Canine Cardiomyopathy
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Introduction

Cardiomyopathy is defined as disease of the heart muscle. Dilated cardiomyopathy (DCM) is the most common form in dogs and is characterized primarily by a decrease in the myocardial contractility with secondary chamber dilation. There are various other disease states that can impair myocardial contractility in dogs and cats. Many of these are secondary causes and rarely lead to actual myocardial failure.[1] Causes of secondary cardiomyopathy include parvovirus and *Trypanosoma cruzi* infections (and other less common infectious agents), hypothyroidism, hyperthyroidism, doxorubixin toxicity, sepsis, physical injury (electric shock, trauma, heat stroke), and nutritional deficiencies. While these causes constitute less than 10% of clinical cases of severe myocardial dysfunction and failure, it is important that they are ruled out before making a diagnosis of primary (idiopathic) cardiomyopathy, which is a progressive disease of unknown cause. The presentation, diagnosis and treatment of primary cardiomyopathy will mainly be covered in this summary and breed specific conditions will also be discussed. An emerging form of secondary cardiomyopathy related to dietary factors will then be presented in some detail.

Presentation

The overall prevalence of DCM in dogs is relatively low as compared to degenerative valve disease. Although any type of dog can be affected with DCM, it is generally a condition diagnosed in large and giant breeds. Doberman pinschers, great Danes, boxers, Irish wolfhounds, Saint Bernards, Labradors and Golden Retrievers are some of the most commonly affected breeds. As it is a form of acquired heart disease, the prevalence of DCM increases with age. Dogs with mild-moderate disease often have no associated clinical signs. Although a soft heart murmur due to functional mitral regurgitation and/or an arrhythmia may be present, many dogs with early DCM have no significant findings on physical exam. Some dogs with DCM can progress to congestive heart failure, which typically manifests as tachypnea, dyspnea and coughing. A relatively short history of clinical signs is often reported by owners and the author has found that large breed dogs are typically quite stoic in their signs of heart failure. Therefore, CHF should always be a differential in any adult dog that is a breed at risk for DCM with the appropriate clinical signs, even in the absence of any abnormalities on physical exam. Dogs with advanced DCM can also experience syncope, often due to arrhythmias or poor perfusion. These signs often occur with exertion. While pulmonary edema is the most common manifestation of CHF in dogs, ascites and pleural effusion may also be present. There may be a recent history of weight loss and/or weakness. After the onset of CHF, many dogs with DCM often have a soft left apical systolic heart murmur, a gallop sound, an/or arrhythmia on physical exam. The most common arrhythmias in dogs with DCM include ventricular premature contractions and atrial fibrillation.

Diagnosis

Echocardiography is the primary tool for diagnosing DCM. It is important to rule out secondary causes of myocardial dysfunction prior to making a diagnosis of primary (idiopathic) DCM. This can often be done via a thorough history and ancillary diagnostics (CBC/Chem/T4/UA). The primary echocardiographic abnormality in dogs with DCM is an increase in both the end-systolic and end-diastolic chamber sizes and a subsequent decrease in the estimates of systolic function (i.e. fractional shortening). These changes are subtler in the early stages of the disease and often progressive in severity over time. There can be varying degrees of left atrial enlargement, which serves as a predictive factor for congestive heart failure. If a dog presents in CHF, the left atrium is almost always severely dilated. If there is concern for CHF based on the echocardiogram and/or clinical history, thoracic radiographs are recommended. As arrhythmias are often present in dogs with DCM, electrocardiography is typically recommended, and especially if abnormalities are noted on auscultation. If the dog has a significant arrhythmia on exam or a history of syncope/weakness, a Holter monitor should be performed. Finally, genetic testing for DCM is available for some breeds and is discussed in more detail in subsequent sections.

Treatment

Occult Cardiomyopathy

Unfortunately, minimal literature has been published on the treatment of dogs with DCM prior to the onset of CHF (also termed occult cardiomyopathy). The primary published study investigated the benefit of pimobendan in

delaying the progression of preclinical DCM in Dobermans (the PROTECT study).[2] This study did find that the administration of pimobendan to Dobermans with preclinical DCM prolongs the time to the onset of CHF and extends survival. A similar study showed a benefit to treatment of preclinical Irish wolfhounds with pimobendan.[3] While the results are specific to Dobermans and Irish wolfhounds, many cardiologists often extrapolate the findings to other breeds with a clear diagnosis of DCM. The author typically uses moderate chamber enlargement and moderate systolic dysfunction on echocardiography as indications to consider treatment with pimobendan. With that said, the use of this drug often incurs a significant and life-long financial commitment by owners and, therefore, a clear diagnosis should be made prior to its prescription. A single retrospective study also reported that benazepril may delay the progression of preclinical DCM, although this evidence is less convincing.[4] The author will consider the use of an ACE inhibitor (benazepril or enalapril) prior to the onset of CHF in a dog with significant left atrial dilation and/or progressive left ventricular dilation on subsequent exams. Clinically significant arrhythmias are often detected in the occult phase of the disease and particularly in Doberman Pinschers. Treatment of arrhythmias is expanded upon in subsequent sections.

Congestive Heart Failure

Acute Treatment: For the acute treatment of congestive heart failure, the acronym FONS+P can be used. F refers to furosemide, the primary medication used to clear pulmonary edema. The author typically uses a starting bolus of 2mg/kg (range 1-4mg/kg), ideally given via the IV route (or IM). Repeat 2mg/kg boluses can be administered hourly, however, a total dosage of greater than 8mg/kg in a 4-hour period should be avoided. For life-threatening pulmonary edema, a constant rate infusion of furosemide (0.66-1mg/kg/hr) can also be used following the initial bolus. Supplemental oxygen (O), if needed, should be administered. Although less commonly used, vasodilatory agents can also be considered. Nitroglycerin (N) is a venodilator that can be administered as a paste (1/2" paste per 10kg BW on pinna of ear) to decrease preload. Nitroprusside is a veno- and arteriodilator that is typically reserved for dogs with concurrent systemic hypertension. Anxiety associated with dyspnea should be treated with sedation (S). The author typically administers butorphanol at 0.2mg/kg IV. Finally, if the patient can take oral medications, pimobendan (P) should also be administered in the acute setting (0.25-0.3mg/kg PO). If the dog cannot receive oral medications and/or is too sick to wait for the effect oral administration, dobutamine can be used. In this setting, dobutamine is primarily being used to provide inotropic support and can be particularly useful in hypotensive patients. Dobutamine is often started at 1ug/kg/min and up-titrated every 15-30 minutes to a maximum of approximately 10-15 ug/kg/min.[5] Proper and optimal nursing care is also important to maintain patient comfort and temperature during treatment. Mechanical treatments (abdominocentesis and/or thoracocentesis) should be performed, as needed to relieve effusions

Chronic Treatment: Once a patient has been successfully treated for CHF acutely (if necessary), they should be transitioned to oral medications for home-based care. Furosemide should be administered to effect, but the author typically uses a starting dose of 2mg/kg BID. For recurrent episodes of CHF, dose increases in furosemide are recommended. An ACE inhibitor should be started or continued. The author typically uses enalapril 0.5mg/kg BID, although benazepril is also commonly prescribed. Pimobendan should also be started or continued (0.25-0.3mg/kg BID). Finally, spironolactone (2 mg/kg SID-BID) should also be started after the onset of congestive heart failure. Recheck bloodwork (primarily renal values and electrolytes) is imperative and should be performed 3-14 days after initiating therapy (exact time depends on baseline renal function). If significant alternations in renal values are noted, dose reduction(s) should be considered.

Arrhythmias

Atrial fibrillation and ventricular ectopy are the two most common clinically significant arrhythmias in dogs with DCM. Dogs with atrial fibrillation and underlying DCM often have rapid ventricular response rates. Heart rates on presentation often exceed 200 beats/min, especially in the presence of concurrent CHF. Such rapid rates are associated with decreased survival times because they can further contribute to myocardial failure and worsen CHF.[6] If atrial fibrillation with a rapid ventricular response rate (>150/min) is identified on surface ECG, treatment is recommended. It is important to realize that the goal of therapy is not conversion to normal sinus rhythm, but rather to decrease to the ventricular response rate to a more physiologically appropriate range. Combination therapy with diltiazem and digoxin has been shown to provide superior rate control as compared to monotherapy with either of

these medications.[7] As such, both of these medications are often prescribed simultaneously in dogs with AF and a rapid ventricular response rate. However, care should be taken with digoxin, in particular, as this drug has a relatively high side effect profile and narrow therapeutic range. The author typically prescribes digoxin at 0.003-0.005mg/kg BID. Digoxin also has an added benefit in DCM by providing some positive inotropic effects, although significant GI and neurologic side effects are possible, especially in the presence of renal disease. Serum digoxin levels are commonly monitored with chronic treatment. Diltiazem has both standard and long-acting preparations and the exact formulation should always be specified when this drug is prescribed. The standard formulation is typically prescribed at 0.5-2mg/kg TID while the long acting is 3mg/kg BID. Doses of both digoxin and diltiazem can be up-titrated based on the patient's resting heart rate and clinical response.

Ventricular arrhythmias are also common in dogs with DCM. Dobermans and boxers, in particular, have a high prevalence of ventricular arrhythmias, although any breed can be affected. Clinical signs associated with ventricular arrhythmias can range from weakness, restlessness, agitation, and syncope. Some dogs can also experience sudden death secondary to ventricular tachycardia that terminates in ventricular fibrillation. Any dog that presents with a sustained ventricular tachyarrhythmia should be treated with lidocaine. The author typically uses an initial bolus of 2mg/kg IV given over approximately 1 minute. This bolus can be repeated, however, side effects often occur at total doses greater than 6mg/kg. If conversion to sinus rhythm is achieved, a constant rate infusion of lidocaine can be used. Sotalol is one of the most commonly used oral anti-arrhythmic drug from chronic management of ventricular arrhythmias in dogs. The starting dose of sotalol is usually 1-2 mg/kg BID. However, as sotalol has beta-blocker properties (negative inotrope), this drug should be used cautiously in patients with moderate-severe myocardial dysfunction.[8] Mexiletine is another commonly prescribed ventricular anti-arrhythmic in dogs. Mexiletine is typically used in combination with sotalol if adequate control of the arrhythmia cannot be obtained with sotalol alone. Mexiletine is also used as a single agent if severe myocardial dysfunction is present and the negative inotropic properties of sotalol want to be avoided. The dose of mexiletine is 4-8mg/kg TID, although some dogs can experience significant GI side effects even within this range. Goals of chronic therapy for ventricular arrhythmias should include not only decreasing the frequency of the arrhythmia but also the complexity. This includes suppressing any episodes of ventricular tachycardia as well as decreasing the frequency of couplets, triplets, and R-on-T morphology as all of these factors can increase the risk of sudden loss of life. It is important to notify owners that, even with seemingly good control of a dog's ventricular arrhythmia while on medical therapy, we can likely never fully mitigate the risk of sudden death.

While surface ECGs in the office are a good starting point for assessing the baseline rhythm and response to therapy, a Holter monitor is often considered the gold standard. A Holter monitor is a 24- or 48-hour ambulatory ECG that helps to assess the frequency and complexity of the arrhythmia in the dog's normal environment.

Doberman Cardiomyopathy

Doberman Pinschers are one of the most frequently affected breeds with DCM. DCM in Dobermans is a familial disease with an autosomal dominant inheritance pattern.[9] Two genetic mutations that can lead to the development of DCM in Dobermans have been identified.[10] These two genes are generally referred to as PDK4 (DCM1) and DCM2. While mutations in either gene can independently lead to the development of DCM, dogs that carry both are at the highest risk for the disease. Any interested owner or breeder is encouraged to submit genetic testing through the North Carolina State Veterinary Genetics Lab. The prevalence of DCM in Dobermans has been estimated at be as high as 63%.[11] Many Dobermans can have a long preclinical period during which no clinical signs are present. Female Dobermans tend to be, on average, older (median age=9.5 years) than males (median age=7.5years) at the onset of CHF.[12] Most dogs are between the ages of 5-10 years of age when they die, although the disease can develop at any time. CHF often develops acutely and can be rapidly progressive in Dobermans. With that said, the author has found the breed to be very stoic in their signs of CHF. Ventricular arrhythmias are common in this breed and can often be present prior to the detection of echocardiographic abnormalities. In fact, sudden death caused by ventricular arrhythmias, can occur in at least 25-30% of affected dogs in the occult phase of the disease (i.e. prior to the onset of CHF).[13] As such, Holter monitoring should always be recommended to any Doberman owner if there is a diagnosis of or concern for DCM. Holter monitoring is also a component of DCM screening in this breed. Unfortunately, after the onset of CHF in Dobermans with DCM, the prognosis is poor. The author typically quotes an estimated survival time of 3-6 months with standard medical therapy after the onset of CHF in this breed.[14] Furthermore, in-hospital

treatment of their CHF can also be difficult and often requires treatment with dobutamine. As stated above, there is evidence that justifies the use of pimobendan prior to the onset of CHF as this drug can help delay the onset of clinical signs and improve overall survival.[2]

Arrhythmogenic Right Ventricular Cardiomyopathy

Boxer dogs have a unique form of cardiomyopathy that is often called Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC or Boxer cardiomyopathy). ARVC is a heritable disorder in this breed that is characterized by fibrofatty replacement of the right and, sometimes, left ventricular myocardium.[15] It has an autosomal dominant inheritance pattern.[16] A specific gene has been identified in Boxer dogs that can lead to the development of ARVC. The mutation is related to a gene that encodes for striatin, a desmosomal protein that plays a role in myocardial integrity.[17] A test for the striatin mutation is currently available through the North Carolina State Veterinary Genetics Lab. Dogs with a homozygous mutation are at a higher risk then those that are heterozygous. It is important to also realize that some Boxer dogs can develop ARVC in the absence of the striatin mutation, suggesting that multiple genes are likely involved.

ARVC is a form of acquired heart disease that develops in adult dogs. Three major forms of the disease have been described.[15] Many dogs are asymptomatic with occasional ventricular premature contractions (concealed form of disease). The overt form of the disease is characterized by tachyarrhythmias that manifest as syncope, exercise intolerance, or other related signs. Finally, in the third and least common form of the disease, dogs develop myocardial dysfunction that often results in CHF. A presumptive diagnosis of ARVC is often made on physical exam based on the presence of an arrhythmia in a middle-aged Boxer dog. However, it is important to note that some degree of ventricular premature contractions (VPCs) can be normal in any adult dog. There are also other causes of VPCs in dogs (i.e. systemic illness, splenic/hepatic neoplasia, electrolyte disturbances) and, therefore, additional diagnostic testing is often performed to rule out comorbidities. If an alternative explanation for the VPCs cannot be found, the clinician should have a high suspicion for ARVC. Baseline ECG testing is recommended to document the VPCs. A Holter monitor is often strongly recommended to evaluate the frequency and complexity of the arrhythmia over a longer period of time. The identification of >300VPCs in 24 hours in an adult Boxer is strongly suggestive of ARVC, especially with significant complexity (couplets, triplets, ventricular tachycardia).[15] Some dogs, especially those with myocardial dysfunction, can present with a heart murmur and/or signs of congestive heart failure. An echocardiogram is recommended in all patients with a suspicion for ARVC. With that said, many dogs with ARVC have normal echocardiograms, as the disease is often at a microscopic level, especially in the early stages. However, dogs with overt myocardial dysfunction can be identified, which impacts management. If there are signs of CHF, thoracic radiographs are recommended. Syncope happens in approximately 1/3 of affected dogs and, while uncommon, sudden death can occur.[18] Treatment of dogs with ARVC is generally targeted towards the use of ventricular antiarrhythmic medications. If a dog has systolic dysfunction and, more importantly, CHF, standard therapy according to the guidelines discussed above is also recommended. The primary goal of treatment of any ventricular arrhythmia is to decrease the risk of the development of signs such as syncope and sudden cardiac death. It is also important to realize that antiarrhythmic medications can also occasionally have paradoxical proarrhythmic effects and, therefore, treatment decisions should always be best on appropriate ECG and Holter criteria. Sotalol is the primary anti-arrhythmic medication used in Boxers, although mexiletine is often added if dual therapy is needed. The reader can refer to the arrhythmias section above for more information regarding these medications. The prognosis for dogs with ARVC can be relatively good, especially in the absence of systolic dysfunction. Many dogs live for years symptom free, even after being started on anti-arrhythmic medications.

Other Cardiomyopathies

Additional forms of breed-specific cardiomyopathies have been reported in the veterinary literature. It is important for the clinician to be aware of the unique features of these conditions as there is often significant variability in the clinical disease course and treatment protocols. There is also published literature, which should be referenced to better inform owners. Great Danes and Irish Wolfhounds are well reported to be affected by DCM.[19,20] American Cocker Spaniels have a unique form of DCM that can be responsive to supplementation with taurine and L-carnitine.[21] The prognosis associated with this condition can often be quite good, as the myocardial changes may be reversible and many patients can be weaned from their cardiac medications, even after the onset of CHF. Golden retrievers have also been reported to be susceptible to the development of taurine-deficiency associated DCM.[22]

There is a case series on Dalmatians, which highlights a possible dietary link and the development of DCM in this breed.[23] Eight out of the nine dogs in this report were fed a low-protein diet formulated for the prevention of urate uroliths. A juvenile and rapidly progressive for of DCM has been reported in young Portuguese water dogs.[24] Finally, ARVC has been described in English bulldogs and is similar to the form of disease that is seen in Boxers, although the risk of congestive heart failure is higher.[25]

Nutritional (Secondary) Cardiomyopathy

In July 2018, the FDA announced that it had begun investigating possible links between dogs fed certain foods and the development of DCM.[26] This investigation arose out of an increasing number of atypical breeds developing cardiomyopathy that had been fed boutique, exotic-ingredient, and grain free (BEG) diets. According to data release by the FDA, the majority of the diets are dry dog food and a large proportion contain peas and/or lentils, although foods high in potato, sweet potato, and chickpeas were also implicated.[27] Approximately 90% of the implicated diets have been labeled "grain-free" while 10% contained grains, some of which are vegan or vegetarian. While there has been growing concern that nutritional cardiomyopathy may be related to taurine deficiency, this is likely not the whole story. In a recent publication, two groups of affected dogs were identified: dogs with DCM specifically related to taurine deficiency and dogs with DCM associated with separate, but yet unknown, dietary factors.[28] There are various possibilities as to why BEG diets may contribute to the development of DCM, however, no definitive cause and effect relationship has been established and the link is likely multifactorial. Although published data is currently limited, there are emerging recommendations for this condition. If DCM is diagnosed in a dog that is eating a BEG, vegan, vegetarian, or home-cooked diet, it is recommended that taurine concentrations are measured in both plasma and whole blood (whole blood recommended if only one sample submitted). Other dogs in the household should be screened for DCM, if they are eating the same diet. The diet should be changed for any affected dog. The author typically recommends a food made by a well-established manufacturer and should contain standard ingredients (e.g. chicken, beef, rice, corn, wheat, etc). Taurine supplementation is also often recommended, even if concentrations are measured as normal. The general dose of taurine is as follows: 250mg BID for dogs <10kg, 500mg BID for dogs 10-25kg, and 1,000mg BID for dogs >25kg. Recheck echocardiography is recommended 3-6 months following diet change and supplementation, however, it can take some dogs up to 1 year to show improvement.

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