suggestive of an autosomal recessive mode of inheritance.

creased; however, no distinct crackles were auscultatable. Mild end expiratory effort was noted. The 2nd day after presentation as a clinically normal pup, the dog was weaker and anorectic. Auscultation revealed a grade V/VI pansystolic murmur with the point of maximal intensity at the left apex. A prominent gallop rhythm was also noted, and pulses were of a short duration and weak. Crackles became auscultatable bilaterally in the thorax several hours later, and a bolus of 1 mg/kg furosemide was administered IV. Over the following 2 hours, crackles became more prominent, as did tachypnea and dyspnea. During this period, the pup vomited and remained severely depressed. An EKG exam demonstrated sinus tachycardia (HR=190 beats/minute) but was otherwise unremarkable. Another bolus of IV furosemide was administered; however, the pup remained in respiratory distress and was euthanized and submitted for postmortem. A CBC and serum and urinary biochemical analyses on pup 10 did not reveal any abnormalities. Radiographic abnormalities for pups 4, 10, and 11 included pulmonary interstitial patterns characteristic of edema in all 3 pups and cardiomegaly in 2.

The treatment for 7 pups consisted of emergency supportive care to stabilize the cardiovascular system, including 1 or more of the following: cardiopulmonary resuscitation (n = 3); digoxin (n = 1), furosemide (n = 3), nitroglycerine (n = 1), oxygen (n = 3), corticosteroids (n = 1), fluids (n = 1), epinephrine (n = 2), and aminophylline (n = 1).

Pedigree Analysis

Pedigree analysis revealed common ancestry of 8 of the POWD affected with DCM (Fig 2). One female was the dam of 4 affected pups, the granddam of 2 affected pups, the great-granddam of 1 pup, and a half-sister to the remaining affected pup. Another family of POWD sharing no common ancestor to pup 10 within 6 generations did include the 4 additional affected pups. All 12 affected pups

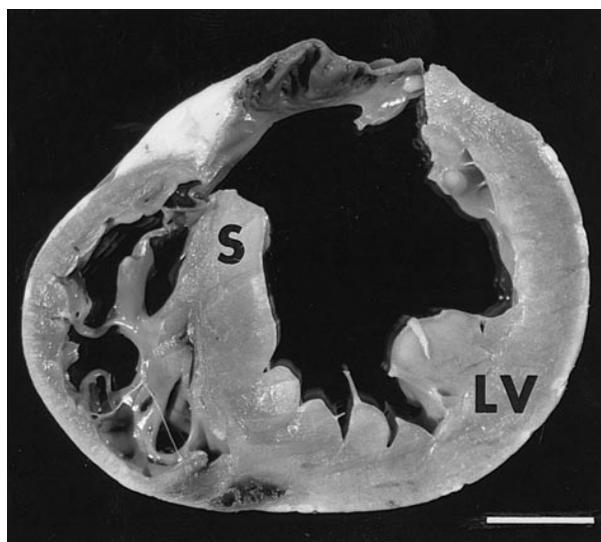


Fig 3. Transverse section of heart from pup 10 with dilated cardiomyopathy. The heart is globoid due to diffuse chamber dilation, which is most pronounced for the left ventricle and atrium. S = septum; LV = left ventricular free wall. Bar = 1 cm.

were produced by phenotypically normal parents. Both males (n = 5) and females (n = 7) were affected. Based upon these findings, the pedigree is most consistent with an autosomal recessive mode of inheritance, but a polygenic mode of inheritance cannot be ruled out without further test breedings. Although there are several anecdotal reports of pups dying with clinical signs similar to those reported here, the true incidence of this disease in the POWD breed cannot be determined at this time.

Postmortem Results

Entire hearts of 9 pups were available for examination, but only sections of heart were submitted for the remaining 3 pups. Of the 9 hearts examined, all had similar changes (Fig 3). The hearts were enlarged and globoid with rounding of the apex. The left auricle was markedly dilated, often larger than the right auricle. The left ventricle was dilated and easily compressible from the epicardial surface. On cut section, the left ventricular lumen was expanded with flattening of papillary muscles. The left ventricular free wall thickness was noticeably reduced (measurements of thickness were not routinely made). The endocardium of the left ventricle was diffusely opaque, corresponding histologically to endocardial fibrosis. The right ventricle and atrium were also dilated, but these changes were not as pronounced as that seen in the left hemiportion of the heart. A patent foramen ovale (1 × 0.4 cm) was noted in case pup 2. No other structural abnormalities were found in the remaining 8 hearts.

Lung changes were noted grossly at postmortem in 5 pups; lungs were wet and rubbery, congested, and slightly firm. Lungs from 11 pups were examined histologically. Interstitial edema and alveolar histiocytosis were noted in all pups, and in 7 pups there was minimal to mild acute interstitial pneumonia with infiltrates of neutrophils and the presence of alveolar fibrin and necrosis of individual cells

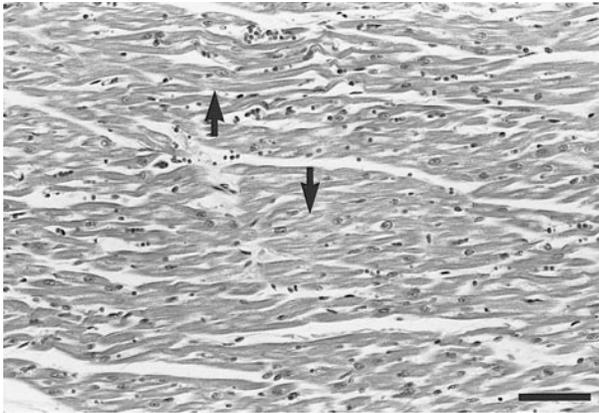


Fig 4. Histologic section of myocardium from pup affected with dilated cardiomyopathy. The interstitial space between the myofibers is prominent. The myofibers are generally thinner than normal and disorganized; their size varies markedly. The swollen, cleared areas of the sarcoplasm are obvious at this magnification (arrows). Hematoxylin and eosin. Bar = 61 μ m.

in the septa. Erythrophagocytosis was noted in only 1 pup (9); however, red blood cells were noted in alveoli in all 11 pups examined. The changes are consistent with those found in congestive heart failure and secondary hypoxia. The mild acute interstitial inflammation may have also been the result of mild aspiration during the bouts of dyspnea.

Other changes noted at postmortem or from tissues submitted were consistent with those resulting from heart failure. Hepatic congestion was found histologically in the 6 pups where liver was available for evaluation. Hepatomegaly was reported in 6 pups; hepatic capsular fibrin was also reported in 1 pup. These gross findings are consistent with passive hepatic congestion of cardiac origin. Peritoneal cavity ascites was reported in 2 pups, and pleural effusion (transudate) was reported in 1 pup.

Histologic Examination

Heart tissue from 5 normal breed-matched dogs (4 pups 6–18 weeks of age and one 4-year-old adult dog) were compared with that of affected pups. The changes in the myocardium from affected pups were most obvious upon examination of longitudinal sections of myofibers. The myofibers were accentuated by an interstitium expanded by clear space that did not stain with special stains for mucopolysaccharides, lipid, or glycogen and was therefore consistent with edema. The myofibers often appeared irregular in thickness and wavy to bent; many myofibers appeared to taper or branch. These changes created a disorganized appearance of the myofibers in some areas when examined at low magnification (Fig 4). There was a generalized loss of the normal pattern of cross-striations in affected myofibers, and intercalated discs were not seen. The irregularity in myofiber thickness was due predominately to swelling and clearing of the sarcoplasm, which resulted in an overall decrease in staining intensity when compared with normal myocardium (Fig 5). The zones of clearing in the myofibers were multifocal and segmental and typically included prominent perinuclear staining with pinpoint eosinophilic granular material (Fig 5). This granular material

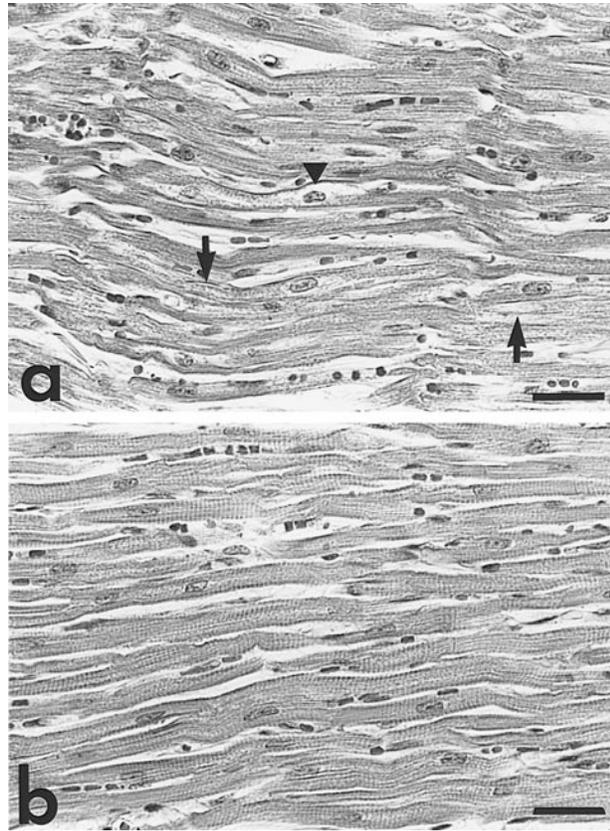


Fig 5. Histologic appearance of myocardium from POWD affected with DCM (a) and from a clinically normal pup (b). The myofibers from the affected dog (a) are expanded segmentally by cleared areas of the sarcoplasm, which are typically prominent in perinuclear regions (arrowhead) but extend to affect large areas of the fibers, leading to loss of regular cross-striations (arrows). There is greater nuclear size/shape variability in the affected heart when compared with tissue from a breed/age-matched control dog (b). Hematoxylin and eosin. Bars = 57 μ m.

stained dark blue with phosphotungstic acid–hematoxylin, which is consistent with mitochondria. However, the cleared areas of the myofiber sarcoplasm did not stain with special stains for mucopolysaccharides, lipid, or glycogen, which suggests that the swelling was due to accumulation of intracellular fluid (hydropic change).

There was no histologic evidence of myocardial fibrosis in any pup when tissues were examined with a trichrome stain. Myofiber nuclei had marked size variability, with karyomegaly and occasional indented nuclei. The nuclei also were slightly more hyperchromatic when compared with the nuclei from normal myocardium. These nuclear changes are consistent with those described in cases of myocardial hypertrophy.¹² On cross-section, the changes in the myofibers were more difficult to appreciate when compared with normal myocardium; the most prominent changes included nuclear hyperchromasia and myofibers of irregular shape and size that often appeared more angular.

Myocardial inflammation was absent in all except pup 2, in which rare mixed inflammatory cells (neutrophils, lymphocytes, and macrophages) were noted associated with the endocardium and perivascularly. Rare Anitchkow cells

were noted in the interstitium of case pup 12. Myofiber degeneration and necrosis were also absent in all pups examined. Coronary arterial and venous vasculatures were histologically normal. Skeletal muscle obtained from the extremities was also histologically normal.

Discussion

DCM is characterized by generalized dilation of both atria and ventricles of the heart.² Clinical manifestations of DCM result from decreased pump function leading to reduced cardiac output. A narrow pulse pressure may be detected on physical examination, and ventricular gallops typically develop once cardiac decompensation occurs. Body cavity and pulmonary fluid accumulation and hepatomegaly result from a compensatory increase in preload and the decreased forward movement of the blood through the heart to the arterial system. The most striking clinical signs are related to hypoxia and hypoperfusion, with weakness, exercise intolerance, syncope, coughing, respiratory distress, and tachypnea frequently observed. The development of these clinical signs typically occurs late in the course of disease and is ominous.¹³ Murmurs due to consequent valvular insufficiency occur if dilation is severe enough to enlarge the valve annulus. Arrhythmias are a common finding, as are radiographic and echocardiographic evidence of heart enlargement. Echocardiographic findings consistent with cardiac enlargement include increased end-diastolic and end-systolic ventricular volumes and increased atrial diameter; changes are more frequently detected on the left side. The shortening fraction is typically lowered, with a decreased left ventricular free wall thickness. An additional common feature is a reduced left ventricular ejection time. Death is due to congestive heart failure or fatal arrhythmias.

The histologic changes noted in cases of DCM are not pathognomonic for DCM nor are they indicative of a specific cause. In the dog, as in humans, the histologic changes differ among individuals, but several changes are commonly found in all DCM cases, including 1 or more of the following: myofiber degeneration (vacuoles or fracturing) and necrosis, interstitial fibrosis in areas of myofiber loss, mononuclear (lymphoplasmacytic and histiocytic) inflammation, infiltration of adipocytes, and myofiber atrophy. Myofiber hypertrophy is also a common compensatory occurrence because the affected hearts have increased weights. Variable myofiber size with thin and wavy fibers has also been reported.¹⁴

Ultrastructural changes are also inconsistent among cases of canine DCM and include myofibrilysis (disorientation and loss of myofibrils), increased intermyofibrillar space, sarcoplasmic reticulum dilation, interstitial edema, thickening of Z-bands, mitochondria of irregular shape and size, and increases in the numbers of mitochondria, glycogen granules, lysosomes, lipofuscin granules, and lipid vacuoles.¹⁴⁻¹⁷ Additional mitochondrial changes include swollen and disrupted cristae, myelin figure formation, and spherical intramitochondrial inclusions. In general, the ultrastructural changes are also nonspecific and have been noted in a variety of chronic cardiac diseases. Some changes indicate an increase in cell breakdown products, ie, lipofuscin and myelin figures. Other changes are most likely compen-

satory and related to deranged energy metabolism (mitochondrial changes, lipid and glycogen accumulation) and hypertrophy (Z-band thickening).¹⁵

The causes of DCM can be divided into 2 major categories: primary (idiopathic) and secondary. Secondary DCM is the result of cardiac dysfunction due to extracardiac factors that affect cardiac function. These factors are usually systemic in origin and include infectious agents, toxins, and inflammatory or neoplastic conditions that result in destruction of the myocardium and acquired or inherited metabolic diseases that affect myofiber function.¹ Primary or idiopathic DCM principally or exclusively affects the myocardium, and the etiology is unknown. The clinical determination of idiopathic DCM is based upon the absence of underlying systemic, coronary, valvular, structural (congenital), hypertensive, or pericardial disease. Suspected causes of idiopathic DCM include inherited (genetic) defects, infectious agents (enteroviral), immunologic disease, and endstage disease of unknown origin (toxic, infectious, inflammatory).^{12,18,19} The latter proposed etiologies are based upon the finding of inflammatory infiltrates in the myocardium. The only definitive virus-induced DCM described in the dog is parvoviral myocarditis. Pups affected with parvoviral myocarditis are between 2 and 16 weeks of age with no apparent familial, breed, or sex predilection.²⁰ Histologically, the changes in the myocardium correspond to a lymphocytic, end-stage myocarditis with myofiber loss and replacement by extensive fibrosis. In early stages of disease, viral inclusions are noted in myofibers, often without concurrent inflammation. Subacute changes include myofiber necrosis and mild inflammatory infiltrates.

Immune-mediated myocarditis leading to endstage DCM has also been suggested as a possible etiological subset of human DCM,^{18,19} but an immune-mediated cause of canine DCM has not been proved. A subset of human DCM appears to have a genetic basis. Inherited DCM can be further subdivided into disorders of substrate and energy metabolism, storage diseases, and disorders of mechanisms yet to be determined that are classified as heritable because of evidence of familial relatedness.^{19,21,22} In other forms of human cardiomyopathy, such as hypertrophic cardiomyopathy, genetic defects have been related to contractility proteins (cardiac beta-myosin heavy chain), cytoskeletal proteins, and proteins involved in either signal transduction or metabolism.¹⁹ Similar defects have not been found to date for DCM in dogs.

Other etiologies that have been considered for DCM in humans and animals revolve around defects in energy metabolism or decreased levels of compounds that protect against oxidative damage. These problems include deficiencies in magnesium, thiamine, selenium, vitamin E, and taurine.²³⁻²⁵ Deficiencies of these compounds have not been thoroughly explored in the dog.²⁶ Catecholamine excess has also been suggested in human DCM because DCM has been identified in patients with actively secreting pheochromocytomas and in animals given catecholamines.²⁷ The exact mechanism of catecholamine-induced cardiomyopathy is unknown.

In dogs, idiopathic DCM is generally suspected to be heritable based upon the various breed predilections, but heterogeneous underlying biochemical/metabolic defects

are suspected. Substantive evidence supporting the possible underlying causes or mechanisms is quite limited. Decreased myocardial L-carnitine concentrations have been noted in related Boxer dogs with DCM and in some Doberman Pinschers with DCM.^{28,29} However, L-carnitine concentrations are also lowered with advanced cardiac disease of any cause, and therefore a lower concentration is not a definitive indicator of underlying cause.²³ Supplementation may serve to enhance remaining cardiac function.

Decreased cardiac myosin levels have been noted in clinically normal Doberman Pinschers and Doberman Pinschers affected with DCM when compared with cardiac myosin levels in other dog breeds.³⁰ Lower myosin levels may predispose the heart to failure due to diminished protective effects against cellular hypoxia. The myoglobin concentration noted in clinically normal Doberman Pinschers was similar to cardiac myoglobin concentrations in dogs with heart failure experimentally induced by rapid ventricular pacing.³⁰ These findings indicate that changes in myoglobin concentration may be important in the progression of heart failure and that it may be an important component of the DCM of Doberman Pinschers. However, the fact that experimentally induced heart failure resulted in a lowering of myoglobin may also suggest that the lowered myoglobin found in the clinically normal Doberman Pinschers may simply be yet another indicator of underlying cardiac dysfunction due to some other etiology. In the same study, mitochondrial ATPase activity was 45% lower in both clinically affected and normal Doberman Pinschers when compared with normal dogs. A similar decrease was also noted in experimental models of heart failure, suggesting again that this finding is most likely a result rather than a cause of heart failure.³⁰

McCutcheon et al³¹ examined myocardial metabolite and enzyme levels for the major metabolic pathways for energy production and calcium transfer in Doberman Pinschers with DCM. They found significant decreases of metabolites and enzymes associated with mitochondrial ATP production. The greatest decreases were found for the mitochondrial respiratory chain enzymes and myoglobin. The authors conceded that their findings do not indicate whether the decreased mitochondrial energy production is a primary or secondary defect. Comparison with experimentally induced models of heart failure will help resolve this question. Lower concentrations of enzymes and myoglobin in DCM of Doberman Pinschers may not be unique to that form of DCM but may be secondary compensatory changes of the failing heart.

The clinical and postmortem findings in the 12 affected POWD described in this report are consistent with the findings reported for other canine DCM. The heart:body weight ratios available for 3 of the pups were all above 1%, which is greater than that reported for normal dogs (0.084%).³² The lack of apparent underlying systemic or structural causes for DCM in these dogs places this form of DCM in the category of primary or idiopathic DCM, and the apparent autosomal recessive pattern of inheritance is consistent with a familial disease.

The histologic features noted in the myocardium are subtle and lack changes associated with chronicity, ie, fibrosis or inflammation found in other forms of canine DCM. The

changes in the myofibers and interstitium were diffusely distributed in the myocardium of affected POWD but were most pronounced in the left ventricular and septal myocardium. The cause of the expanded interstitium was edema, and the myofiber swelling and loss of cross-striations was attributable to cytoplasmic fluid accumulation (hydropic change) and an apparent increase in the numbers of mitochondria as confirmed by use of special stains to detect the deposition of lipid, glycogen, or mucopolysaccharides, which may have expanded the interstitium and sarcoplasm. Hydropic change is a nonspecific indicator of membrane dysfunction caused by a defect in energy production or structural membrane failure. Although myofibers were thinner than normal, the increased heart weights and the nuclear hyperchromasia and size variability are consistent with myofiber hypertrophy. Myofiber splitting/branching and disarray, noted in other forms of cardiomyopathy, were also noted in the myocardium of the affected POWD. There was no evidence of active myofiber necrosis in the 12 pups examined. Thus, myocardial decompensation probably is acute and rapidly fatal, precluding cellular degeneration that would be noted histologically.

There was no evidence for myocardial storage disease as a cause for POWD DCM. Eleven of the POWD pups lacked any evidence of cardiac inflammation; however, a single pup did have rare perivascular and endocardial inflammation. The significance of the inflammation noted in the single pup is unknown. The general lack of inflammation suggests that the underlying cause is most likely not infectious or immune mediated. However, because this is a preliminary description of a new DCM, the possibility of underlying infectious or immune-mediated causes should still be considered. There was no indication that this DCM was the result of primary vascular disease; all coronary vasculature examined histologically and at postmortem was normal. Skeletal muscle obtained from the extremities of affected pups was histologically normal, indicating that a primary DCM is present in the POWD breed. There was also no clinical evidence of noncardiac skeletal muscle involvement. The finding of Anitchkow cells in the interstitium of 1 pup is nonspecific. Anitchkow cells are mesenchymal cells located in the myocardial interstitium and are suspected to be activated myofibroblasts, considered indicative of myocardial damage.³³

The clinical course of the POWD DCM was distinctive. The age of onset noted in the POWD (13 ± 7.3 weeks) is the youngest for any form of canine DCM, and the progression of disease (sudden death to 5 days) is significantly more rapid than has been reported in other dogs with DCM (0.5–24 months). All pups either died suddenly without previous clinical signs or had vague clinical signs related to left ventricular failure for 1–5 days prior to death, and treatment did not affect outcome in these pups. Pups evaluated prior to death had signs referable to left ventricular failure and radiographic, electrocardiographic, and echocardiographic indices consistent with a diagnosis of DCM. Serum biochemical and urine analyses and CBCs were within normal ranges for the pups examined, and urinary metabolic screening for inborn errors of metabolism did not indicate inherited metabolic diseases such as mucopolysaccharidosis and several amino acidurias (data not shown). Unfortunately,

ly, no additional biochemical evaluations for serum constituents more specific for cardiac disease, eg, creatine phosphokinase or plasma carnitine, were performed on these pups.

The true prevalence of DCM in the POWD breed cannot be determined at this time. The POWD are a relatively new breed in the United States, and they comprise a small population. All of the current US dogs came from foundation stock originating in Portugal, hence the gene pool is small. Several breeders in the USA and Portugal have anecdotally reported sudden death in young pups, but the causes of these deaths have not been investigated.

This study was limited by the lack of available fresh tissues and active cases for more complete analysis. Future investigations should be designed to expand information concerning biochemical, molecular, and histologic/ultrastructural changes and to confirm the mode of inheritance. POWD DCM also may serve as a useful canine model for DCM.

This newly described familial DCM of the Portuguese Water Dog breed appears to have an autosomal recessive mode of inheritance. It is distinguished clinically from other forms of canine DCM by the young age at onset (13 ± 7.3 weeks) and the rapid clinical course (days). The preliminary histologic findings suggest that this DCM is not the result of an infectious or immune-mediated etiology, but it is most likely caused by an underlying molecular (biochemical/structural) defect.

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