CLINICAL EVALUATION AND MANAGEMENT OF DILATED CARDIOMYOPATHY IN DOGS

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DECLARATION

I hereby declare that the thesis entitled "**CLINICAL EVALUATION AND MANAGEMENT OF DILATED CARDIOMYOPATHY IN DOGS"** is a bonafide record of research work done by me during the course of research and that the thesis has not previously formed the basis for the award to me of any degree, diploma, associate ship, fellowship or other similar title, of any other University or Society.

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Introduction

1. INTRODUCTION

The dog is the most popular pet - enthusiastic, attentive, loyal, loving, friendly, playful and amusing. A dog will affect every household member and even a small illness can create worry among the family members. It is very unfortunate that a companion and pet like dog has a shorter lifespan than its owner. As the age advances chances of getting geriatric diseases also is more. In middle aged to older dogs cardiac diseases are more common than one might think. Dogs and cats can be affected by many different types of cardiac disease including arrhythmias, diseases of the heart muscle (cardiomyopathy), congenital defects, and age induced degenerative cardiac (valve) disease. Early diagnosis and management of cardiac diseases can improve not only the quality of life but also prolong the duration of life.

Cardiomyopathies are diseases of heart muscle. The World Health Organization (WHO) in 1980 defined cardiomyopathies as "heart muscle diseases of unknown cause," to distinguish cardiomyopathy from cardiac dysfunction due to known entities such as hypertension, ischemic heart disease, or valvular disease. In the 1995 classification, the cardiomyopathies were defined as "diseases of the myocardium associated with cardiac dysfunction. ” They were classified according to anatomy and physiology into the following types, *viz.* dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and unclassified cardiomyopathies.

Dilated cardiomyopathy (DCM) is characterized by dilation and impaired contraction of one or both ventricles. Affected patients have impaired systolic function and may or may not develop overt heart failure (HF). The presenting manifestations can include atrial and/or ventricular arrhythmias, and sudden death can occur at any stage of the disease. A diagnosis of DCM requires evidence of dilatation and impaired contraction of the left ventricle or both ventricles. Dilated cardiomyopathy, characterised by systolic dysfunction (decreased muscle strength/decreased contractility), dilation of ventricular cavity (eccentric hypertrophy), mild thinning of the ventricular walls and increase of total ventricular mass.

The clinical presentation may be subtle and include the gradual development of exercise intolerance and weight loss. However, more commonly, these early indications are overlooked and the diagnosis of DCM is not established until congestive heart failure (CHF) develops and the patient is presented for coughing, dyspnea, tachypnea, wasting, arrhythmia and sometimes ascites. For the symptomatic patient, it is important for the clinician to rule out other possible causes for the clinical signs, such as pericardial effusion, pneumonia, neoplastic disease, undiscovered congenital heart disease. For the asymptomatic patient, the challenge lies in differentiating normal variation and cardiac or non-cardiac pathologies from DCM.

Treatment of DCM includes angiotensin conversion enzyme inhibitors, angiotensin receptor blockers, diuretics, positive inotropic agents and antiarrhythmic agents including digoxin. Judicious inhibition of renin – angiotensin system is the widely accepted way of treatment of DCM in dogs. Recently other pathways of angiotensin II

production were identified. Blocking angiotensin at the receptor level by using angiotensin II receptor antagonist may be a better way of treatment. Introduction of angiotensin II receptor antagonist in the treatment of human cardiac diseases gave a promising result in the outcome of the disease. Valsartan is an angiotensin receptor blocker (ARB) which blocked angiotensin II by selectively blocking the binding of angiotensin II to the angiotensin – 1 (AT 1) receptor. So addition of valsartan can improve the quality and survival rate of affected dogs. Hence the study has been undertaken with the following objectives

1. To study the occurrence of DCM in dogs using non invasive techniques *viz.* radiography, electrocardiography and echocardiography.

2. To evaluate the efficacy of angiotensin II receptor antagonist for the clinical management of DCM.

Review of literature

2. REVIEW OF LITERATURE

Dilated cardiomyopathy (DCM) could be defined as a cardiovascular disease in which the degree of myocardial dysfunction was not explained by the abnormal loading conditions or the extent of ischaemic damage. According to 1995 World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) dilated cardiomyopathy might be idiopathic, familial/ genetic, viral and/ or immune or alcohol associated (Richardson *et al.*, 1996).

2.1. ETIOLOGY

2.1.1. Idiopathic

Valentine *et al.* (1989) stated that in addition to the profound skeletal muscle lesions, a distinctive cardiomyopathy had been recognized in Duchenne muscular dystrophy and Becker muscle dystrophy patients. Skeletal muscle lesions were mild in Becker muscle dystrophy when compared with Duchenne muscular dystrophy and severe cardiomyopathy developed in later stages of diseases.

Jacobs (1996) stated that primary and idiopathic were the terms used to denote the disease originated from myocardium with unknown etiology and pathogenesis.

Olson *et al.* (1998) opined that idiopathic DCM might be caused by relatively subtle molecular defects in force transmitting proteins, like actin leading to myocytes dysfunction and heart failure and missence mutations in dystrophin had been identified in X- linked DCM.

Petric and Tomsic (2008) reported that the most common form of DCM in dog was idiopathic, as many of the processes that led to myocardial injury in dogs remain to be determined.

2.1.2. Genetic / Hereditary

Valentine *et al.* (1989) studied the genesis of cardiac lesions in dogs from first day to six years of age and characteristic feature of late onset cardiac lesions were similar to that occurring in Duchenne dystrophy, a consistent feature of canine X – linked muscular dystrophy.

OrtizLopez *et al*. (1997) observed that a novel missence mutation in exon 9 of dystrophin causing an abnormality at H_1 led to cardio specific phenotype of X – linked cardiomyopathy (XLCM) resulted in loss of membrane integrity and eventual loss of function. This might be due to continual stress placed on beating pump and inability of dystrophin to interact with actin or other proteins as mutated dystrophin could not bind to calmodulin.

An autosomal dominant mode of inheritance of DCM was reported in Irish Wolfhounds and recommended regular examination of heart of all breeding dogs. (Vollmar, 2000)

Garcia *et al.* (2001) reported that mutations in the mitochondrial transport protein (e.g. Carnitine acylcarnitine translocase), changes in the calcium transport and metabolism, and apoptic processes triggered dilated cardiomyopathy in human beings.

Meurs *et al.* (2001) described five subtypes of DCM in human beings. Two of these had an autosomal mode of inheritance, including classic form of DCM (ventricular dilation and systolic dysfunction) and

another one characterised by conduction disturbances (second and third degree atrioventricular and bundle branch block). Two others had autosomal recessive mode of transmission, one characterized by skeletal muscle involvement with rapid progression and poor prognosis. The fifth had autosomal mode of inheritance. Authors also suggested that DCM in Great Dane might be an X- linked recessive trait caused by mutations in the dystrophin gene.

Dilated cardiomyopathy was familial in Dobermann Pinschers, Boxers, Cocker Spaniel, Newfound Land and Portuguese Water Dogs. An autosomal dominant inheritance in a family of Dobermann Pinschers and English cocker spaniels with reduced penetrance was reported by Petric *et al.* (2002).

McEwan *et al.* (2003) stated that canine DCM was suspected of having a genetic basis. An autosomal dominant transmission was reported in Irish wolfhound, Newfoundland and Dobermann Pinscher.

Belanger *et al.* (2005) reported autosomal recessive transmission in a family of Portuguese Water Dogs with juvenile taurine deficient DCM.

2.1.3. Nutritional

Gavaghan and Kittleson (1997) reported plasma taurine concentration of less than 2 nmol/mL in an American Cocker Spaniel presented with dyspnoea associated with pulmonary oedema and a left ventricular shortening fraction of 9%.

Tidholm *et al.* (2001) reviewed the nutritional abnormalities causing myocardial hypokinesis in dogs which included L - carnitine and Taurine deficiencies.

Belanger *et al.* (2005) reported a reversible taurine – deficient dilated cardiomyopathy in five related Golden Retrievers. Baseline plasma taurine concentrations in the five affected dogs were ranged from 2 – 20 nmol/mL against a normal concentration of 69 – 166 nmol/mL. Significant improvements were recorded within 3 – 6 months of starting taurine supplementation.

Gompf (2005) opined that there were many possible causes of taurine deficiency in canines. One potential cause was insufficient synthesis of taurine due to lack of amino acid precursors in the diet or animal's inability to synthesis taurine. Other causes included impaired absorption, increased metabolic need, altered taurine conjugated bile acid circulation and increased urinary excretion of taurine or its precursors.

2.1.4. Viral and / or Immune Mediated

Kawai (1999) opined that the persistence of viral RNA in the myocardium beyond 90 days after inoculation, confirmed by the method of polymerase chain reaction, T-cell–mediated immune responses and apoptotic cell death might be the factors associated with viral myocarditis mediated dilated cardiomyopathy.

Nho *et al*. (1997) stated that canine parvo virus was detected in myocardial cells in 9 out of 25 dogs examined, with myocarditis despite the paucity of reports of myocardial infection.

Schowengerdt *et al*. (1997) identified parvo virus by polymerase chain reaction (PCR) in three patients with myocarditis. Among these, one presented with cardiac arrest leading to death, one developed DCM, and the other one gradually improved.

Badorff *et al.* (1999) reported that entero viral infection particularly coxsackie B virus caused dilated cardiomyopathy in humans. Authors also reported that entero viral infection of cardiac myocytes led to disruption of cytoskeleton through enteroviral protease 2A mediated cleavage of dystrophin. Loss of membrane integrity and defective force transmission initiated a cascade of events which eventually led to dilated cardiomyopathy.

Kearney *et al*. (2001) reviewed that myocarditis was a common cause of dilated cardiomyopathy and viruses causing myocarditis included, coxsackie (A, B) , adenovirus, influenza (A, B) , herpes simplex, cytomegalovirus, varicella-zoster virus , epstein-Barr virus, mumps, rubella, rubeola, vaccinia , rabies , coronavirus, hepatitis B and human immuno deficiency virus (HIV) in human beings. The direct effects of virus mediated toxicity included focal necrosis of myocytes in the absence of an inflammatory cell infiltrate within three days of infection. At the same time host immune system begin to clear the virus from the myocardium, with or without the aid of cytokines. If the initial immune response was ineffective and the virus was not eliminated, chronic myocarditis could evolve, with the potential development of dilated cardiomyopathy.

Nishimura *et al.* (2001) reported that disruption of gene encoding the negative immunoregulatory receptor PD – 1 in mice caused dilated cardiomyopathy with severely impaired contraction and sudden death by congestive heart failure. Affected heart showed diffuse deposition of immunoglobulin G on the surface of cardiomyocytes.

Sundstrom and Ansari (2001) reviewed that HIV induced adhesion of leukocytes to vascular endothelium and transmigration of HIV infected

leukocytes into cardiac parenchymal tissues were initial step in the pathogenesis of immune mediated dilated cardiomyopathy in AIDS.

Tidholm *et al.* (2001) reviewed the immunological process involved in the pathogenesis of DCM. Autoantibodies had been detected both in humans and experimental animals against the cardiac receptor, the mitochondria, the mitochondrial ADP/ATP translocator and α and β-myosin heavy chains.

Vollmar *et al.* (2003) stated that viral infection could be a potential etiology for DCM, since viral cytotoxicity, autoimmune response and viral persistence might be resulted in structural and functional derangement of cardiac tissue.

Goel *et al*. (2005) reported a case of dilated cardiomyopathy in humans associated with celiac disease characterised by chronic malabsorption in individuals ingesting grain containing gluten. Increased absorption of antigens and infectious agents through damaged intestine resulted in myocardial damage by immune mediated mechanisms.

Guerriguttenberg *et al*. (2008) reported that chronic chagasic cardiomyopathy was the most serious manifestation of Chagas' disease. Involvement of the parasite also in the chronic phase had been documented. *Trypanosoma cruzi* DNA was consistently found in myocardial biopsies of patients with chagasic cardiomyopathy, but not in seropositive patients without cardiac involvement. Antigen stimulation persisted throughout the chronic stage, perpetuating myocardial inflammation even though parasites were not detectable in myocardial biopsies.

2.1.5. Metabolic

Klein and Ojamaa (2001) reviewed that hypothyroidism caused low cardiac output by bradycardia, reduced ventricular filling and a decrease in cardiac contractility. Phospholamban and Ca^{2+}-ATPase were regulated by triiodothyronine by changes in the gene transcription and these were critical in active transport of calcium into lumen of sarcoplasmic reticulam which determined systolic contractility function and diastolic relaxation.

Phillips and Harkin (2003) observed dilated cardiomyopathy in two Great Danes that were diagnosed concurrently with hypothyroidism and following treatment with appropriate doses of levothyroxin showed significant improvement in myocardial contractility suggesting the role of hypothyroidism in dilated cardiomyopathy.

Both hypertension and cardiomyopathy were induced in rats experimentally implanted with transplantable pheochromocytomas. (Vogel and Fritz, 2003)

2.1.6. Toxin Induced

Toyoda *et al*. (1998) opined that doxorubicin caused a dose-dependent cardiomyopathy and proposed mechanisms for doxorubicin cardiac toxicity included release of superoxides leading to conversion of membrane unsaturated fatty acids to lipid peroxides, which inhibited biosynthesis of coenzyme Q_{10} (ubiquinone) and sodium-potassium adenosinetriphosphatase. In addition, doxorubicin caused release of compounds such as histamine, arachidonic acid metabolites, platelet activating factor, and calcium, which could cause myocytes injury.

Garcia *et al*. (2001) reported that zidovudine caused mitochondrial DNA depletion which inhibited DNA polymerase of HIV virus and DNA polymerase gamma which was found in cardiomyopathy patients.

2.2. SIGNALMENT

Lombard (1984) reported that in the entire group of 12 Dobermann Pinschers affected with dilated cardiomyopathy eleven were males and one was a female. Their age ranged from 3 – 12 years with a mean of 6 years. The average weight was 36 kg with a range of 25 – 59 kg.

Calvert and Wall (2001a) stated that cardiomyopathy was a common disorder of Dobermann Pinschers, characterised by a long preclinical or occult phase of progressive myocardial failure with disturbances of cardiac rhythm and increased risk of death.

Tidholm *et al.* (2001) reported that age of onset of clinical signs in DCM varied considerably, although most dogs were initially presented at an age of five to seven years.

Petric *et al*. (2002) observed that out of 52 dogs of different breeds with DCM, 21 were Dobermann Pinschers and 31 belonged to other breeds which included German shepherd (13%), German boxer (8%), Great Dane (6%), Rottweiler (6%) and others (67%).

Prevalence of DCM increased with age and males were usually over represented in the population of dogs with congestive heart failure (CHF). Prevalence was very high in certain breeds (Deerhound 6%, Dobermann 5.8%, Irish wolfhound 5.6%, Great Dane 3.9%, Boxer 3.4% and Newfoundland 1.3%) (McEwan *et al.*, 2003).

Jordan *et al.* (2007) reported that age of onset of DCM in 10 Cocker Spaniel dogs (eight males and two neutered females) ranged from 3 to 14 years with a mean of 7.7 years.

2.3. PATHOGENESIS

Badorff *et al*. (1999) found that purified coxasackie virus protease 2A cleaved dystrophin *in vitro* and dystrophin was also cleaved during coxasakie virus infection of cultured myocytes and in infected mouse heart, which led to impaired dystrophin function. A molecular mechanism had been suggested through which entero virus infection contributed to pathogenesis of acquired forms of DCM.

Borgarelli *et al.* (1999) stated that *B* adrenergic downregulation occurred early in course of DCM in dogs and the mean value of lymphocytic B_1 – adrenergic receptor number in asymptomatic DCM group was double compared to that of symptomatic DCM group but was not statistically significant. The authors also reviewed that the autonomic disturbance had been divided into three phases. In the early stage, decreased cardiac output activated the sympatho- adrenal and renin angiotensin system reflexively. The middle stage was characterized by a compensatory hypervolaemia and cardiac enlargement which stimulated baroceptor of afferent vessels causing a normalization of sympathetic nerve activity. Finally, the restraining influence of the cardiac and vessel baroceptors of the sympathetic nervous system and renin angiotensin system was impaired, which resulted in generalized neurohormonal activation (end stage).

Re *et al.* (1999) compared the levels of myocardial and lymphocyte adrenergic receptor concentrations in adult Great Danes affected by DCM

to those of normal healthy animals. Total *B*, *B1* and *a* adrenergic receptors were significantly down regulated both in lymphocyte and myocardial cell membranes of affected dogs and suggested sympathetic activation.

Hein *et al.* (2000) suggested that, a morphological basis of reduced contractile function existed in chronic heart failure due to DCM. The cytoskeletal and membrane associated proteins were disorganised in amount and contractile myofilaments and the proteins of the sarcomeric skeleton including titin, *a* – actinin, and myomesin were significantly decreased. The authors also reviewed the role of cytoskeleton in congestive heart failure and stated that microtubular densification might be a cause for cardiac hypertrophy and congestive heart failure as it caused increased load on myocytes and impeded sarcomere motion. In DCM a morphologic basis of reduced contractile function existed and the cytoskeletal and membrane associated proteins were disorganised.

McEwan (2000b) stated that angiotensin II had a number of effects on the central nervous system, including increased thirst stimulation, increased sympathetic drive and release of vasopressin from posterior pituitary leading to fluid retention and vasoconstriction. The author also stated that ventricular wall stress due to vasoconstriction, increased filling pressures and thin wall versus dilated ventricular lumen compromised coronary perfusion, myocardial hypoxia, acidosis, and thus predisposed to arrhythmia.

Barlucchi *et al.* (2001) stated that level of angiotensin II increased significantly with cardiac decompensation. Cardiac myocytes could synthesise Angiotensin II and activation of p53 function with ventricular pacing up regulated the myocyte renin - angiotensin system and the

generation and secretion of Angiotensin II. Angiotensin II promoted myocyte growth and death, which contributed to the development of heart failure.

Sundstrom and Ansari (2001) reviewed that degradation of the extracellular matrix metalloproteinase during reparative remodeling resulted in 'myocyte slippage' and thinning or dilation of the ventricular myocardium.

Vasoconstriction and sodium and water retention resulted from hormonal changes in response to heart failure were beneficial initially, but eventually became detrimental and contributed to progression and clinical signs of heart failure. Serum thyroid hormone levels were decreased in many nonthyroidal illnesses including congestive heart failure. Because thyroid hormones were necessary for normal depolarization of heart and myocardial function, altered thyroid hormone concentrations might be detrimental in dogs with heart failure Chastain and Panciera (2002).

Carey and Syragy (2003) reviewed that cardiac myocyte possessed a local renin – angiotensin system in human beings. Atrial natriuretic peptide and isoproterinol up- regulated renin and angiotensin gene expression. In addition, mechanical stretch of ventricular myocytes increased angiotensin II release which was responsible for increased local angiotensin II production in DCM.

Phillips and Harkin (2003) reported that hypothyroidsm led to dilated cardiomyopathy in Great Danes that was partially or fully reversible following thyroid hormone replacement therapy. Hypothyroidism has to be considered in all Great Danes presenting with systolic failure.

Menaut *et al.* (2005) stated that in dogs with degenerative valve diseases and DCM had increased sympathetic tone which led to increased ventriclular response rate as conduction through AV node was in part dependent on sympathetic tone.

Nakata *et al.* (2005) reviewed that impairment of norepinephrine transporter function (uptake I mechanism) at presynaptic neurons reduced myocardial uptake of norepinephrine. Augmentation of sympathetic drive in failing heart accelerated leakage and spill over of norepinephrine at nerve endings, contributing to an increase in cardiac post synaptic drive in congestive heart failure.

Jordan *et al.* (2007) suggested that the reason for pulsus alterans in dilated cardiomyopathy might be due to alternation of both filling and loading due to alternation in the contractile state of sick myocardium related to altered reactions of the sarcoplasmic reticulum which was mediated through ryanodine receptors.

Oyama *et al.* (2008) identified a molecular mechanism involving RyR_2 (Ryanodine) receptor dysfunction due to depressed Calstabin 2 expression and intracellular Ca^{2+} leak in arrhythmogenic right ventricular cardiomyopathy in Boxer dog.

2.4. CLINICAL SIGNS

According to Jacobs (1996) clinical manifestations of cardiomyopathy were commonly associated with congestive heart failure (CHF) and low cardiac output heart failure, characterized by depression, weakness and cool pale cyanotic extremity.

Abbott (1998) reviewed that compression of mainstem bronchi by an enlarged atrium was an important cause of cough, particularly in geriatric small breed dogs with mitral valve disease and weight loss often occurs in patients with CHF and could be profound in dogs with DCM, which was overlooked by owners due to ascities.

According to McEwan (2000a) in large and giant breeds such as Newfound Lands, St. Bernard, Deerhounds, Old English Sheep Dogs, Golden Retrievers, Labrador Retrievers and German Shepherd, the disease tended to have a slower progressive cause, eventually causing congestive heart failure, which was often biventricular.

Vollmar (2000) graded CHF due to DCM in Irish Wolfhound as mild to moderate in dogs with exercise intolerance, increased respiratory rates and efforts, along with radiographic signs of cardiomegaly and as moderate to severe in dogs with signs such as cachexia, anorexia, dyspnoea at rest or profound exercise intolerance and radiographic evidence of cardiomegaly.

Coughing (8 dogs), exercise intolerance (6 dogs) and weight loss were the common clinical abnormalities encountered in 17 Great Dane dogs with DCM. (Meurs *et al.*, 2001)

Pertric *et al.* (2002) studied DCM in Dobermann Pinschers and observed cough (79%), exercise intolerance (43%), dyspnoea (36%), anorexia (71%) vomiting (14%), abdominal distension (7%), syncope (14%), and fast heart rate (14%) as clinical signs.

According to McEwan *et al.* (2003) clinical signs in dogs with DCM and CHF included breathlessness or dyspnoea, cough, depression, exercise

intolerance, inappetance, syncope, weight loss, abdominal distension and polydipsia.

Vollmar *et al.* (2003) reported echocardiographic evidence of DCM in healthy and active Dobermann Pinscher puppies and observed acute clinical signs including pulmonary oedema and even death, when cardiac decompensation occurred.

DeFrancesco (2004) reviewed that cough associated with cardiogenic pulmonary oedema tended to be softer and less intense than cough in dogs with primary respiratory disease which was usually nonproductive, honking or dry.

Guglielmini and Civitella (2004) reported signs of depression and weakness in a nine year old German Shorthaired Pointer the day after dystocia which was diagnosed as Dilated cardiomyopathy.

Billen and Israel (2005) reported transient artioventricular block as the etiology for syncopal event in a six year old male German Shepherd with artial fibrillation and DCM. Lethargy of one year and intermittent dyspnoea of six months duration were also observed.

Tidholm (2006) observed polydipsia in 15% of dogs with DCM

2.5. CLINICAL EXAMINATION

Abbott (1998) stated that body temperature and quality of pulse were usually normal in animals with CHF and pathologic arrhythmia resulted in variation in pulse strengths and rates. The author also added that in many patients with DCM, a murmur of mitral valve insufficiency was present.

Vollmar (2000) observed that typical findings on auscultation in Irish Wolfhounds with DCM were cardiac arrhythmias, a gallop sound or a left apical systolic murmer and in some dogs end respiratory crackles.

Most common cardiac cause of dyspnoea was left heart failure causing pulmonary oedema (Goodwin, 2001).

Meurs *et al.* (2001) stated that the most common clinical findings in Great Danes at the time of diagnosis of dilated cardiomyopathy were systolic left apical murmer, ascites and gallop rhythm.

Guglielmini and Civitella (2004) diagnosed a case of dilated cardiomyopathy which revealed tachypnoea (60 breaths/minutes) capillary refill time of 2 seconds, and weak arterial pulse by physical examination.

Tidholm (2006) reported that the major findings on clinical examination were dyspnoea at rest in all dogs, a systolic murmer (grades II – III/VI) in 56% dogs and ascites in 6% dogs. Pulmonary oedema was present in 60 dogs, and pleural effusion in two dogs with dilated cardiomyopathy.

Jordan *et al*. (2007) reported that phonocardiogram of Cocker spaniel dogs affected with dilated cardiomyopathy showed alterans of second heart sound, which was absent in every other beat. There was also an alteration of first heart sound, characterised by a more pronounced with a strong contraction and a less pronounced sound with a weak beat.

Martin *et al*. (2008) observed that the most common clinical findings in dogs with dilated cardiomyopathy were weak pulse (39%), murmer (33%), mucosal pallor (16%), ascites (15%) and a gallop sound (10%).

2.6. DIAGNOSIS

2.6.1. Electrocardiography

Thomas (1987) stated that rapid development of atrial fibrillation (AF) from normal sinus rhythm within a period of 4 months was more suggestive of congestive cardiomyopathy than chronic valvular disease and reviewed that signs of right ventricular enlargement were more difficult to assess in lean dogs.

Calvert *et al.* (1997) reported that Doberman Pinschers with dilated cardiomyopathy having episodes of sustained (more than 30 sec.) ventricular tachycardia were at increased risk of sudden death. The author also observed that in overtly healthy Dobermann Pinschers, the number of ventricular premature complexes (VPC) considered to be abnormal could not be stated unequivocally, but most of the dogs that were less than 4 years old had less than 1 VPC on a 24 hour Holter monitoring. The number of dogs with detectable VPC increased with age. But most dogs had less than 10 VPC in 24 hours. More than 100 VPC in 24 hours was consistant with cardiomyopathy.

Strickland (1998) stated that atrial flutter was commonly encountered in dogs with chronic heart failure secondary to degenerative valvular disease or idiopathic DCM.

Brownlie and Cobb (1999) observed that DCM was often associated with tachydysrrhythmias, particularly atrial fibrillation (AF) in Irish Wolfhound. Presence of AF in any age group must therefore be regarded as a possible indication of occult DCM.

Calvert *et al.* (2000) studied results of ambulatory electrocardiography in overtly healthy Dobermann Pinschers with echocardiographic abnormalities and stated that number of VPC per 24 hours during the initial holter recording was positively correlated with the number of couplets and triplets of VPC and number of ventricular escape beats and negatively correlated with left ventricular fractional shortening.

McEwan (2000a) reviewed that ventricular ectopies in Boxers had a characteristic appearance, being upright in leads II and AVF which was consistant with right ventricular origin. Tall R waves and left bundle branch block were seen in DCM of Cocker Spaniels.

Vollmar (2000) opined that the significance of ventricular premature depolarization in Irish wolfhound was different to that in Doberman pinscher and Boxer when associated with dilated cardiomyopathy. Atrial fibrillation and VPC especially were observed more frequently in severly affected Irish wolfhound dogs. Left anterior fascicular block with left axis deviation in frontal plane also were seen.

Calvert and Wall (2001a) studied ambulatory electrocardiography in overtly healthy Dobermans with equivocal echocardiographic evidence of dilated cardiomyopathy and observed that ventricular tachycardia and fibrillation occurred in 25-30 % of dogs. Abnormalities such as VPC and ventricular tachycardia could be identified in dogs with occult DCM, regardless of whether they had echocardiographic abnormalities or not.

Calvert and Wall (2001b) stated that reduced heart rate variability (HRV) was detected only in Dobermann Pinschers with most severe myocardial failure. Thus HRV in less severely affected dogs was not

reduced, or the normal sinus arrhythmia rendered HRV relatively insensitive.

Goodwin (2001) reported that atrial premature complexes (APC) were usually seen in association with atrial enlargement, degenerative valvular diseases, congenital heart diseases, cardiomyopathy, hypoxia, atrial neoplasia and chronic obstructive pulmonary disease.

Meurs *et al.* (2001) observed electrocardiographic abnormalities *viz.* atrial fibrillation (12 dogs) and VPC (3 dogs) in Great Dane dogs with DCM. The high prevalence of AF (71%) was suggested to be due to the larger size of atria in the Great Dane.

Martin (2002) reviewed that ECG should be used as a diagnostic aid that might support a clinical suspicion of heart enlargement and not as a means of diagnosing heart enlargement. The author also reviewed that tall R waves were suggestive of left ventricular enlargement and R wave in lead I which was greater than lead Π or AVF might be associated with hypertrophy and increase in the amplitude of the R waves in lead I, Π, ΙΙΙ might be associated with dilatation and other ECG features which were be suggestive of left ventricular enlargement included prolonged QR duration, ST segment sagging or coving or a shift in the mean electrical axis to the left.

Spier and Meurs (2004) screened Boxers with dilated cardiomyopathy using signal averaged electrocardiography (SAECG) and results suggested that SAECG was a useful noninvasive diagnostic test to evaluate dogs affected with cardiomyopathy and to identify individuals at risk for cardiac related death.

Guglielmini and Civitella (2004) reported sustained ventricular tachycardia in nine year old German shephered dog with dilated cardiomyopathy. After Lidocaine therapy, sinus tachycardia with left bundle branch block was detected, which was due to delayed intraventricular conduction resulted from left atrial enlargement.

Billen and Israel (2005) reported that AF, VPC, and ventricular tachycardia were common arrhythmias in dogs with DCM and syncope.

Menaut *et al.* (2005) observed that AF was usually associated with dilated cardiomyopathy and degenerative valve diseases.

In a retrospective study of 369 cases of dilated cardiomyopathy by Martin *et al*. (2008) reviewed that mean heart rate based on ECG recording was 175 beats/minute with an increasing rate with higher class of heart failure. Atrial fibrillation was recorded in 45% of dogs and tended to be more common in large and giant breeds of dogs. Ventricular premature complexes (VPC) were seen in 31% of dogs, most commonly in Boxers and Doberman. The great majority of dogs (89%) were presented with an arrhythmia.

Petric and Tomsic (2008) reviewed that low amplitude impulses following QRS segment called ventricular late potentials resulted from areas of myocardial fibrosis which were detected in signal averaged electrocardiography.

Scollan *et al*. (2008) reported atrial dissociation in a four year old, 31 kg male Boxer dog which was treated for arrhythmogenic right ventricular cardiomyopathy. Atrial dissociation was characterized by the presence of an ectopic atrial rhythm that did not result in ventricular depolarization and interfer with the basic rhythm.

2.6.2. Radiography

Wyburn and Lawson (1967) reported that left ventricle was the cardiac chamber most commonly involved in hypertrophy or dilatation. On the lateral plane, the caudal border of the heart became bulged so that it overlaid the diaphragmatic shadow to an increased extent.

Thomas (1987) studied radiographic features of congestive cardiomyopathy in eight Cocker Spaniels and the appearance of cardiac silhouettes on thoracic radiographs indicated a marked heart enlargement, typically of a biventricular nature with a left atrial enlargement and tracheal elevation in all cases.

Goodwin and Lombard (1990) reported that thoracic radiographs provided essential information about overall cardiac size, shape, enlargement of individual cardiac chambers and the presence of aneurismal or post stenotic dilatations

Buchanan and Bucheler (1995) stated that vertebral heart size of normal dog was 9.2 – 10.2 vertebrae. The caudal vena cava was 0.62 – 0.88 vertebrae in comparison to the length of the vertebrae over the tracheal bifurcation.

Vollmar (2000) observed that CHF was mild to moderate when radiography revealed cardiomegaly with left atrial enlargement, pulmonary venous distension, increased pulmonary densities typical of pulmonary oedema, a small amount of pleural effusion, hepatomegaly or mild ascites.

Radiographic abnormalities in 17 Great Dane dogs with DCM included pulmonary oedema in 10 dogs, generalized cardiac enlargement

in nine dogs, left atrial enlargement in four and pleural effusion in two dogs (Meurs *et al*., 2001).

Martin (2002) reviewed that chest radiographs were often considered more reliable than ECG as an indicator of cardiac enlargement.

Ristic (2004) opined that blood vessels could be assessed for signs related to heart failure. In congestive heart failure size of veins became increased and congested. Caudal vena cava increased 1.0 – 1.5 times the width of aorta. Pulmonary artery, vein and bronchus were of equal width. Pulmonary edema was caused when engorged pulmonary veins eventually leak fluid.

Lanber *et al.* (2005) suggested that cardiac illnesses causing cardiomegaly could be diagnosed using radiography of lateral thorax and VHS in cases with insufficient diagnostic tools. On the other hand, normal heart size did not always mean that there was no heart disease. Because of these reasons determination of VHS only was not sufficient for diagnosing heart disease.

Martin *et al.* (2008) observed that 80% of the dogs with DCM showed cardiomegaly and 74 % of the dogs showed congestion due to pulmonary oedema or pleural effusion.

2.6.3. Echocardiography

Bayon *et al*. (1994) studied M mode echocardiography in growing Spanish Mastiffs, and results suggested that the direct measurements showed a good correlation to body weight in young animals, so also in adults, and the indirect measurements like Fractional shortening (FS) %, interventricular septum thickness (IVS) %, left ventricular free wall

thickness (LVW) % and ratio of aortic diameter to left atrial diameter (AO/LA) % might be considered as independent of age and body weight after the age of 2 months.

Richardson *et al.* (1996) reported that ventricular dilatation with reduced systolic function on echocardiography could be considered as diagnostic feature of DCM.

Calvert *et al.* (1997) stated that the echocardiographic variables considered as unequivocally abnormal were left ventricular Fractional shortening (FS) less than 25%, left ventricular internal end diastolic dimension more than 45 mm in dogs weighing less than 38 kg and greater than 49 mm in dogs weighing more than 37 kg, E- point to septal separation (EPSS) greater than 8mm and mean velocity of circumferential shortening (vcf) less than 1.5 circumferences.

Tidholm *et al.* (1998) reported that FS (less than 25%) in conjunction with radiographic evidence of cardiac enlargement and typical signs of congestive heart failure might be acceptable for clinical diagnosis of DCM in dogs.

Brownlie and Cobb (1999) observed that in addition to the left side abnormalities, all the DCM dogs showed marked right ventricular enlargement on B mode images which was difficult to measure objectively. The author also observed that in cases with AF, the FS was very variable. In a group of 40 asymptomatic Wolfhounds with AF, mean FS% was 23.4, and in 8 Wolfhounds which developed DCM mean FS% was 24%.

Jacobs *et al.* (2000) stated that end diastolic and end systolic ventricular volumes could be normalized to body surface area (BSA) to

give an end diastolic volume index (EDV – 1) and end systolic volume index (ESV – 1) in units ml/m^2 . The formula to calculate canine body weight in grams was;

BSA (m^2) = 10.1 X [(Weight in grams)] $^{0.667}$ X 10^{-4}

McEwan (2000a) reviewed that if left atrial pressure was increased, the interatrial septum could be seen to bulge towards right in DCM.

Calvert and Wall (2001b) stated that values for left ventricular internal end diastolic dimension equal to or less than 47mm, left ventricular internal end systolic dimension equal to or less than 37mm and left ventricular FS more than or equal to 30% in Dobermann Pinschers should be considered normal.

Left ventricular systolic and diastolic diameters in 17 Great Dane dogs with DCM determined by means of echocardiography ranged from 4.0 to 9.4 cm and from 5 to 11.1 cm respectively. Left ventricular systolic and diastolic diameters indexed to body surface area (cm/m^2) ranged from 2.69 to 7.52 cm/m^2 and from 3.3 to 8.9 cm/m^2 respectively. Fractional shortening ranged from 8 – 23%. End systolic volume index ranged from 108 to 564 m/m^2. (Meurs *et al*., 2001)

McEwan *et al*. (2003) opined that in presence of significant mitral regurgitation in dogs, FS might be misleading and an ejection fraction less than 40% was abnormally low. An ESV-1 over 80ml/m^2 offered an equivocal evidence for systolic dysfunction. Normal canine ESV – 1 had been suggested to be less than 30 ml/m^2. Ratio of LV diastolic length (from right parasternal long axis four chamber view) to the M mode LV diastolic dimension less than 1.65 represented increased sphericity.

Jordan *et al.* (2007) studied DCM in 10 Cocker Spaniels and the authors reported that there was significant palpable alteration in pulse amplitude. At mitral valve level, increased E – point to septal separation and alternation of mitral valve opening pattern, with absent mitral A peaked every other beat also was observed.

Martin *et al*. (2008) observed that all 369 dogs with DCM as defined by echocardiographic criteria had dilated left ventricles consistent with DCM, additionally the left ventricular diastolic diameter to left atrial diameter ratio was approximately one. In contrast, dogs with primary mitral valve disease usually had a left atrial diameter in excess of the left ventricular diastolic diameter and left ventricular systolic diameter was higher than the normal range, and this was supportive of the Cornell index being useful in the diagnosis of DCM.

Petric and Tomsic (2008) stated that value of fractional shortening (FS) between 20- 25% in Dobermann Pinschers were equivocal findings, but FS less than 15% suggested strong evidence of DCM, although values from 18-22% had been observed in normal Dobermann Pinschers. Major criteria for diagnosis of DCM included LV systolic and diastolic dimensions exceeding 95% confidence intervals of normal M mode values relative to the breed, increased left ventricular sphericity, FS less than 20 – 25% and left ventricular ejection fraction less than 40%. Proposed minor criteria included presence of arrhythmia in proposed breeds, increased EPSS, AF, increased Pre-ejection period of the aortic or pulmonary flow : Ejection time of the aortic or pulmonary flow (PEP: ET), FS in equivocal ranges and left or biatrial enlargement.

2.6.4. Haemato- biochemical Parameters

Hematological finding of 12 dogs with dilated cardiomyopathy revealed mild, poorly regenerative anaemia in 2 dogs. Clinical chemistry showed azotemia, creatininaemia, hypoalbuminaemia, elevated liver enzymes (Alkaline phosphatase and Alanine amino transferase). Thyroid hormone levels had low values in 3 out of 5 dogs (Lombard, 1984).

According to Jacobs (1996), hyponatremia and hypoprotenemia might develop in DCM and usually associated with severe congestive heart failure.

Gavaghan and Kittleson (1997) reported the normal value for sodium and potassium in dog as 145 – 154 mmol/L and 4.1 – 5.3 mmol/L respectively.

Abbott (1998) reviewed that the results of complete blood count and serum chemistry profile were often normal in patients with CHF, although severe failure might be complicated by prerenal azotemia, hyponatriemia and a stress leukogram. Mild elevations of the liver enzymes were also noted in patients with right sided CHF.

Normal serum creatinine concentration in dogs ranged from 0.3 to 1.3 mg/dl (DiBartola, 2000).

Sisson *et al.* (2000) found out that in DCM, serum electrolyte and protein concentrations were often within the normal range but in some cases there might be mild hypoprotenemia and hyponatremia and modestly elevated serum liver enzymes, bile acids , increased serum urea and creatinine concentrations.

Guglielmini and Civitella (2004) reported a case of dilated cardiomyopathy which showed anemia and leukocytosis with a mature neutrophilia. Mildly high glucose and urea concentration and high amylase activity were detected in serum biochemical analysis.

Ristic (2004) stated that haematology and biochemistry were helpful to investigate potential concurrent diseases. Measurement of electrolytes, blood proteins, renal and hepatic parameters were all useful to assess the drug therapy.

2.6.5. Biochemical Markers

Wyatt *et al.* (1998) compared the values of CPK – MB concentration in eight dogs without heart disease and 11 dogs with heart disease including mitral valve insufficiency, atrial fibrillation, supraventricular and ventricular ectopy, DCM, heart worm disease and tricuspid insufficiency. It was found that the median and mean CPK – MB concentrations for the non cardiac diseased groups were 7.7 pmol/L and 20.1 pmol/L respectively whereas for the dogs with cardiac disease they were 4.8 pmol/L and 14.7 pmol/L respectively and they were not significantly different. In conclusion CPK – MB concentration was not suitable indicator of cardiac failure in dogs.

Galatius *et al.* (1999) reported that in patients with idiopathic dilated cardiomyopathy plasma endothelin and von Willybrand Factor (vWF) concentrations were elevated both in CHF and after heart transplantation. Plasma vWF increased further as a result of heart transplantation in contrast to plasma endothelin, which remained elevated at the same level. Although there was a direct association between plasma endothelin and

vWF in both disease states, different independent determinants of their plasma levels were demonstrated.

Wei and burnett (2000) opined that endothelin was an endothelium derived potent vasoconstrictor and sodium – regulating peptide. Plasma concentration of endothelin was increased in congestive heart failure of human and animals.

Ristic (2004) reviewed that pro atrial natriuretic peptide (proANP), a precursor of atrial natriuretic peptide, was released in response to atrial enlargement, and increased levels were found in dogs with heart failure. A pro ANP level above 1750 fmol/ml indicated heart failure.

Nakata *et al.* (2005) reviewed that plasma brain natriuretic peptide (BNP) level had emerged as a powerful marker in the diagnosis of cardiac failure. Cardiac I – metaiodo benzyl-guanidine (MIBG) also enabled non invasive delineation and evaluation of cardiac sympathetic activity or norepinephrine content in human hearts as MIBG was a norepinephrine analogue which was taken up by uptake - I mechanism and stored in presynaptic neurons and released *via* exocytosis like epinephrine.

Tidholm *et al*. (2005) opined that plasma vasopressin and urine cortisol – to – creatinine ratio was significantly increased in dogs with clinical signs of DCM. Urine epinephrine – to – creatinine ratio and urine norepinephrine – to – creatinine ratio were also significantly increased in dogs with clinical signs of DCM.

2.6.6. Pathology

Valentine *et al.* (1989) observed focal white, chalky areas of mineralization in cross sections from left ventricular papillary muscles,

septum, and left ventricular free wall in dogs aged from, 6.5 months to 1.5 years and that was absent in 6 year old dog with X linked muscular dystrophy associated with cardiomyopathy. Ultrastructural studies revealed loss of thick and thin filaments, Z band alterations, dilated sarcoplasmic reticulam and accumulation of mitochondria. Sub epicardial fibrosis was a consistent, characteristic lesion in the affected dogs.

Calvert *et al.* (1997) observed multifocal interstitial fibrosis and replacement of muscle fibers of heart with collagen and fat in dogs that died suddenly due to DCM. Histopathological lesions consistant of cardiomyopathy included multifocal areas of interstitial fibrosis and foci of variable sized muscle fibers, some of which had been replaced by fibrous connective tissue and fat cells in rare instances. Lesions were more severe in left ventricular papillary muscles followed by interventricular septum.

Tidholm *et al*. (1998) studied the prevalence of attenuated wavy fibers in myocardium of 70 dogs which were clinically suspected to have DCM and 64 out of 65 had attenuated wavy fibers, 5 had disease other than DCM. Authors also stated that major histopathological finding in dogs, cats and human beings with DCM was a high frequency of myocytes, which were thinner than normal and had a wavy appearance, so called attenuated wavy fibers, in the myocardium.

McEwan (2000a) stated that Boxers with DCM were atypical in that they showed characteristic histopathological changes which affected the myocardium, with a fibrofatty infiltrate replacement of cardiomyocytes which, predominantly or initially, affected the right ventricle.

Petric *et al*. (2002) stated that post mortem findings considered diagnostic of DCM were enlarged heart with severe dilatation of left or all 4 chambers, with thin walls, dilated atrioventricular (AV) ring and no significant changes in valvular apparatus and other heart structures. Mild myxomatous AV valve degeneration was considered as insignificant finding. Pulmonary oedema and hepatic congestion were also observed.

McEwan *et al*. (2003) described two distinct histopathological forms of DCM, the attenuated wavy fibre type of DCM and the fatty infiltration – degenerative type of DCM. Cardiomyopathy of Boxers included myocytolysis, myofibre degeneration, vacuolization and myocyte atrophy with extensive fibrosis and fatty infiltration.

Tidholm and Jonsson (2005) reviewed that development of attenuated wavy fiber was not a response to chamber dilatation and stretching of myocytes and might represent an early pathological change in the myocardium of dogs with dilated cardiomyopathy. Because attenuated wavy fibers were detected in Newfoundlands with a known predisposition to dilated cardiomyopathy, but without clinical or echocardiographic evidence of heart disease.

2.7. TREATMENT

Tidholm (2006) opined that treatment of dogs with congestive heart failure attributable to dilated cardiomyopathy might include inotropic agents, such as digoxin, and phosphodiesterase inhibitors and calcium sensitizers, diuretics and inhibitors of renin - angiotensin - aldosterone system and / or sympathetic system.

2.7.1. Inhibitors of Renin – Angiotensin – Aldosterone System

The Cooperative Veterinary Enalapril (COVE) Study Group (1995) evaluated effect of enalapril in dogs with heart failure caused by acquired valvular disease or dilated cardiomyopathy. Enalapril was administered at a dose rate of 0.5 mg/kg sid or bid and significant improvement was noticed.

Spinale *et al*. (1997) isolated simultaneous indices of isolated myocyte membrane potential and contraction from four groups of dogs which included: DCM group (chronic pacing induced), DCM group treated with angiotensin conversion enzyme inhibitor (fosinopril @ 30 mg/kg bid), DCM group with specific nonpeptide angiotensin – II receptor antagonist (BMS – 186295 @ 30 mg/kg bid) and control group. The author reported that angiotensin conversion enzyme inhibitor (ACEI), during progression of DCM improved myocyte function where as angiotensin receptor II antagonist had selective effect on myocyte electrophysioplogy, thus both had unique and different mechanism of action with cardiomyopathic disease.

Valsartan significantly reduced the combined end point of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure, when added to prescribed therapy. Adverse effect on mortality and morbidity in the group receiving valsartan, an ACE inhibitor, and a beta-blocker was observed which arised concern about the potential safety of this specific combination. (Cohn and Tognoni , 2001)

Shi *et al*. (2002) opined that renin – angiotensin system was important in the process of ventricular remodeling associated with congestive heart failure. Angiotensin conversion enzyme inhibitor (ACEI)

and angiotensin 1 – receptor blocker prevented collagen accumulation in the non – infracted myocardium after myocardial infarction and angiotensin – II had shown to promote collagen synthesis by cultured fibroblasts and to reduce collaginase activity.

Despite ACE inhibition, angiotensin II levels eventually returned to nearly normal levels, because the chymase enzymes, an alternate pathway for angiotensin conversion. Angiotensin-receptor blockers worked by blocking the effects of angiotensin II at the angiotensin 1 receptor, which allowed beneficial effects at the angiotensin II receptor. When angiotensin-receptor blockers were taken alone, the inactivation of bradykinin proceeded normally, without the beneficial accumulation promoted by ACE inhibitors. The use of an ACE inhibitor in combination with an angiotensin-receptor blocker could offer benefits by allowing bradykinin to accumulate while blocking the deleterious consequences of angiotensin II (Scow *et al*., 2003).

Ehrlich *et al.* (2006) opined that ACE-inhibitors and angiotensin receptor blockers appeared to reduce AF and prevent AF related complications. Angiotensin conversion enzyme inhibitors and angiotensin receptor blockers improved left ventricular haemodynamics and reduced atrial stretch, suppressed angiotensin-II-induced fibrosis and directly modulated ion-channel function.

2.7.2. Diuretics

Darke (1994) reviewed that diuresis was vitally important in control of volume overload in congestive heart failure. Loop diuretics such as furosemide were most often employed @ 2 – 4 mg/kg bid. Dehydration,

hypokalemia and reduced cardiac output were undesirable complications of long term therapy at higher doses.

McEwan (2000b) reviewed that diuretics were essential in the control of congestive heart failure in DCM. Furosemide along with spironolactone was preferred by the author since spironolactone prevented some of the direct actions of aldosterone on myocardium.

Ware and Keene (2000) opined that in refractory heart failure, diuretics such as spironolactone @ 1-2mg/kg PO every 12 hours or spironolactone hydrochlorothiazide @ of 1-2mg/kg PO every 12 hours could be added. Spironolactone, a potassium sparing aldosterone antagonist should be used cautiously in patients receiving an ACEI or potassium supplement.

Sisson *et al*. (2000) stated that furosemide was the most commonly used diuretic in cardiac diseases. It was a potent diuretic which would rapidly reduce cardiogenic pulmonary edema in most instances by decreasing intravascular volume and hence preload.

2.7.3. Antiarrhythmic Agents

2.7.3.1. *Class I Agents (Sodium Channel Inhibittors)*

Sisson *et al*. (2000) reviewed that tocainide was more effective in suppressing ventricular arrhythmias in Dobermann pinschers than other class I drugs tested, but there was no evidence of increased survival.

Calvert and Brown (2004) observed that administration of class IA agents (procainamide 15 – 20 mg/kg tid, Quinidine gluconate 8 – 9 mg/kg tid) or class IB agents (tocainide 15 – 20 mg/kg tid, mixeletine 5 – 8

mg/kg tid) to Dobermann Pinschers with severe ventricular arrhythmia secondary to dilated cardiomyopathy showed a quantitative improvement within few days. But worsening of arrhythmia progressively more refractory to treatment was common after 2 – 6 months of progressive myocardial failure.

2.7.3.2. *Class II Agents (Beta Receptor Blockers)*

Nikolaidis *et al*. (2006) reported that combined α_1, β_1 and β_2 adrenergic receptor antagonist such as carvedilol was superior to β_1 selective adrenergic receptor antagonist like metaprolol. Carvedilol was superior as it increased stroke volume and cardiac volume higher than metaprolol in addition to suppression of norepinephrine levels and increased myocardial spill over of norepinephrine. Carvedilol also found to increase myocardial glucose uptake in advanced DCM, suppressed glucagon and improved renal, hepatic,skeletal muscle blood flow.

Tidholm (2006) stated that the use of beta blocking drugs in dilated cardiomyopathy was controversial due to their negative inotropic effect and the author also stated that propranolol had been reported to prevent development of CHF in dogs with tachycardia induced heart disease by inhibiting calcium leak through ryanodine receptors in the sarcoplasmic reticulam.

Nasr *et al.* (2007) reviewed that beta blockers appeared to effectively prevent the occurrence of AF in patients with heart failure even though they had no atrial stabilising properties. They prevented either adverse ventricular remodeling with decrease in left ventricular and atrial end diastolic pressure, attenuation of actions of sympathetic nervous

system on automaticity and conduction in the heart or by prevention of atrial ischemia and fibrosis.

2.7.3.3. *Class III Agents (Potassium Channel Inhibittors)*

Calvert and Meurs (2000) reported that Amiodarone at the dose rate of 10 mg/kg bid for 1 week and then 8 mg/kg once daily was a unique antiarryhthmic agent that could be more effective at preventing sudden death in occult cardiomyopathy in Dobermann Pinschers although long term efficacy remained to be proved.

In the case of ventricular tachycardia in Boxers and Dobermanns, commonly used antiarrhythmic drugs included sotalol at the dose rate of 2 mg/kg q12h, amiodarone at the dose rate of 8-10 mg/kg bid and reduced to 5 mg/kg sid after 6 months; should be used with caution due to irreversible hepatoxicity, or a combination between mexiletine at the dose rate of 5-8 mg/kg tid and a low dose atenolol (Haggstrom, 2008).

2.7.3.4. *Class IV Agents (Calcium Channel Blockers)*

Sisson *et al*. (2000) reported that calcium channel blockers like nifedipine and verapamil might exacerbate congestive heart failure. Other calcium channel blockers like amlodipine decreased sympathetic nervous activity and increased exercise capacity in human and canine model of nonischemic DCM.

Wei and Burnett (2000) opined that Felodipine, a calcium channel antagonist, was effective in reducing vascular resistance in states of generalized vasoconstriction as it inhibited circulating and local renal endothelin which was found to be elevated in congestive heart failure.

Tripathi (2008) opined that verapamil had potent negative inotropic effect due to interference with Ca^{2+} mediated excitation contraction coupling in the myocardium. But diltiazem had less direct cardiac effect compared to verapamil as it caused less hypotension and myocardial depression.

2.7.4. Positive Inotropic Agents

Darke (1994) reported that a positive inotropic agent like dobutamine at the dose rate of 5 – 20 μg/kg/min by intravenous infusion was useful in severe cardiomyopathy. But this form of treatment required intensive monitoring.

Borgarelli *et al.* (2001) reviewed that dogs with DCM responded to digoxin by increased contractility and lack of response in some dogs was caused by an altered intracellular handling of calcium in the myocytes as a consequence of damaged intracellular structures like sarcoplasmic reticulam.

Tidholm (2006) evaluated the effect of treatment of digoxin (mean dose of 0.009 mg/kg/day) and furosemide (mean dose of 3.6 mg/kg/day) for the initial treatment of DCM. Propanolol (mean dose of 2.4 mg/kg/ day) was added in the regimen after signs of congestive heart failure were resolved. Median survival time was 126 days with 34 % survival rate.

2.7.5. Phosphodiesterase Inhibittors

Smith *et al*. (1997) observed that in the absence of beta agonists, the phosphodiesterse III inhibitors like milrinone had reduced inotropic effects in vitro in failing human and canine myocardium. Canine CHF induced by rapid ventricular pacing was associated with a time dependent down

regulation of several phosphodiesterse III mRNA in myocardial tissue which caused reduced response to phosphodiesterase III inhibitors.

Gordon *et al*. (2006) described that pimobendan's calcium sensitization of the contractile apparatus was achieved by enhancement of the interaction between calcium and the troponin C complex, resulting in a positive inotropic effect that did not increase myocardial oxygen consumption. Overall, pimobendan enhanced systolic function by improving the efficiency of contraction and by limiting the arrhythmogenic side effects of other positive inotropes which had a sole mechanism of action of increasing myocardial intracellular calcium. Pimobendan was well tolerated @ 0.25 mg/kg orally bid.

2.7.6. Nutritional Supplimentation

McEwan (2000b) reviewed that coenzyme Q 10 at the dose rate of 30 – 40 mg bid might be beneficial in dogs with DCM which had defects in oxidative phosphorylation. and had antioxidant properties. The author also stated that omega 3 fatty acids decreased production of cytokines and inflammatory mediators. Omega 3 fatty acids included eicosapentaenoic acid at the dose rate of 40 mg/kg and docosahexaenoic acid at the dose rate of 25mg/kg were useful in the treatment of DCM.

Freeman *et al.* (2003) opined that nutritional modifications suggested for management of cardiac disease included sodium restriction and caloric supplementation including taurine, L – Carnitine, Coenzyme Q10 and n - 3 poly unsaturated fatty acids.

Belanger *et al.* (2005) opined that taurine was a sulfur containing amino acid which increased cardiac inotropy by potentiating calcium uptake by the sarcoplasmic reticulum, increased sensitivity of the

myofilaments to calcium, and affected the long lasting (L – type), voltage – dependent calcium channels. Taurine was also a natural antagonist of angiotensin II.

Gompf (2005) proposed that, any dog with low plasma L –carnitine levels (12 – 38pmol/L) should be supplemented with L – carnitine at the dose rate of 1000 mg orally tid for dogs weighing less than 25 kg and 2000 mg orally for dogs weighing 25 – 40 kg.

Materials and methods

3. MATERIALS AND METHODS

The study was conducted in the Department of Clinical Veterinary Medicine, College of Veterinary and Animal Sciences, Mannuthy during the period of 2008 – 2009.

3.1. SELECTION OF ANIMALS

3.1.1. Diseased Animals

Dogs brought to the Veterinary College Hospital, Mannuthy and University Veterinary Hospital, Kokkalai with signs of cardiac problems *viz.* lethargy, weakness, dyspnoea, cough, syncope and exercise intolerance were used for the study. They were screened for cardiac problem by detailed clinical examination as per the proforma (Annexure I).

Based on electrocardiographic, radiographic and echocardiographic abnormalities eight confirmed cases of dilated cardiomyopathy were selected and utilised for further treatment studies with enalapril @ 0.5 mg/kg body weight, furosemide and spironolactone @ 2 mg/ kg body weight and valsartan @ 2 mg/ kg body weight orally twice daily for a period of one month and these animals were serially numbered from case No. 1 to 8.

3.1.2. Normal Animals

Six apparently healthy adult dogs brought for vaccination were considered as normal group. All the haematological and serum biochemical parameters which were studied in diseased group were assessed for the normal group also. Electrocardiography of normal group was recorded.

3.2. PARAMETERS STUDIED

All the animals were evaluated for following parameters before and on 15th and 30th day of the treatment. Echocardiographic observations were performed on the day of admission and on day 30 of treatment and radiographic observations on the day of admission only.

1. Signalment and History
2. Clinical examination
3. Electrocardiography
4. Radiography
5. Echocardiography
6. Clinical pathology
   A. Haematology
      - Total RBC (millions/per cu. mm)
      - Haemoglobin (Hb) (g/dl)
      - Volume of packed red cells (VPRC) (percent)
      - Total leukocyte count(TLC) (per cu. mm)
      - Differential count (DC) (percent)

   B. Serum biochemistry
      - Creatine kinase (CK) (U/L)
      - Serum sodium, potassium (mEq/L)
      - Serum creatinine (mg/dl)
7. Response to treatment

3.3. PROCEDURES ADOPTED

3.3.1. Clinical examination

Detailed history and results of clinical examination including temperature, pulse and respiration of eight selected dogs were recorded as per the method of Houston (2000), paying special attention to the cardiovascular system.

3.3.2. Electrocardiography

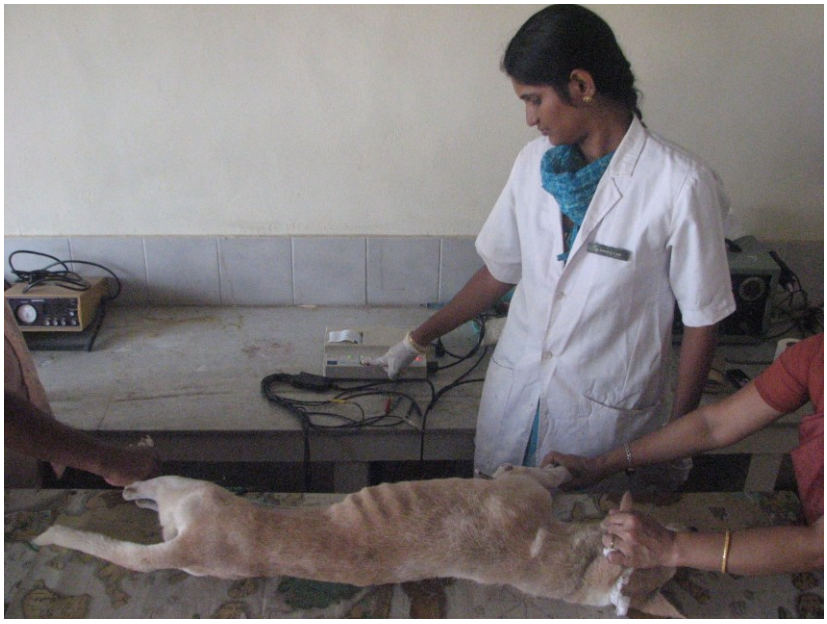
Electrocardiogram were recorded using BPL – CARDIART _ 6108® ECG machine on the day of admission, 15^{th} and 30^{th} day of treatment. Three standard bipolar limb leads (I, II, III) and three augmented unipolar limb leads (aVR, aVF, aVL) were used for the study (Bolton, 1975).

According to the procedure of Goodwin (2001) and Martin (2002), animals were placed in right lateral recumbency and the electrodes were attached over the elbow and stifle joints of the forelimbs and the hind limbs respectively after applying electrode jelly. Electrocardiograms were recorded in BPL – CARDIART® paper strips at the speed of 25 mm per second and sensitivity of 1 mv = 10mm. The recorded ECG tracings were evaluated and photographed later (Plate 1).

3.3.3. Radiography

Lateral plane radiographs of thorax of diseased animals were taken for cardiac evaluation. Size of the X – ray film and radiographic factors varied depending upon the size and chest girth of patients.

Plate 1. Recording ECG



According to the procedure of Buchanan and Bucheler (1995) vertebral heart score was calculated in lateral radiographic views. The long axis of the heart was measured from the ventral border of the left main stem bronchus to the most distant ventral contour of the cardiac apex using an adjustable caliper, which was then repositioned over thoracic vertebrae beginning with the cranial edge of fourth thoracic vertebra. The distance to the caudal caliper point was estimated to the nearest 0.1 vertebra (v). The maximal short axis of the heart in the central third region, perpendicular to the long axis was recorded in the same manner starting at fourth thoracic vertebra. The short and long axis dimensions were then added to yield a vertebral/heart sum which was termed the vertebral heart size (VHS). The maximal diameter of the caudal vena cava (CVC) was measured and compared to the length of single vertebra dorsal to the tracheal bifurcation (usually fifth thoracic vertebra) (Plate 2).

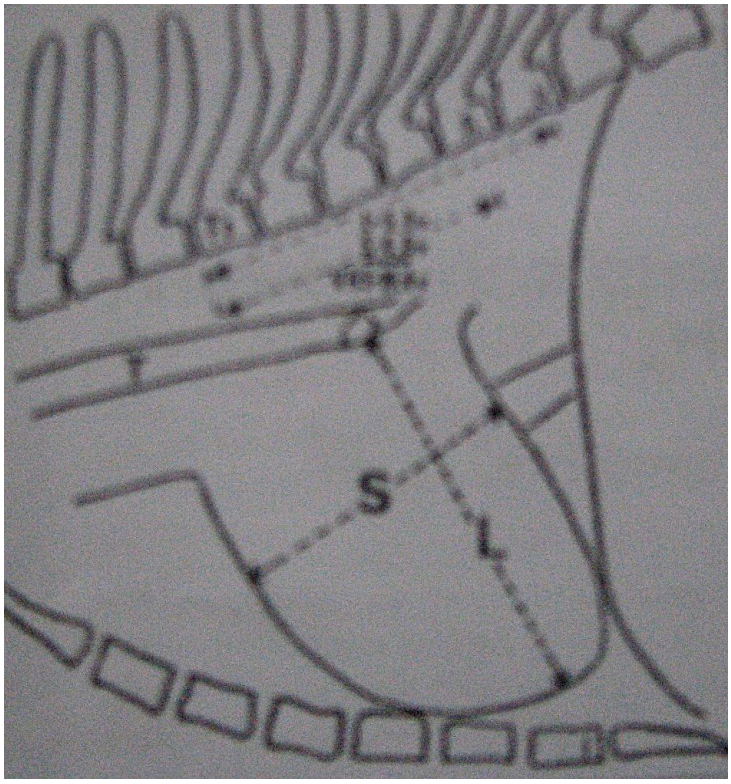
3.3.4. Echocardiography

Animals were subjected to ultrasound scanning of the heart using L&T SYMPHONY ® 4.0 scanner. Dogs were examined in left lateral recumbency. Both two - dimensional and M – mode echocardiography in left and right parasternal view of the heart was obtained using 7.5 MHz transducer. Left ventricular dimensions were measured in the right parasternal short axis view (Plate 3). Values for each parameter were determined by the average of three to five cardiac cycles (Bayon *et al.,* 1994 and Vollmar, 1999).

Direct measurements were as follows:

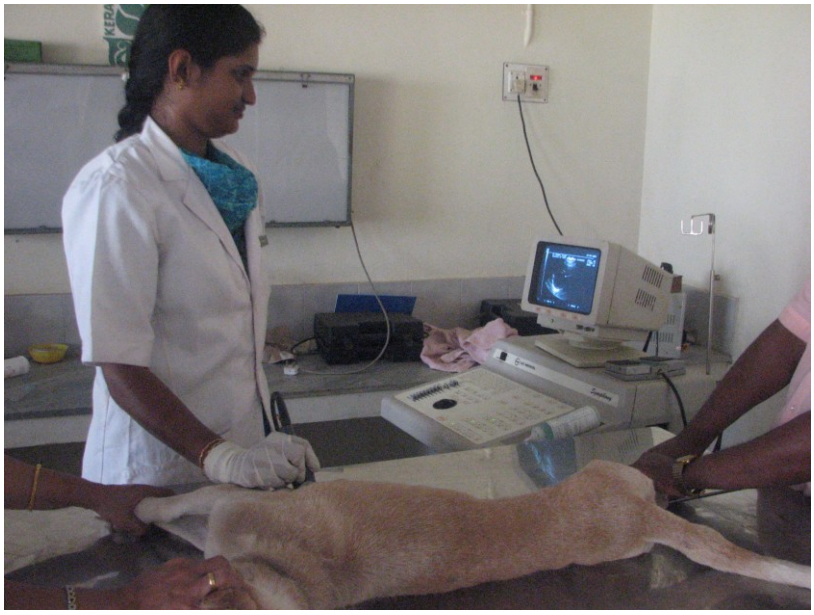
- Left ventricular internal dimensions at end systole
- Left ventricular internal dimensions at end diastole

Plate 2. Calculation of vertebral heart score



S - Short axis of the heart
L – Long axis of the heart
VHS = S + L

Plate 3. Echocardiographic examination of dogs



From the direct measurements taken, the indirect measurements were calculated as follows;

Shortening fraction (FS) = (LVIDd – LVIDs) / LVIDd

End systolic volume index was calculated according to Teichholz cube formula.

End Systolic Volume (ESV) (ml) = $7 (LVIDs)^3 / (2.4 + LVIDs)$

End Diastolic Volume (EDV) (ml) = $7 (LVIDd)^3 / (2.4 + LVIDd)$

Ejection Fraction (EF) = (EDV – ESV) / EDV

3.4 CLINICAL PATHOLOGY

3.4.1. Haematology

Clinical materials were collected from diseased dogs on the day of admission, 15 th and 30 th day of treatment. Five milliliter of whole blood was collected from saphenous or cephalic vein of the patient in dry glass vials with EDTA @ 1-2 mg per milliliter of blood as anticoagulant (Benjamin, 1998). The values of total RBC, haemoglobin, volume of packed red cells, total leukocyte count and differential count were determined as per the method of Schalm *et al.* (1975).

3.4.2. Serum Biochemistry

Blood samples (approximately 5 ml) were collected from saphenous or cephalic veins of each animal having dilated cardiomyopathy on the day of admission, 15th and 30th day of treatment. Samples were taken in a clean, dry test tube without anticoagulant for separating serum for biochemical analysis. Sera thus separated were stored at $^{-}20^0$C till further analysis.

Serum creatine kinase, creatinine, potassium and sodium were estimated. Serum creatine kinase and creatinine were estimated by spectrophotometry in Merck 200 spectrophotometer using commercially available kits (AGAPPE Diagnostics). Serum sodium and potassium were estimated using SYSTRONICS 128 ® flame photometer.

3.5. TREATMENT

Dogs confirmed of having DCM were treated with enalapril @ 0.5 mg/kg body weight, furosemide and spironolactone @ 2 mg/ kg body weight and valsartan @ 2 mg/ kg body weight orally twice daily for a period of one month.

3.5.1. Enalapril

An ester prodrug with very little angiotensin converting enzyme (ACE) inhibitor activity became active when converted (hydrolysed) in the liver to the diacid enalaprilat, which was a very potent ACE inhibitor. Angiotensin converting enzyme inhibitors are the most important class of neurohormonal antagonists for treating congestive heart failure. This agent blocks conversion of angiotensin I to the circulating octapeptide, angiotensin II which is a potent vasoconstrictor. Anticipated changes include decreased atrial and ventricular filling pressures, decreased peripheral vascular resistance and increased cardiac output.

3.5.2. Valsartan

Valsartan is an angiotensin receptor blocker (ARB) which blocked vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the angiotensin – 1 (AT 1) receptor and causing bradykinin accumulation. Action of valsartan is independent of angiotensin II synthesis. Valsartan had 20,000 fold affinities for AT 1 receptor than angiotensin – 2 (AT- 2) receptor. Following oral administration valsartan

recovered mainly as unchanged drug, with only 20 % of the dose recovered as metabolites.

3.5.3. Furosemide and Spironolactone

Diuresis is vitally important for controlling volume overload in DCM. Furosemide was a loop diuretic and spironolactone is a potassium sparing aldosterone antagonist.

3.6. RESPONSE TO TREATMENT

Treatment response was monitored based on clinical response, electrocardiography, echocardiography, haematology and serum biochemistry.

3.7. STATISTICAL ANALYSIS

Data collected on various parameters were statistically analyzed by paired samples T test as described by Snedecor and Cochran (1994) at 1% level of significance.

Result

4. RESULT

Dogs presented to the Veterinary College Hospital, Mannuthy and University Veterinary Hospital, Kokkalai with clinical signs suggestive of cardiac problems formed the material for the present study. All the cases were subjected to detailed clinical examination, electrocardiography, radiography, echocardiography and haematobiochemical assays. According to the test results and findings, a total of eight cases with dilated cardiomyopathy (DCM) were selected and utilised for further treatment studies.

4.1 SIGNALMENT

Signalment of eight selected dogs having DCM is given in Table 1.

4.1.1. Age

Dilated cardiomyopathy (DCM) was more commonly observed in middle aged dogs. Age of affected dogs ranged from 2 to 13 years with a mean of 6 ± 1.25 years.

4.1.2. Sex

Sex wise prevalence of DCM in dogs revealed that both males and females were equally affected. There were four females (50 %) and four males (50 %).

4.1.3. Breed

The breed wise distribution of DCM indicated that Labrador Retriever was more prone to dilated cardiomyopathy (37.5 %) followed by Boxer (25 %), German Shepherd Dog (12.5 %), Spitz (12.5 %) and Non-descript (12.5 %) (Fig.1).

Table 1. Signalment of dilated cardiomyopathic dogs

Case No.	breed	age (years)	sex
1	Spitz	7	male
2	Non-descript	13	female
3	Labrador Retriever	2	female
4	Boxer	4	female
5	Boxer	3	male
6	Labrador Retriever	4	male
7	Labrador Retriever	8	male
8	German Shephered	7	female

4.2. CLINICAL SIGNS

Major clinical signs observed in affected animals were anorexia, polydypsia, cough, dyspnoea, abdominal distension, exercise intolerance, oedema of the limbs and syncope. Exercise intolerance and dyspnoea were present in all cases. Cough and Ascites were present in 37.5 % and 75 % of cases respectively (Plate 4). Other symptoms associated with DCM were anorexia (75 %), polydypsia (50 %), syncope (25 %) and oedema of hind limbs (25 %). (Table 2, Fig. 2)

Case No. 8 died on day 3.

4.3. CLINICAL EXAMINATION

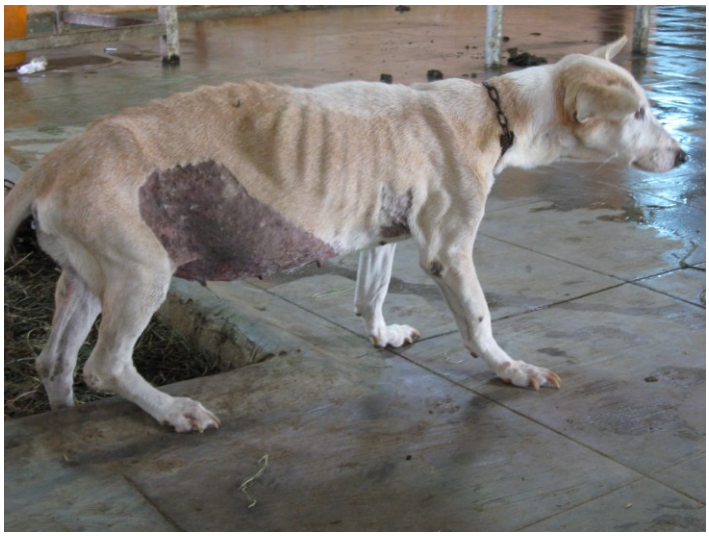
Clinical parameters (temperature, pulse and respiration) on day 1, 15 and 30 are presented in Table 3.

Mean temperature, pulse and respiration rates on the day of admission were 38.47 ± 0.63ºC, 112.25 ± 10.86/min and 31.38 ± 1.91/min respectively. Irregular pulse was present in 37.5 % of the cases on the day of admission. Femoral pulse was weak in 75 % of the cases. Mucous membranes were pale in 25 % of the cases.

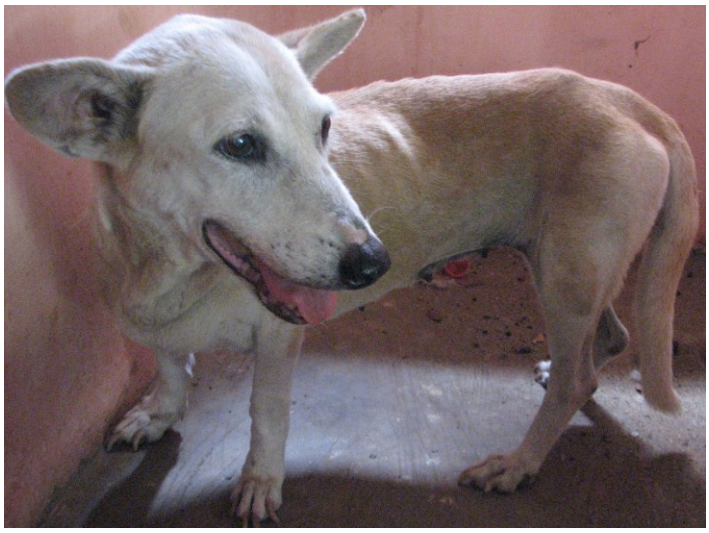
Thoracic auscultation revealed tachycardia in 25 % of the cases. Pulse deficit was present in 50 % of the cases. Pulmonary crackles were detected in 75% of the cases. Ascites was confirmed by tactile percussion and later by ultrasonography in 75 % of the cases. Jugular venous distension and positive hepatojugular reflex were present in all the cases in which ascites was present.

Mean temperature was 38.67 ± 0.33ºC and 38.76 ± 0.17ºC on day 15 and 30 respectively. Pulse rates were 145.71 ± 21/min and 126 ± 15.66/min on day 15

Plate 4. Clinical signs



a. Before treatment



b. After treatment

Table 2. Clinical signs of dilated cardiomyopathic dogs

Signs	No. of animals	Percentage of animals
Cough	3	37.50%
Exercise intolerance	8	100%
Dyspnoea	8	100%
Ascites	6	75%
Oedema of limbs	2	25%
Syncope	2	25%
Anorexia	6	75%
Polydypsia	4	50%

Fig.1. Breedwise prevalence of DCM in dogs

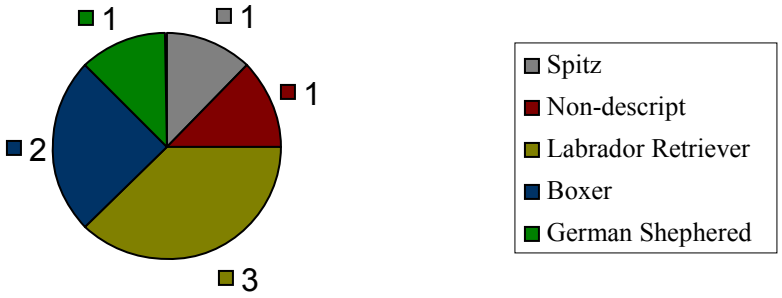


Fig. 2.Clinical signs of dilated cardiomyopathy in dogs

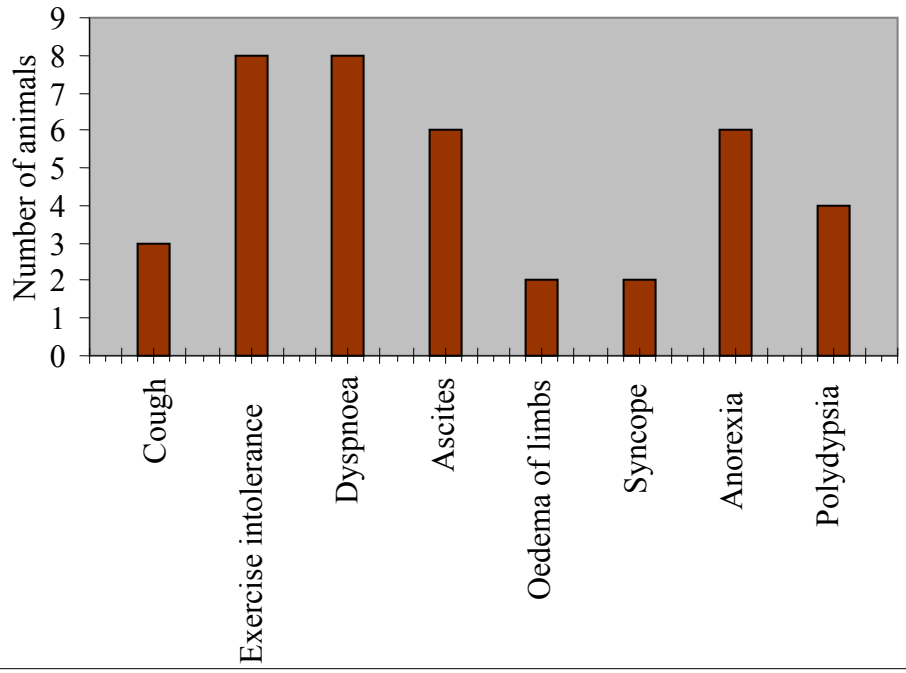


Table 3. Clinical parameters of dilated cardiomyopathic dogs on day 1, 15 and 30 of treatment

Parameters	Day 1	Day 15	Day 30
Pulse (per minute)	112.25 ± 10.86	145.71 ± 21.00	126 ± 15.66
Respiration (per minute)	31.38 ± 1.91	28.43 ± 2.70	27.67 ± 1.96
Temperature (°C)	38.47 ± 0.63	38.67 ± 0.33	38.76 ± 0.17

and 30 respectively. Mean respiration rates were 28.43 ± 2.70/min and 27.67 ± 1.96/min on day 15 and 30 respectively.

4.4 DIAGNOSIS

4.4.1. Electrocardiography

Mean values of ECG parameters of normal and diseased animals on day 1, 15 and 30 are listed in Table 4.

Mean heart rate of normal dogs was 110 ± 18.45 beats/min. Sinus rhythm was present. Amplitude and duration of P wave, duration of PR segment, amplitude of R wave, duration of QRS complex, duration of ST segment, T wave amplitude and duration on day 1 were 0.3 ± 0.04 mv, 0.03 ± 0.00 sec, 0.10 ± 0.01sec, 1.45 ± 0.14 mv, 0.04 ± 0.00 sec, 0.09 ± 0.00 sec, 0.31 ± 0.03 mv and 0.06 ± 0.01 sec respectively.

Mean heart rate on day 1 was 150.5 ± 19.36 beats/min. Sinus rhythm was present in all eight cases. Two cases had sinus tachycardia (case No. 1 and case No. 7). Atrial fibrillation was present in case No. 3. Ventricular premature complexes (VPC) were present in case No. 4 and case No. 8. Ventricular pre-excitation was present in case No. 7 (Plate 5).

Mean values of P wave amplitude and duration, duration of PR segment, amplitude of R wave, duration of QRS complex, duration of ST segment, T wave amplitude and duration on day 1 were 0.15 ± 0.05 mv, 0.05 ± 0.01 sec, 0.10 ± 0.03 sec, 1.4 ± 0.44 mv, 0.05 ± 0.01 sec, 0.09 ± 0.02 sec, 0.28 ± 0.06 mv and 0.06 ± 0.01 sec respectively.

Mean heart rate on day 15 was 176.14 ± 28.38 beats/min. Atrial fibrillation was present in case No. 3. Out of two cases having VPC on day 1, one animal

was died (case No.8) on day 3 and one (case No.4) developed atrial tachycardia on day 15. No VPC were detected on day 15. Ventricular pre - excitation was present in case No. 7 on day 15 and died on day 17.

Mean values of P wave amplitude and duration, duration of PR segment, amplitude of R wave, duration of QRS complex, duration of ST segment and T wave amplitude and duration on day 15 were 0.15 ± 0.04 mv, 0.05 ± 0.01 sec, 0.06 ± 0.01 sec, 1.28 ± 0.38 mv, 0.04 ± 0.00 sec, 0.07 ± 0.02 sec, 0.28 ± 0.06 mv and 0.05 ± 0.01 sec respectively.

On day 30, mean heart rate was 164.67 ± 30.36 beats/min. Sinus rhythm was present in all eight cases. No atrial fibrillation was observed in case No.3. Atrial tachycardia was still present in case No. 4 (Plate 6).

Mean values of P wave amplitude and duration, duration of PR segment, amplitude of R wave, duration of QRS complex, duration of ST segment and T wave amplitude and duration on day 30 were 0.15 ± 0.02 mv, 0.05 ± 0.01 sec, 0.07 ± 0.01 sec, 1.22 ± 0.38 mv, 0.04 ± 0.00 sec, 0.09 ± 0.02 sec, 0.27 ± 0.06 mv and 0.06 ± 0.01 sec respectively.

Statistically no significant differences could be observed in the measurements of ECG values on day 15 and day 30 when compared to day 1.

4.4.2. Radiography

On radiographic examination generalized cardiomegaly was present in 75 % of the cases. All the cases had tracheal elevation. Pulmonary congestion was observed in 75 % of the cases. Pericardial effusion was present in 12.5 % of the cases(Plate7).

Table 4. Electrocardiographic measurements of normal and dilated cardiomyopathic dogs on day 1, 15 and 30 of treatment

Parameters		Normal dogs	Diseased dogs		
			Day 1	Day 15	Day 30
Pwave	amplitude (mv)	0.30 ± 0.04	0.15 ± 0.05	0.15 ± 0.04	0.15 ± 0.02
	duration (sec)	0.03 ± 0.00	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
PR segment (sec)		0.10 ± 0.01	0.10 ± 0.03	0.06 ± 0.01	0.07 ± 0.01
QRS complex	amplitude (mv)	1.45 ± 0.14	1.40 ± 0.44	1.28 ± 0.38	1.22 ± 0.38
	duration (sec)	0.04 ± 0.00	0.05 ± 0.01	0.04 ± 0.00	0.04 ± 0.00
ST segment (sec)		0.09 ± 0.00	0.09 ± 0.02	0.07 ± 0.02	0.09 ± 0.02
T wave	amplitude (mv)	0.31 ± 0.03	0.28 ± 0.06	0.28 ± 0.06	0.27 ± 0.06
	duration (sec)	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01

Vertebral heart score of normal and dogs affected with DCM are listed in Table 5.

Vertebral heart score of normal dogs was 9.7 ± 0.67 vertebrae (v). Long axis and short axis dimensions were 5.24 ± 0.39 v and 4.46 ± 0.38 v respectively. Vertebral size of caudal vena cavae was 0.75 ± 0.02 v.

Vertebral heart score was calculated in all cases. Mean cardiac length and width were 6.05 ± 0.46 v and 5.58 ± 0.40 v respectively. Vertebral heart sizes ranged from 8.7 v to 14.4 v and mean value was 11.50 ± 0.85 v. Vertebral size of caudal vena cavae ranged from 0.71 v to 0.88 v with a mean value of 0.79 ± 0.03v. All the values were above the normal range which indicated cardiomegaly.

4.4.3. Echocardiography

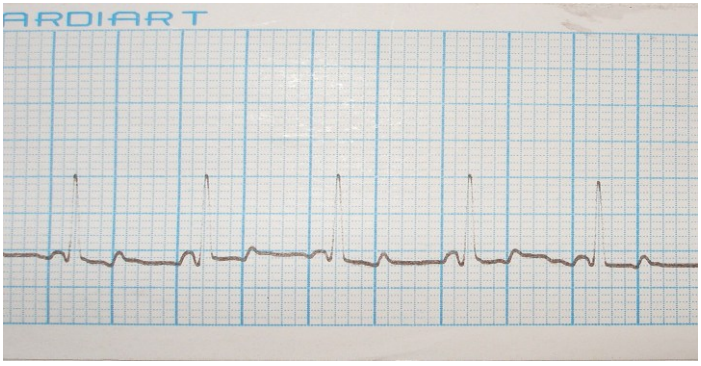
Echocardiographic evaluation of four chamber view revealed left ventricular dilatation in all cases. Pericardial effusion which was detected radiographically was confirmed by echocardiography as an anechoic area in pericardial space in cardiac four chamber view (Plate 8).

Fractional shortening equal to or more than 25 % and ejection fraction of 40 % or above were considered normal in dogs. Left ventricular end diastolic diameter (LVED d) and Left ventricular end systolic diameter (LVED s) were varied according to body weight.

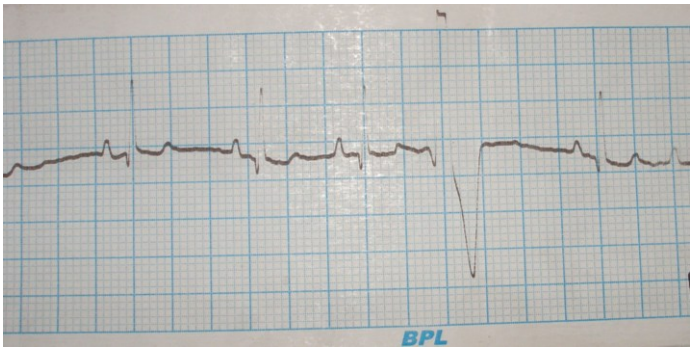
M–mode measurements of DCM dogs on day 1 and 30 are listed in Table 6.

M–mode measurements showed reduced myocardial contractility in all cases. Mean values of LVED d and LVED s were 6.02 ± 0.50 cm and 4.84 ± 0.43cm respectively. Fractional shortening (FS) was 19.80 ± 1.71 %. Mean of

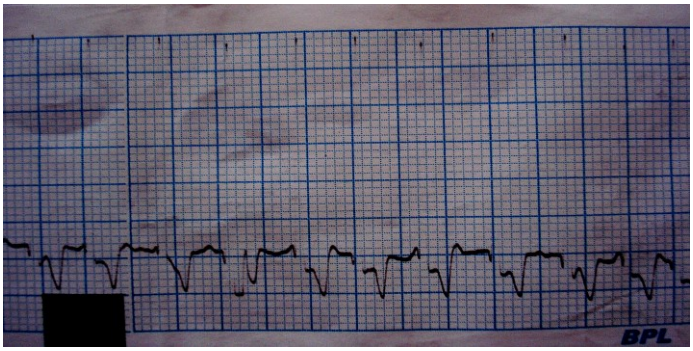
Plate 5. Electrocardiographic changes in DCM dogs



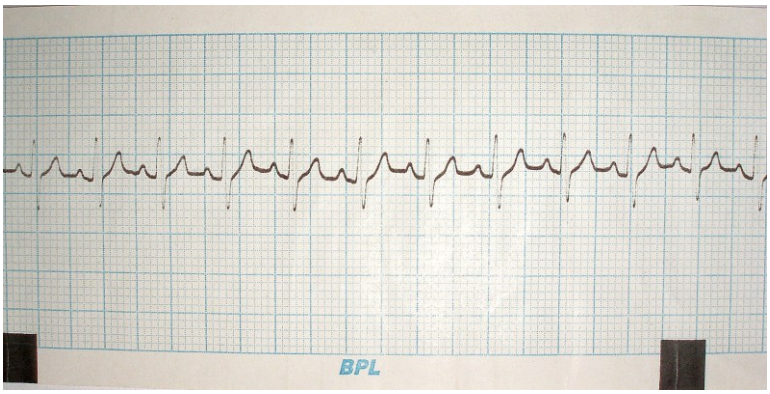
a. Ventricular pre – excitation case No. 7



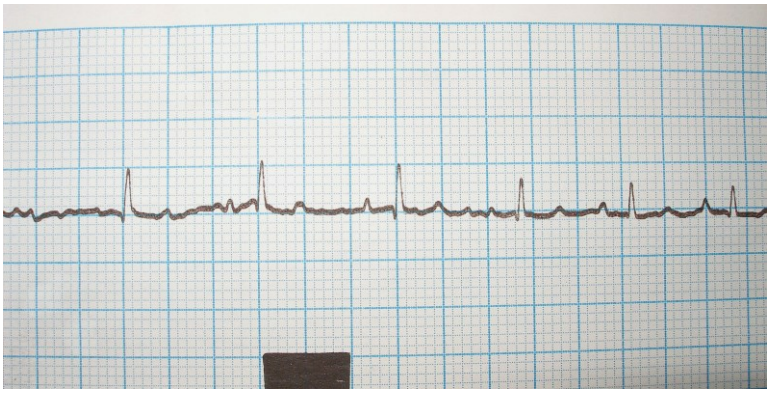
b. Ventricular Premature Complex case No. 8



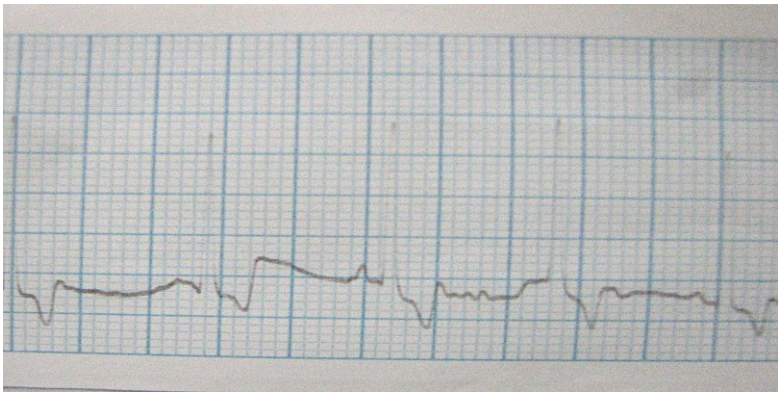
c. Atrial fibrillation case No. 3



d. Reduced R amplitude (ascites)

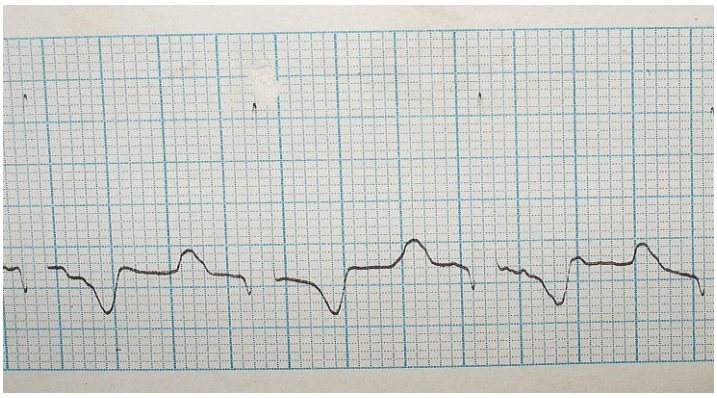


e. Reduced R amplitude (ascites)

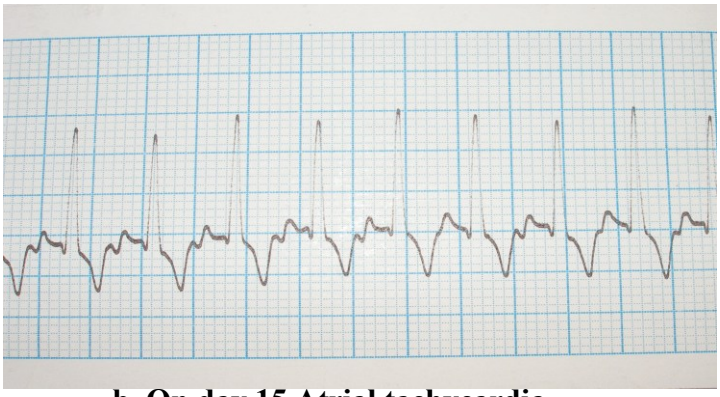


f. Electrical alternance (pericardial effusion)

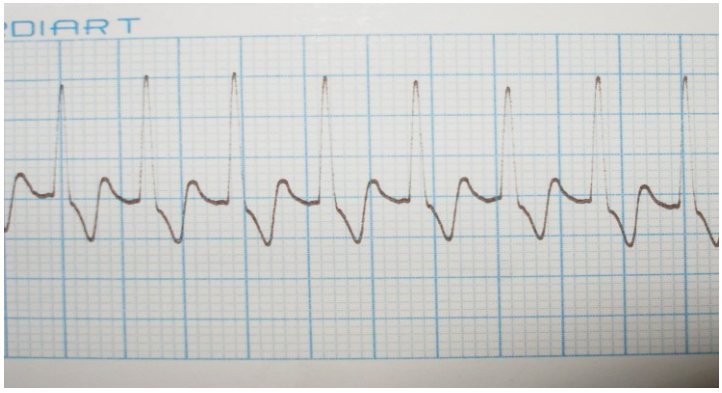
Plate 6. ECG changes of case No. 4 (Boxer) showing no response to treatment



a. On day 1



b. On day 15 Atrial tachycardia

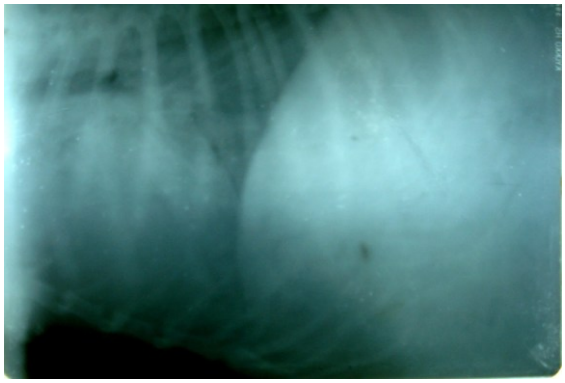


c. On day 30 Atrial tachycardia

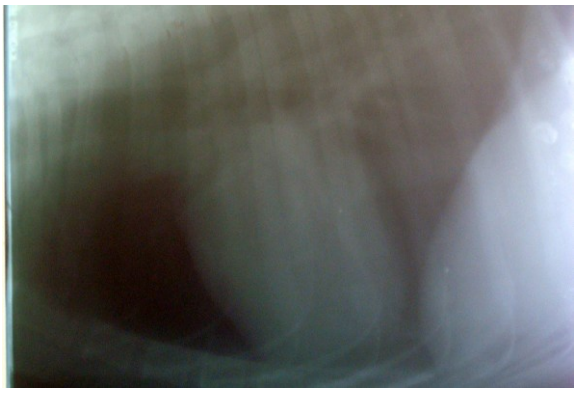
Table 5. Vertebral heart score of normal and dilated cardiomyopathic dogs

Parameter	Normal dogs	DCM dogs
Caudal vena cava (v)	0.75 ± 0.02	0.79 ± 0.03
Cardiac length (v)	5.24 ± 0.39	6.05 ± 0.46
Cardiac width (v)	4.46 ± 0.38	5.58 ± 0.40
VHS (v)	9.70 ± 0.67	11.50 ± 0.85

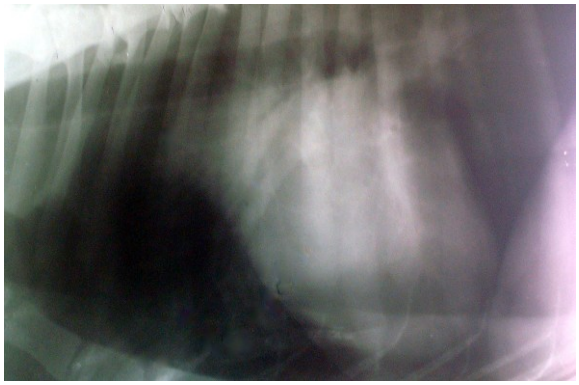
Plate 7. Skiagram of dilated cardiomyopathic dogs



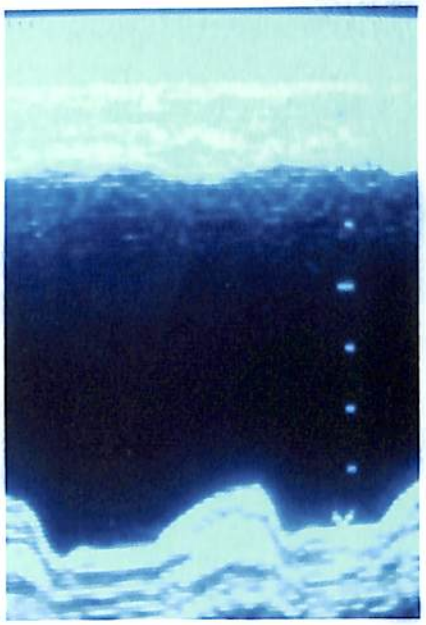
a. Cardiomegaly



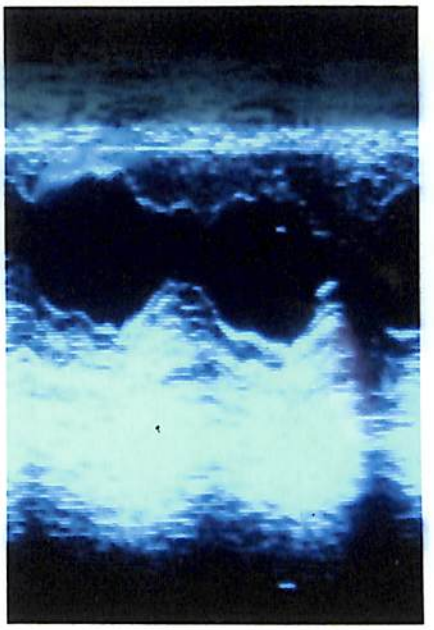
b. Cardiomegaly



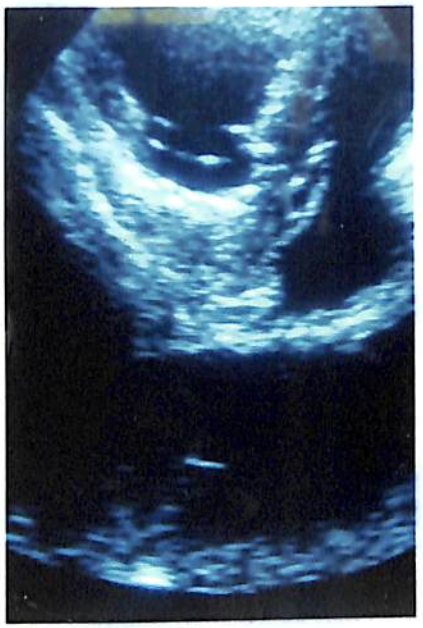
c. Pericardial effusion



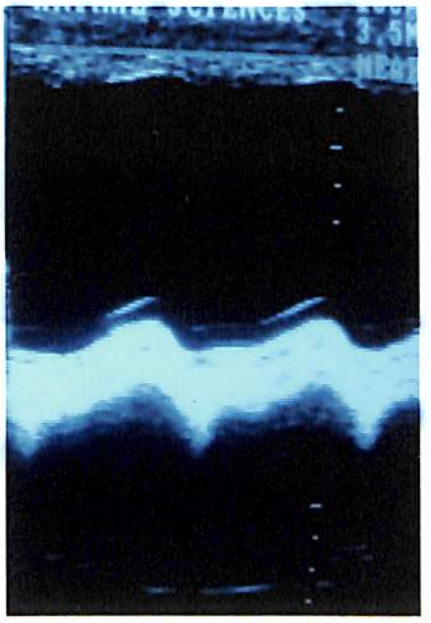
c



d



e



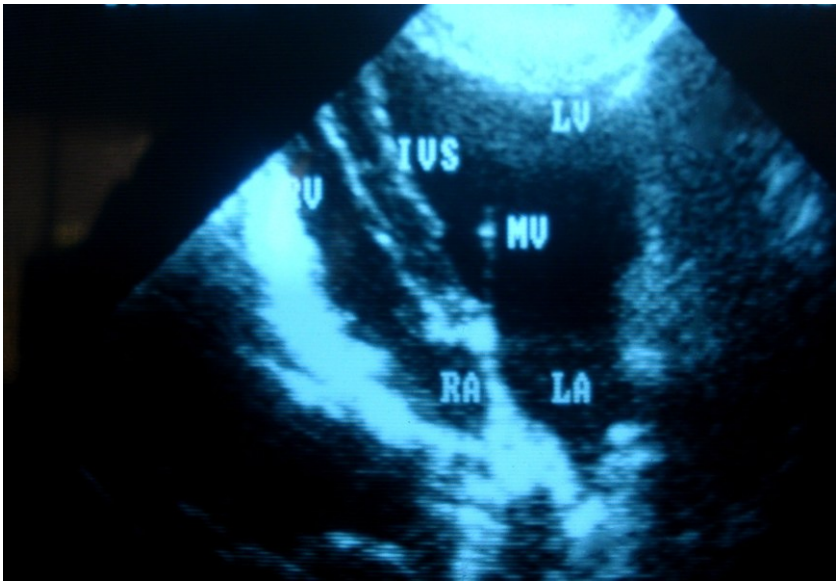
f

c. M- mode echocardiography showing reduced contraction
d. M – mode echocardiography showing irregular contractions
e. Apical view showing pericardial effusion
f. M- mode echocardiography showing pericardial effusion

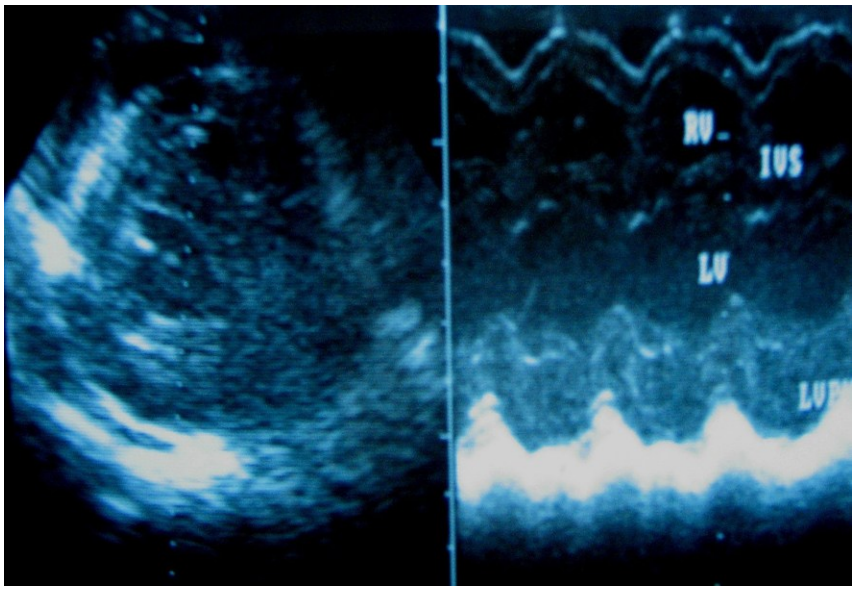
Table 6. Echocardiographic M - mode measurements of dilated cardiomyopathic dogs on day 1 and 30.

Observation period	LVED d (cm)	LVED s (cm)	FS (%)	EDV (ml)	ESV (ml)	EF (%)
Day 1	6.02 ± 0.50	4.84 ± 0.43	19.80 ± 1.71	214.58 ± 40.43	118.14 ± 21.99	43.43 ± 4.16
Day 30	5.29 ± 0.75	4.32 ± 0.78	19.93 ± 0.03	150.35 ± 49.33	100.23 ± 41.90	40.25 ± 0.06

Plate 8. Echocardiogram of dilated cardiomyopathic dogs



a. Apical four chamber view showing left ventricular dilatation



b. Ventricular short axis view and M- mode

end diastolic and systolic volumes were 214.58 ± 40.43 ml. and 118.14 ± 21.99 ml respectively. Ejection fraction was 43.43 ± 4.16 %.

Left ventricular dilatation was evident in all cases on day 30. Mean value of LVED d was 5.29 ± 0.75 cm and of LVED s was 4.32 ± 0.78 cm. Fractional shortening (FS) was 19.93 ± 0.03 %. Mean of end diastolic and systolic volumes were 150.35 ± 49.33 ml. and 100.23 ± 41.90 ml respectively. Ejection fraction was 40.25 ± 0.06 %. There was no significant difference in the M – mode measurements on day 30 when compared to day 1.

4.4.4. Clinical Pathology

4.4.4.1. *Haematology*

Results of haematological studies are presented in Table 7.

4.4.4.1.1. *Haemogram*

The mean values of total erythrocyte count, haemoglobin concentration and volume of packed red cells (VPRC) in normal dogs were 7.02 ± 0.46 millions/cu.mm, 14.03 ± 0.80 g % and 38.13 ± 2.89 % respectively. The corresponding values on diseased dogs on day 1 were 6.5 ± 0.93millions/cu.mm., 11.67 ± 1.59 g % and 32.61 ± 4.24 % respectively. Statistically significant ($p \leq 0.01$) reduction could be observed in the mean values of RBC, haemoglobin and VPRC when compared to the normal dogs (Fig. 3 and Fig.4).

On day 15 of treatment, mean values of RBC, haemoglobin concentration and VPRC were 4.66 ± 0.67 millions/cu.mm., 9.45 ± 1.63 g % and 28.45 ± 4.08% respectively. A statistically significant ($p \leq 0.05$ and $p \leq 0.01$) reduction could be observed in the mean values of RBC and haemoglobin on day 15 when compared to day 1.

Table 7. Haematological values of normal and dilated cardiomyopathic dogs on day 1, 15 and 30 of treatment

Parameters		Normal dogs	Diseased dogs		
			Day 1	Day 15	Day 30
RBC (millions/cu.mm)		7.02 ± 0.46^{A}	6.5 ± 0.93^{Ba*}	4.66 ± 0.67^{b*}	4.64 ± 1.70 ^{*b}
Hb (g %)		14.03 ± 0.80^{A}	11.67 ±1.59 ^{Ba*}	9.45 ± 1.63 ^{b**}	9.45 ± 1.60 ^{b*}
VPRC (%)		38.13 ± 2.89 ^{A}	32.61 ± 4.24 ^{B*}	28.45 ± 4.08	28.82 ± 4.27
TLC (per cu.mm)		13900 ± 516.40	15191.67± 3346.70	11983.33 ± 2351.80	11300 ± 1865.30
DC	N	77.17 ± 1.94	73.33 ± 9.59	76.33 ± 3.32	75.17 ± 2.54
	L	21.83 ± 4.58	23.50 ± 9.77	20 ± 2.49	21.5 ±2.23
	M	0	1.0 ± 0.82	0.83 ± 0.54	0.67 ± 0.49
	E	1.0 ± 0.33	2.17 ± 0.60	2.83 ± 0.95	2.67 ± 0.88

*Represents a significant difference ($p \leq 0.05$) compared to day 1
** Represents a highly significant difference ($p \leq 0.01$) compared to day 1
Means within the same row of the same parameters with different superscript differ.
A, B compared with control a, b compared with day 1 values

Fig. 3. Total erythrocyte count of normal and diseased dogs (DCM) on day 1, 15 and 30 of treatment

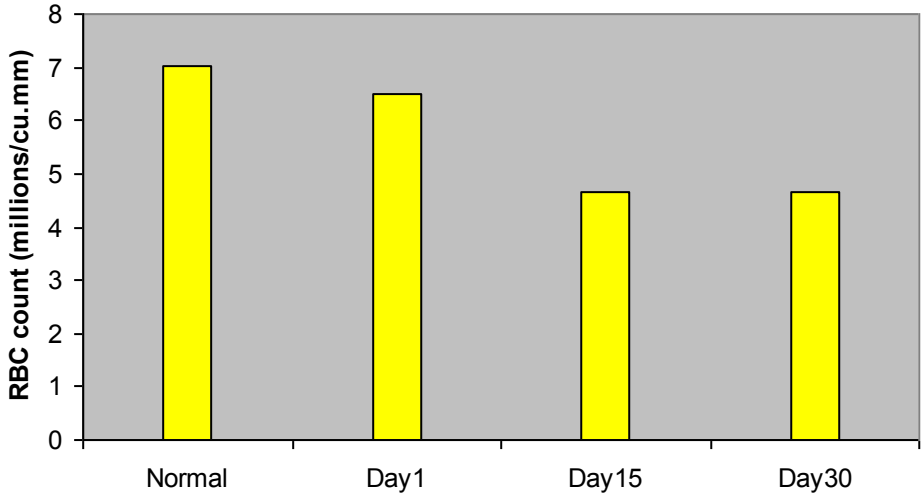
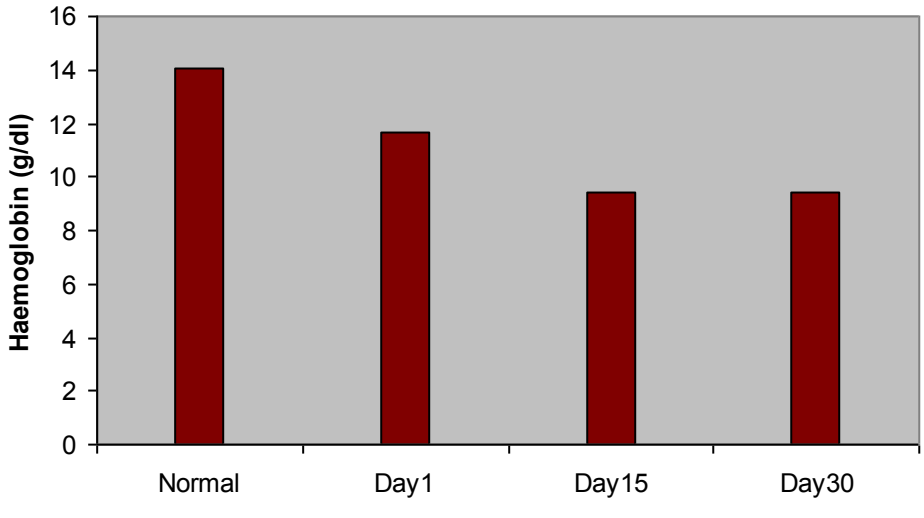


Fig. 4. Mean haemoglobin value of normal and diseased dogs (DCM) on day 1, 15 and 30 of treatment



On day 30, the mean values of RBC, haemoglobin and VPRC were 4.64 ± 1.70 millions/cu.mm., 9.45 ± 1.60 g % and 28.82 ± 4.27 % respectively. Mean value of RBC and haemoglobin on day 30 showed a significant ($p \leq 0.05$) reduction when compared to day 1 values.

4.4.4.1.2. *Leukogram*

Mean values of total leukocyte count (TLC) in normal dogs were 13,900 ± 516.40/cu.mm. The mean values of neutrophil, lymphocyte and monocyte and eosnophil in normal dogs were 77.17 ± 1.94, 21.83 ± 4.58, 0 and 1.00 ± 0.33 per cent respectively. The corresponding values of DCM dogs on day 1 were 15191.67 ± 3346.70/cu.mm., 73.33 ± 9.59, 23.50 ± 9.77, 1.00 ± 0.82 and 2.17 ± 0.60 per cent respectively.

Mean values of total leukocyte count, neutrophil, lymphocyte, monocyte and eosnophil were 11,983.33 ± 2351.80 /cu.mm., 76.33 ± 3.32, 20.00 ± 2.49, 0.83 ± 0.54 and 2.83 ± 0.95 per cent respectively on day 15 and 11,300 ± 1865.30/cu.mm., 75.17 ± 2.54, 21.5 ± 2.23, 0.67 ± 0.49 and 2.67 ± 0.88 per cent respectively on day 30. Statistical analysis did not reveal any abnormal change between normal dogs and affected animals on day 1, 15 and 30.

4.4.5. Biochemical Parameters

Serum biochemical values of normal and diseased dogs on day 1, 15 and 30 were presented in Table 8.

Mean values of creatinine, CPK, sodium and potassium of normal dogs were 0.88 ± 0.09 mg/dl, 38.30 ± 4.7 U/L, 138.50 ± 1.2 mEq/L and 4.10 ± 0.30mEq/L respectively.

Table 8. Serum creatinine, CPK, sodium and potassium control and dilated cardiomyopathic dogs on day 1, 15 and 30 of treatment

Parameters	Normal dogs	Diseased dogs		
		Day 1	Day 15	Day 30
Creatinine (mg/dl)	0.88 ± 0.09	1.08 ± 0.16	1.45 ± 0.27 [a]	2.19 ± 0.31 [*b]
CPK (U/L)	38.3 ± 4.70 [A]	230.83 ± 52.46 [B**]	267.50 ± 64.34 [a]	142.50 ± 55.14 [*b]
Sodium (mEq/L)	138.50 ± 1.20	142.83 ± 2.57	148.33 ± 2.97 [a]	142.67 ± 2.50 [*b]
Potassium (mEq/L)	4.1 ± 0.30	4.22 ± 0.23	4.73 ± 0.23	4.75 ± 0.24

* Represents a significant difference ($p \leq 0.05$) compared to day 1

** Represents a highly significant difference ($p \leq 0.01$) compared to day 1

Means within the same row of the same parameters with different superscript differ.

A, B compared with control a, b compared with day 1 values.

Fig. 5. Mean value of serum creatinine of normal and diseased (DCM) dogs on day 1, 15 and 30 of treatment

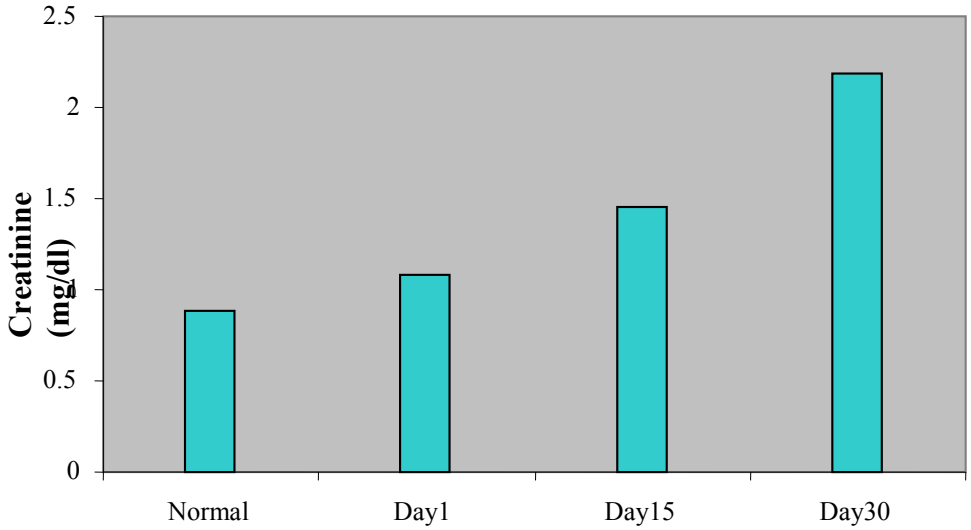


Fig. 6. Mean value of serum CPK of normal and diseased (DCM) dogs on day 1, 15 and 30 of treatment

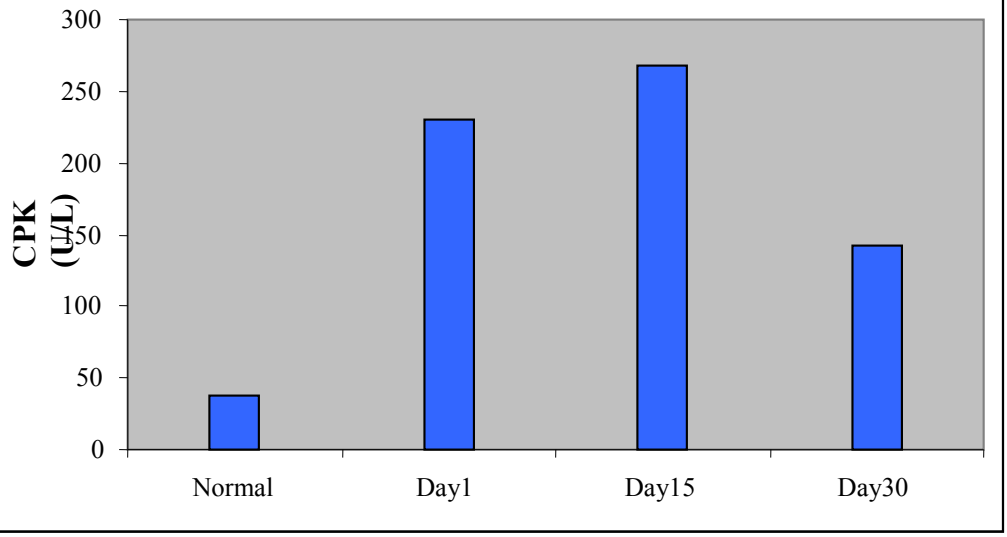
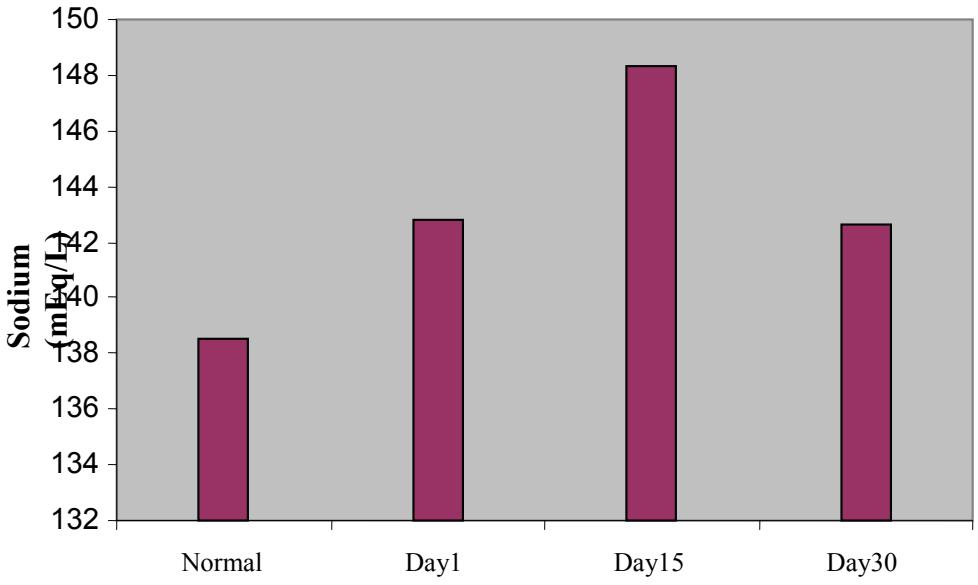


Fig. 7. Mean value of serum sodium of normal and diseased (DCM) dogs on day 1, 15 and 30 of treatment



Mean values of creatinine, CPK, sodium and potassium of DCM dogs on day 1 were 1.08 ± 0.16 mg/dl, 230.83 ± 52.46 U/L, 142.83 ± 2.57 mEq/L and 4.22 ± 0.23 mEq/L respectively (Fig 5, Fig. 6 and Fig. 7). Statistical analysis revealed significant increase in the CPK value ($p \leq 0.01$) when compared to normal dogs.

On day 15, the mean values of creatinine, CPK, sodium and potassium were 1.45 ± 0.27 mg/dl, 267.50 ± 64.34 U/L, 148.33 ± 2.97 mEq/L and 4.73 ± 0.23 mEq/L respectively. No statistically significant difference could be observed on day 15 values when compared to day 1.

On day 30, the mean values of creatinine, CPK, sodium and potassium were 2.19 ± 0.31 mg/dl, 142.50 ± 55.14 U/L, 142.67 ± 2.50 mEq/L and 4.75 ± 0.24mEq/L respectively. Statistical analysis revealed a significant ($p \leq 0.01$) increase in creatinine value on day 30 when compared to day 1. Creatine phosphokinase and sodium on day 30 showed statistically significant ($p \leq 0.01$) reduction when compared to day 15.

4.5. TREATMENT

All eight cases diagnosed of having DCM were utilized for treatment studies. enalapril @ 0.5 mg/kg body weight, valsartan @ 2 mg/kg body weight and lasilactone @ 2mg/kg body weight twice daily orally were given to all cases. During the treatment period case No. 8 died on third day and case No. 7 on 17^{th} day.

4.5.1. Response To Treatment

Clinical improvement was present in five cases. Clinical signs including anorexia, polydypsia, cough, dyspnoea, abdominal distension, exercise intolerance, oedema of the limbs and syncope were reduced in five cases except

case No.4. In case No.4 ascites was not reduced and no clinical improvement was shown.

Out of eight cases which were diagnosed of having DCM case No.8 was died on day 3 and case No.7 on day 17 due to congestive heart failure. Out of six cases five cases (87.5 %) are still surviving. Case No. 1 survived for a period of 7 months from the first day of treatment.

On day 15, appetite was improved in all cases except in case No. 7. Polydypsia was absent in all the cases. Ascites was reduced in four out of six cases. Frequency of cough was also reduced. Dyspnoea was reduced in five cases. Dyspnoea was still present in case No.6 and 7. There was no oedema of limbs in case No. 5 on 15^{th} day. Case No.7 died on day 17.

Electrocardiography revealed no significant change on day 15 and 30 when compared to day 1. Atrial fibrillation was present in case No. 3 on day 1 and absent on day 30. Atrial tachycardia developed in case No. 4 on day 15 which was having VPC on day 1.

Echocardiography revealed no significant change in the M – mode measurements except for a slight increase in the fractional shortening which was not stasistically significant.

A statistically significant reduction could be observed in the mean values of RBC and haemoglobin on day 15 when compared to day 1. Other parameters had no significant abnormality when compared to day 1.

On day 30, only one animal (case No.4) had ascites. Syncope was not reported in any of the cases on 15^{th} and 30^{th} day of review. Frequency of cough was reduced in three cases. One case (case No. 3) developed cough following

the treatment. Skin rashes were present following treatment in two cases (case No.3 and case No.6).

Mean value of RBC and haemoglobin on day 30 showed a significant reduction when compared to day 1. On day 30 a significant increase in creatinine value was present when compared to day 1. Creatine phosphokinase and sodium showed statistically significant reduction when compared to day 15.

4.5.2. Side Effects

One case (case No. 3) developed cough following the treatment. Skin rashes developed following treatment in two cases (case No.3 and case No.6). Anemia which was evidenced by reduction in mean values of RBC and haemoglobin developed following treatment. Atrial tachycardia developed in case No.4 on day 15 and day 30 of treatment.

Discussion

5. DISCUSSION

Dilated cardiomyopathy (DCM) characterised by chamber dilatation and myocardial systolic and diastolic dysfunction is one of the most common heart diseases in dogs. Dilated cardiomyopathy results in reduced cardiac output. Dilated cardiomyopathy can be classified into two broad categories: primary or idiopathic and secondary or specific DCM. Primary DCM refers that disease originated in the myocardium and that the cause and pathogenesis are unknown. Secondary or specific cardiomyopathies are associated with other systemic or metabolic diseases (Jacobs, 1996). Diagnosis of DCM requires active exclusion of other causes of dilated and hypokinetic heart. Stringent diagnosis of DCM requires all the following, left ventricular dilation, depressed systolic function and altered geometry of the left ventricle (increased sphericity).

Eight dogs presented with signs of cardiac problems and later confirmed as DCM by clinical, electrocardiographic, radiographic and echocardiographic examination and haematobiochemical assays were subjected for detailed treatment studies.

5.1 SIGNALMENT

5.1.1. Age

Dilated cardiomyopathy (DCM) was more commonly observed in the middle aged dogs. Age of affected dogs were ranged from 2 to 13 years with a mean of 6 ± 1.25 years which was similar to the observations of Martin *et al.* (2008) who reported that mean age of dogs affected with DCM was 80 months with a range of 3 months to 14.8 years. Similar observation was made by Jordan *et al.* (2007).

5.1.2. Sex

In the present study both males and females were equally affected. There were four females (50 %) and four males (50 %). Similar observation was made by Brownlie and Cobb (1999) in which out of 39 Irish wolfhounds diagnosed for DCM, 20 were males and 19 were females. Male predominance was reported in most of the studies (Petric *et al.,* 2002, Jordan *et al.,* 2007 and Martin *et al.*, 2008). Lack of male predominance might be due to less number of cases in the present study.

5.1.3. Breed

The breed wise prevalence of DCM indicated that Labrador Retriever was more prone to dilated cardiomyopathy (37.5 %) followed by Boxer (25 %), German Shepherd Dog (12.5 %), Spitz (12.5 %) and Non-descript (12.5 %). This was similar to the finding of Martin *et al.* (2008). Out of 35 different dog breeds diagnosed for DCM nearly all were purebred dogs, except four cross bred dogs. The author also reported increased prevalence of DCM in Boxer (53), German Shepherd (24), and Labrador Retriever (20) out of total 369 dogs. Large breeds (more than 15kg) were more likely to have DCM. Similar observation was made by (Ristic, 2004). Increased prevalence of DCM in Labrador Retriever in the present study might be due to their higher number in the population and larger size.

5.2. CLINICAL SIGNS

Major clinical signs in the present study included anorexia, polydypsia, cough, dyspnoea, abdominal distension, exercise intolerance, oedema of the limbs and syncope. Thomas (1987), Meurs *et al.* (2001), Petric *et al.* (2002), and

McEwan *et al.* (2003) made similar observations. Signs suggestive of cardiac disease could be classified into three broad categories which included exercise intolerance, respiratory signs and ascites, pericardial effusion and occasionally peripheral oedema, as suggested by Ristic (2004).

Cough was present in 37.5 % of cases and this might be due to left atrial enlargement and physical bronchial compression as suggested by McEwan (2000b). Ascites and oedema of limbs were present in 75 % and 25 % of cases respectively which was indicative of right sided heart failure. Clinical signs in DCM might be associated with forward failure, left side heart failure or right side heart failure (McEwan, 2000b). Exercise intolerance and dyspnoea were present in all cases which were due to forward failure due to reduced cardiac output. Anorexia and polydypsia were present in 75 % and 50 % of the cases respectively. Polydypsia and anorexia were reported by McEwan *et al*. (2003) in DCM. Syncope occurred in 25 % of cases in the present study. Cardiac disease was the most common cause of syncope in small animals and arrhythmia represent one of the most frequently reported etiologies. Atrial fibrillation, VPC and ventricular pre-excitation were common arrhythmias causing syncope in the present study. These arrhythmias might be responsible for syncope as suggested by Billen and Israel (2005).

5.3. CLINICAL EXAMINATION

Clinical data on day 1, 15 and 30 were within the normal range. Femoral pulse was weak in 75 % of the cases on day 1. There was no significant difference on day 15 and day 30 as compared to day 1.

In the present study rectal temperature was normal with weak pulse that was apparent in severe heart failure associated with low stroke volume as suggested by Abbott (1998). Irregular pulse was present in 37.5 % of the cases which was due

to arrhythmia which resulted in varying pulse strength, rate and pulse deficit . Similar observation was made by Petric *et al.* (2002). In many cases of DCM, there might be no abnormalities on clinical examination of dogs, as stated by McEwan (2000a). Similar finding was made by Martin *et al.* (2008) in which the author reported weak pulse, pale mucosa and no murmers heard since there was no mitral regurgitation.

Thoracic auscultation of affected dogs revealed tachycardia and pulmonary crackles. Pulse deficit was also detected. Pulmonary crackles were due to pulmanory oedema as suggested by Thomas (1987). Left side heart failure caused signs of pulmonary affection and pulmonary congestion (Ristic, 2004).

Positive hepatojugular reflex and venous distension were present in 75 % of the cases. Positive hepatojugular reflex and venous distension were consistent with progressive right sided heart failure (Allen and Mackin, 2001). Biventricular heart failure was present in advanced cases of DCM (McEwan, 2000b).

5.4 DIAGNOSIS

5.4.1. Electrocardiography

Mean heart rate on day 1 was 150.5 ± 19.36 beats/min. Heart rate varied with class of heart failure. This was similar to the finding of Martin *et al*. (2008) who observed that in ISACHC 1 class heart rate were 152 beats /min, in ISACHC 2 class mean heart rate were 163 beats /min. and in ISACHC 3 class heart rate was, 176 beats /min. Resting heart rate was increased above 140 beats /min. in DCM (Ristic, 2004).

Sinus rhythm was present in all eight cases. Two cases had sinus tachycardia (case No. 1 and case No. 7). Sinus tachycardia might be due to increased epinephrine level and increased SA nodal activation which was a

consistent feature of DCM as observed by Menaut *et al.* (2005) and Nakata *et al.* (2005). Atrial fibrillation, VPC, ventricular tachycardia and ventricular pre excitation were the major arrhythmias encountered in the present study. Similar observations were made by Thomas (1987), Brownlie and Cobb (1999), Vollmar (2000), Meurs *et al.* (2001), Billen and Israel (2005), Menaut *et al.* (2005) and Martin *et al.* (2008). Ventricular premature complexes (VPC) were present in case No. 4 in the present study which was a Boxer and VPC was the most important abnormality in Boxer cardiomyopathy (Meurs, 2005).

Ventricular pre-excitation was present in case No. 7. Present finding was concordant with the finding of Keating *et al.* (2003). Ventricular pre-excitation caused tachyarrhythmias which might be life threatening and was characterized by abnormally short PR interval and paroxysms of tachycardia or atrial fibrillation. Tachycardia was one of the causes of myocardial dysfunction in dogs. In the present study PR interval in case No.7 was abnormally short.

Mean values of P wave amplitude and duration, PR segment duration, amplitude of R wave, duration of QRS complex, duration of ST segment and T wave amplitude and duration on day 1 were 0.15 ± 0.05 mv, 0.05 ± 0.01 sec, 0.10 ± 0.03 sec, 1.4 ± 0.44 mv, 0.05 ± 0.01 sec, 0.09 ± 0.02 sec, 0.28 ± 0.06 mv and 0.06 ± 0.01 sec respectively. Except for duration of P wave all values were within the normal range (Bolton, 1975). Duration of P wave was above normal range in the present study which was indicative of left atrial enlargement secondary to left ventricular dilation and subsequent mild mitral regurgitation causing atrial enlargement. Atrial fibrillation (AF) occurred in severe atrial enlargement which was common in idiopathic dilated cardiomyopathy due to valvular insufficiency in severe cases. There was no increase in the amplitude or duration of QRS which was most common ECG finding in DCM. This might be due to ascites which was present in 75 % of the cases and pericardial effusion which was present in 12.5 %

of the cases. Ascites and pericardial effusion caused reduced amplitude of QRS complex. Excessive accumulation of ascitic fluid reduced electrical conductivity to the body surface which coincided with opinion of Pandian (2005).

Mean heart rate on day 15 was 176.14 ± 28.38 beats/min. Mean heart rate was increased due to development of atrial tachycardia in case No.4 and increase in the heart rate of case No.7. Both cases did not respond to the treatment. Sinus rhythm was present in seven cases on day 15. Sinus tachycardia, AF, atrial tachycardia and VPC were the most common arrhythmias detected in the present study. Atrial tachycardia was secondary to atrial enlargement and stretch. Severe DCM might have caused valvular insufficiency and regurgitation causing atrial enlargement leading to atrial tachycardia as explained by Bolton (1975). Ventricular Premature Complexes were not detected on day 15. Ventricular pre excitation was present in case No. 7 on day 15 which died on day 17.

On day 30, mean heart rate was 164.67 ± 30.36 beats/min. Mean heart rate was increased due to development of atrial tachycardia in case No. 4. Sinus rhythm was present in all eight cases. Both ACE-inhibitors and angiotensin receptor blockers appeared to reduce AF and prevented AF related complications. Angiotensin conversion enzyme inhibitors and angiotensin receptor blockers improved left ventricular haemodynamics and reduced atrial stretch, suppressed angiotensin-II-induced fibrosis and directly modulated ion-channel function (Ehrlich *et al.*, 2006).

Mean values of P wave amplitude and duration, PR segment duration, amplitude of R wave, duration of QRS complex, duration of ST segment and T wave amplitude and duration on day 15 were 0.15 ± 0.04 mv, 0.05 ± 0.01 sec, 0.06 ± 0.01 sec, 1.28 ± 0.38 mv, 0.04 ± 0.00 sec, 0.07 ± 0.02 sec, 0.28 ± 0.06 mv and 0.05 ± 0.01 sec respectively. Statistically no significant differences could be observed in the measurements of ECG values on day 15 and day 30 when

compared to day 1. Slight decrease in the PR duration observed in the ECG might be due to increased heart rate (Bolton, 1975). There was not much variation in the ECG measurements on day 15 and day 30 which showed that ECG could be used only for initial diagnosis of cardiac problems only and not for monitoring of drug responses.

5.4.2. Radiography

On radiographic examination generalised cardiomegaly was present in 75 % of the cases. All cases had tracheal elevation. Pulmonary congestion was observed in 75 % of the cases. Pericardial effusion was present in 12.5 % of the cases. Similar observations were made by Petric *et al.* (2002).

Mean cardiac length and width of diseased dogs were 6.05 ± 0.46 vertebrae (v) and 5.58 ± 0.40 v respectively. Vertebral heart sizes ranged from 8.7 v to 14.4v with a mean value of 11.5 ± 0.85 v. Vertebral size of caudal vena cavae ranged from 0.71 v to 0.88 v with a mean value of 0.79 ± 0.03 v. Vertebral heart score above 9.7 ± 0.67 vertebrae (v) was indicative of cardiomegaly and vertebral size of caudal vena cavae more than 0.75 ± 0.1 v was indicative of venous congestion as suggested by Buchanan and Bucheler (1995). In the present study two cases had vertebral heart score within the normal range. Therefore, it could be concluded that cardiac illnesses causing cardiomegaly could be diagnosed using radiography of lateral thorax and VHS in cases with insufficient diagnostic tools. On the other hand, normal heart size does not always mean that there is no heart disease. Because of these reasons determination of VHS only is not sufficient for diagnosing heart disease as explained by Lanber *et al.* (2005).

5.4.3. Echocardiography

Echocardiographic evaluation of four chamber view of dogs affected with DCM revealed left ventricular dilatation in all cases. Similar observations were made by Calvert *et al.* (1997) and Tidholm *et al.* (1998). Pericardial effusion which was detected radiographically was confirmed by echocardiography as an anechoic area in pericardial space in cardiac four chamber view.

M–mode measurements showed reduced myocardial contractility in all cases. Mean value of LVED d was 6.02 ± 0.50 cm and of LVED s was 4.84 ± 0.43 cm which were above the normal values as observed by Calvert *et al.* (1997) and Calvert and Wall (2001a). Mean of end diastolic volume was 214.58 ± 40.43 ml and of end systolic volume was 118.14 ± 21.99 ml. Fractional shortening (FS) had a mean value of 19.80 ± 1.71 % which was less than the normal value of 25%. Dilated cardiomyopathy was primary myocardial disease characterised by reduced myocardial contractility. Initially end systolic diameter and volume increased due to depressed myocardial contractility leading to reduced fractional shortening. As a compensatory mechanism eccentric hypertrophy of heart muscle occurred secondary to renal fluid and salt retention to increase diastolic diameter and volume. But as the contractility is further reduced stroke volume failed to be maintained and heart got enlarged (Calvert, 2001). Ejection fraction had a mean value of 43.43 ± 4.16 %. Ejection fraction was within the normal range. Teichholz formula was used to calculate ejection fraction which was a corrected cube formula that was most accurate for human beings and generally inaccurate in dogs especially in enlarged heart in which left ventricular mass varied as ventricle became globoid which was similar to the suggestion of Kienle and Thomas (2002).

On day 30, there was no significant change in the appearance of four chamber view of heart and also M – mode measurements. This might be due to

short period of observation because changes in ventricular size or function from baseline to 1 month did not predict any subsequent cardiovascular outcomes and a period of nearly 6 months were needed to show considerable improvement **(**Crespo *et al.,* 2008**).**

5.4.4. Haematology

On the first day of treatment mean values of RBC (6.5 ± 0.93millions/cu.mm) and haemoglobin (11.67 ± 1.59 g/dl) were significantly reduced ($p \leq 0.05$ and $p \leq 0.01$ respectively) when compared to the normal dogs. Volume of packed red cells (32.61 ± 4.24 %) was towards the lower limit. Normal to slightly reduced haemocrit values were obtained in DCM and this might be due to fluid retention secondary to heart failure caused by renin angiotensin mechanism causing hemodilution and reduced haemocrit (Martin *et al.*, 2008). Total leukocyte count (15191.67 ± 3346.70/cu.mm) was slightly increased (Guglielmini and Civitella, 2004). Percentage of neutrophil, lymphocyte, monocyte and eosnophil were 73.33 ± 9.59, 23.50 ± 9.77, 1 ± 0.82 and 2.17 ± 0.60 respectively. Slightly increased total leukocyte count along with increased neutrophil count was suggestive of a stress leukogram which was similar to the finding of Abbott (1998), Guglielmini and Civitella (2004) and Ristic (2004).

Mean values of RBC and haemoglobin showed a statistically significant reduction on day 15 ($p \leq 0.05$) and day 30 ($p \leq 0.01$ and $p \leq 0.05$ respectively) when compared to day 1 values. Percentage of reduction in the values were around 28 % which was similar to the finding of Cole *et al.* (2000) who reported 12 to 20 % reduction in haematocrit value in angiotensin converting enzyme deficient mice suggesting role of angiotensin in erythropoesis. Both enalapril and valsartan caused angiotensin deficiency which could be a reason for anemia. Mechanism of development of anemia was uncertain and the authors ruled out

hemolysis, bonemarrow suppression and renal failure. There was no significant difference in the hemodynamic characteristics of the groups receiving enalapril and valsartan alone (Kasama *et al.*, 2003) which showed angiotensin could have direct effect on erythropoesis.

No significant difference could be obtained in total and differential leukocyte count on day 15 and 30 when compared to day 1 values which was according to the finding of Cole *et al.* (2000).

5.4.5. Biochemical Parameters

Mild elevation of creatinine level was observed on day 1 when compared to normal dogs which was not statistically significant. Similar observation was made by Lombard (1984) who reported DCM caused reduced cardiac output and activation of renin – angiotensin mechanism resulting in reduced renal blood flow and mild elevation of creatinine.

Creatine phosphokinase had a mean value of 230.83 ± 52.46 U/L on day 1 which was elevated when compared to normal dogs. Creatine phosphokinase activities were elevated in cardiomyopathies due to reduced coronary perfusion (Cardinet III, 1997).

Mean values of sodium and potassium were 142.83 ± 2.57 mEq/L and 4.22 ± 0.23 mEq/L respectively on day 1. Sodium was within the normal range but towards the lower limit which was in accordance with the finding of Deicas *et al.* (1995). Patients with moderate to severe CHF experienced a significantly reduced renal blood flow and enhanced tubular reabsorption of sodium and free water. Consequent activation of renin – angiotensin – aldosterone mechanism led to mild hyponatrimia. Angiotensin II stimulated thirst and central release of arginine vasopressin which acted directly on the distal tubule and collecting duct to retain water causing excessive water retension. In addition to the fall in renal

blood flow and glomerular filtration rate, number of other yet undefined intrarenal mechanisms also played a role in the hyponatremia of CHF causing a dilutional state with a net reduction in serum sodium concentration in the face of a marked increase in total body sodium. Potassium was within the normal range as suggested by Gavaghan and Kittleson (1997).

On day 15 mean values of creatinine, CPK, sodium and potassium were 1.45 ± 0.27 mg/dl, 267.50 ± 64.34 U/L, 148.33 ± 2.97 mEq/L and 4.73 ± 0.23 mEq/L respectively. Creatinine, sodium and potassium were within the normal range as suggested by Gavaghan and Kettleson (1997). No significant difference could be detected in day 15 values when compared to day 1 values.

Persistant elevation of CPK might be due to reduced coronary perfusion and active myocardial necrosis which was a consistent feature of DCM (Cardinet III, 1997). Nonsignificant increase in potassium might be due to potassium sparing diuretic spironolactone in the treatment schedule (Ware and Keene, 2000). There was a mild elevation in the mean value of sodium on day 15 that might be due to inhibition of angiotensin which was responsible for sodium dilution.

On day 30 mean values of creatinine, CPK, sodium and potassium were 2.19 ± 0.31 mg/dl, 142.50 ± 55.14 U/L, 142.67 ± 2.50 mEq/L and 4.75 ± 0.24 mEq/L respectively. Significant increase for creatinine value was observed on day 30 when compared to day 1 value. According to, Eric *et al.* (1995) older age, diuretic therapy, and diabetes were associated with decreased renal function in enalapril therapy. This might be a cause for significant increase in creatinine concentration on day 30.

Significant reduction ($p \leq 0.05$) in the CPK value might be due to the action of enalapril that improved transmural myocardial perfusion at rest and after chronotropic stress and restored impaired subendocardial coronary flow and

vasodilator reserve in DCM. The effects of enalapril were bradykinin mediated and nitric oxide dependent and were not recapitulated by angiotensin receptor blockers (Nikolaidis *et al.*, 2002). These data suggested the beneficial effects of ACE inhibitors on the coronary circulation in DCM that are not shared by AT_1 receptor antagonists. Following diuretic therapy there was loss of sodium ions which might be responsible for the significant reduction ($p \leq 0.05$) in sodium level on day 30 when compared to day 15 value (Kittleson, 2002).

5.5. TREATMENT

All eight cases diagnosed of having DCM were utilized for treatment studies. Enalapril @ 0.5 mg/kg body weight, valsartan @ 2 mg/ kg body weight and lasilactone @ 2mg/ kg body weight twice daily orally were given to all the cases. During the treatment period Case No. 8 died on third day and case No. 7 on 17th day.

5.5.1. Response To Treatment

Clinical improvement was present in five cases. Clinical signs including anorexia, polydypsia, cough, dyspnoea, abdominal distension, exercise intolerance, oedema of the limbs and syncope were reduced in five cases except case No.4. In case No.4 ascites was not reduced and no clinical improvement was shown.

On day 15, anorexia was present in only one case (case No.7). Polydypsia was absent in all the cases. Ascites was reduced in four out of six cases. Frequency of cough was also reduced. Dyspnoea was reduced in five cases. Dyspnoea was still present in case No.6 and 7. There was no oedema of limbs in case No. 5 on 15th day. The addition of valsartan to an ACE inhibitor and loop diuretic improved cardiac sympathetic nerve activity, left ventricular function,

and symptoms in 16 human patients with reduced ejection fraction (Kasama *et al*., 2003).

There was clinical improvement in all cases except case No. 4 and case No. 7. Case No. 4 was a Boxer and according to Meurs (2005) there was no evidence that any treatment will significantly alter the outcome for Boxer dogs with DCM and in Boxer cardiomyopathy was more often an electrical conduction abnormality than myocardial failure and so Boxer cardiomyopathy represented a different clinical entity and recently called as arrhythmogenic right ventricular cardiomyopathy.

In case No. 7 there was no clinical improvement and animal died on day 17. Supraventricular tachycardia and tachycardia-induced cardiomyopathy might be responsible for death of the patient in the present study. Similar observation was made by Foster *et al*. (2006) in which the author reported the presence of an accessory pathway connecting the right atrium to the right ventricle by electrophysiological studies and confirmed the diagnosis of orthodromic atrioventricular reciprocating tachycardia. Radiofrequency catheter led to ablation of the accessory pathway resulting in permanent resolution of the supraventricular tachycardia and the dog had no further signs of cardiac disease. The successful treatment of this condition highlighted the importance of differentiating tachycardia-induced cardiomyopathy from idiopathic dilated cardiomyopathy. In the present study treatment of dilated cardiomyopathy was adopted which was not successful in tachycardia induced DCM as reported by Foster *et al.* (2006).

On day 30, only one animal (case No.4) had ascites. Case No.4 was a Boxer which did not respond to the treatment adopted. Syncope was not reported in any of the cases on 15^{th} and 30^{th} day of review. The treatments might have improved circulation and myocardial function and reduced arrhythmia which were the causes of syncope (Billen and Israel, 2005). Frequency of cough was reduced in

three cases. One case (case No. 3) developed cough following the treatment. Skin rashes were present following treatment in two cases (case No.3 and case No.6) which were considered as the side effects of enalapril treatment (Kumar *et al.*, 2000).

Out of eight cases which were diagnosed of having DCM case No.8 died on day three and case No.7 on day 17 due to congestive heart failure. Out of six cases five cases are still surviving. Case No. 1 survived for a period of 7 months from the first day of treatment.

5.5.2. Side Effects

One case (case No. 3) developed cough following the treatment. Skin rashes developed following treatment in two cases (case No.3 and case No.6). Anemia which was evidenced by reduction in mean values of RBC and haemoglobin developed following treatment. The side effects of ACE inhibitors were first-dose hypotension, dry cough, acute renal failure, angioneurotic edema, hyperkalemia, skin rashes, fetopathic potential (oligohydramnios, fetal growth retardation, and fetal death may be due in part to fetal hypotension), proteinuria, dysgeusia, neutropenia, glycosuria, and hepatotoxicity. Angiotensin receptor blockers had less side effects and production of dry cough been reduced (Kumar *et al.*, 2000).

Based on the above studies, it could be opined that

1. Diagnosis of DCM requires a combination of clinical examination, electrocardiography, echocardiography, radiography and haematobiochemical studies.

2. Fractional shortening is more significant indicator of cardiac function than ejection fraction in dogs.

3. A combination of enalapril, valsartan and lasilactone could be used for treating DCM and the treatments improve clinical signs and prolong the survival in dogs.

4. Along with the above treatment haematinics also should be added so that anaemia can be counteracted.

Summary

6. SUMMARY

Dogs presented with signs of cardiac problems formed the material for study. All cases were subjected to detailed clinical examination, electrocardiography, radiography, echocardiography and haemato - biochemical assays. According to the test results and findings, a total of eight cases with dilated cardiomyopathy (DCM) were selected and utilised for further treatment studies.

Dilated cardiomyopathy was more commonly observed in middle aged dogs. Age of affected dogs ranged from 2 to 13 years with a mean of 6 ± 1.25 years. Sex wise prevalence of DCM in dogs revealed that both males and females were equally affected. The breed wise distribution of DCM indicated that Labrador Retriever was more prone to dilated cardiomyopathy (37.5 %) followed by Boxer (25 %), German Shepherd Dog(12.5 %), Spitz (12.5 %) and Non - descript (12.5 %).

Major clinical signs included anorexia, polydypsia, cough, dyspnoea, abdominal distension, exercise intolerance, oedema of the limbs and syncope. Exercise intolerance and dyspnoea were present in all cases. Other symptoms associated with DCM included cough (37.5 %), ascites (75 %), anorexia (75 %), polydypsia (50 %), syncope (25 %) and oedema of hind limbs (25 %).

Mean temperature, pulse and respiration were within the normal range. Irregular pulse was present in 37.5 % of the cases on the day of admission. Femoral pulse was weak in 75 % of the cases. Pale mucous membrane was seen in 25 % of the cases. Thoracic auscultation revealed tachycardia (25 %) and pulmonary crackles (75 %). Pulse deficit was present in 50 % of the cases. Ascites was confirmed by tactile percussion and later by ultrasonography in 75 %

of the cases. Positive hepato-jugular reflex and venous distension were present in 75 % of the cases which were features of right sided heart failure.

Mean heart rate was within the normal range. Sinus tachycardia (25 %), atrial fibrillation (12.5 %) and VPC (25 %) were the most common arrhythmias encountered in ECG. Ventricular pre-excitation was present in 12.5 % of the cases. Mean heart rates were increased on day 15 and decreased on day 30. Atrial fibrillation and ventricular premature complexes were absent on day 15 and day 30. Atrial tachycardia was present in 12.5 % of the cases on day 15 and day 30.

Mean values of P wave amplitude and duration, duration of PR segment, amplitude of R wave, duration of QRS complex, duration of ST segment and T wave amplitude and duration on day 1 were 0.15 ± 0.05 mv, 0.05 ± 0.01 sec, 0.10 ± 0.03 sec, 1.4 ± 0.44 mv, 0.05 ± 0.01 sec, 0.09 ± 0.02 sec, 0.28 ± 0.06 mv and 0.06 ± 0.01 respectively. All the ECG measurements were within the normal range except for a slight increase in the P wave duration indicating left atrial enlargement. Statistically no significant differences could be observed in the measurements of ECG values on day 15 and 30 when compared to day 1 which indicate that eletrocardiography could be used for initial diagnosis of cardiac problems and not for monitoring drug response.

Radiographic examination revealed generalised cardiomegaly (75 %), tracheal elevation (100 %), pulmonary congestion (75 %) and pericardial effusion (12.5 %). Vertebral heart score was calculated in all cases. Mean cardiac length was 6.05 ± 0.46 v and mean cardiac width was 5.58 ± 0.40 v. Vertebral heart sizes ranged from 8.7 to 14.4 and mean value was 11.5 ± 0.85 v. Vertebral size of caudal vena cavae ranged from 0.71 to 0.88 v with a mean value of 0.79 ± 0.03 v. All the values were above the normal range indicating cardiomegaly.

Echocardiography revealed cardiac dilatation in all cases. Left ventricular dilatation was evident in all cases in cardiac four chamber view. Pericardial effusion was present in 12.5 % of the cases.

M–mode measurements showed reduced myocardial contractility in all cases. Mean value of LVED d was 6.02 ± 0.50 cm and of LVED s was 4.84 ± 0.43 cm. Fractional shortening (FS) had a mean value of 19.80 ± 1.71 %. Mean of end diastolic and end systolic volumes were 214.58 ± 40.43 ml. and 118.14 ± 21.99 ml respectively with ejection fraction of 43.43 ± 4.16 %. On day 30 mean value of LVED d was 5.29 ± 0.75 cm and of LVED s was 4.32 ± 0.78 cm. Fractional shortening (FS) was 19.93 ± 0.03 %. Mean of end diastolic and systolic volumes were 150.35 ± 49.33 ml. and 100.23 ± 41.90 ml respectively. Ejection fraction was 40.25 ± 0.06 %. There was no significant difference in the M – mode measurements on day 30 when compared to day 1 which indicated the treatment caused no significant alterations on the structure of heart.

The mean values of total erythrocyte count, haemaglobin and volume of packed red cells reduced in DCM dogs on day 1 when compared to normal dogs. A statistically significant reduction was observed in the mean values of RBC and haemoglobin on day 15 and day 30 when compared to day 1. Anaemia might be caused by haemodilution effect due to fluid retension secondary to the activation of renin – angiotensin – aldosterone system.

Mild leukocytosis with neutrophilia was suggestive of stress leukogram. Statistical analysis did not reveal any abnormal change between normal dogs and affected animals on day 1, 15 and day 30.

There was elevation of CPK value on day 1 when compared to the normal dogs which might be due to the cardiac muscle damage occurring in DCM.

Mean values of creatinine, sodium and potassium were within the normal range on day 1. No statistically significant difference could be detected in day 15 values when compared to day 1. Statistical analysis revealed a significant increase in creatinine value of day 30 when compared to day 1. Pre renal azotemia associated with hypoperfusion of kidney due to reduced cardiac output and activation of renin – angiotensin – aldosterone system might be responsible for mild elevation of creatinine. Creatine phosphokinase and sodium on day 30 showed statistically significant reduction when compared to day 15 which might be due to improved coronary circulation and use of diuretics respectively.

All eight cases diagnosed of having DCM were treated using enalapril @ 0.5 mg/kg body weight bid, valsartan @ 2 mg/kg body weight bid and lasilactone @ 2mg/kg body weight bid orally.

Clinical improvement was present in five cases. Clinical signs including anorexia, polydypsia, cough, dyspnoea, abdominal distension, exercise intolerance, oedema of the limbs and syncope were reduced in five cases except case No.4. In case No.4 ascites was not reduced and no clinical improvement was shown.

Out of eight cases which were diagnosed of having DCM case No.8 died on day 3 and case No.7 on day 17 due to congestive heart failure. Out of six cases five cases (87.5 %) are still surviving. Case No. 1 survived for a period of 7 months from the first day of treatment.

On day 30, only one animal (case No.4) had ascites. Syncope was not reported in any of the cases on 15^{th} and 30^{th} day of review. Frequency of cough was reduced in three cases. One case (case No. 3) developed cough following the treatment. Skin rashes were present following treatment in two cases (case No.3 and case No.6).

Anemia which was evidenced by reduction in mean values of RBC and haemoglobin was developed following treatment. Atrial tachycardia was developed in case No.4 on day 15 and day 30 of treatment.

Based on the above studies, it could be opined that

1. Diagnosis of DCM requires a combination of clinical examination, electrocardiography, echocardiography, radiography and haematobiochemical estimates.

2. Fractional shortening is more significant indicator of cardiac function than ejection fraction in dogs.

3. A combination of enalapril, valsartan and lasilactone could be used for treating DCM and the treatment improves clinical signs and prolongs the survival in dogs.

4. Along with the treatment specific for DCM supportives like haematinics also should be added so that anaemia can be counteracted.

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CLINICAL EVALUATION AND MANAGEMENT OF DILATED CARDIOMYOPATHY IN DOGS

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ABSTRACT

Eight dogs presented with clinical signs suggestive of cardiac problems and later confirmed for DCM were utilised for the detailed treatment studies. Signalment, history, electrocardiography, radiography, echocardiography, haematology, serum biochemistry and response to treatment of enalapril @ 0.5 mg/kg bid, valsartan @ 2 mg/kg bid and lasilactone @ 2mg/kg bid orally were studied.

Dilated cardiomyopathy (DCM) was more commonly observed in middle aged dogs. The breed wise distribution of DCM indicated that Labrador Retriever was more prone to dilated cardiomyopathy (37.5 %) followed by Boxer (25 %), German shepherd (12.5 %), Spitz (12.5 %) and non - descript (12.5 %).

Major clinical signs included cough (37.5 %), ascites (75 %), anorexia (75 %), polydypsia (50 %), syncope (25 %) and oedema of hind limbs (25 %). Exercise intolerance and dyspnoea were present in all cases.

Mean temperature, pulse and respiration rates were within the normal range. Clinical examination revealed irregular pulse (37.5 %), weak femoral pulse (75 %) and pale mucous membrane (25 %) on the day of admission. Ascites and pulse deficit were present in 50 % and 75 % of the cases respectively. Thoracic auscultation revealed tachycardia (25 %) and pulmonary crackles (75 %).

Mean heart rate was within the normal range. Sinus tachycardia (25 %), atrial fibrillation (12.5 %) and VPC (25 %) were the most common arrhythmias encountered in ECG. Ventricular pre-excitation was present in 12.5 % of the cases.

All the ECG measurements were within the normal range except for a slight increase in the P wave duration indicating left atrial enlargement. Hence ECG could be used for initial diagnosis of cardiac problem.

On radiographic examination major observations were generalised cardiomegaly, tracheal elevation, pulmonary congestion and pericardial effusion. Vertebral heart score showed significant increase in mean cardiac length, mean cardiac width, mean vertebral heart sizes and mean vertebral size of caudal vena cavae when compared to normal dogs.

Echocardiographic four chamber view revealed left ventricular dilatation all cases. Pericardial effusion was present in 12.5 % of the cases. M–mode measurements showed reduced myocardial contractility in all cases. Fractional shortening (FS) had a mean value of 19.80 ± 1.71 %. Ejection fraction had a mean value of 43.43 ± 4.16 %.

Haematobiochemical studies revealed mild anaemia with leukocytosis and neutrophilia. Anaemia might be caused by haemodilution effect due to fluid retension secondary to the activation of renin – angiotensin – aldosterone system. There was elevation of CPK value on day 1 when compared to the healthy controls which might be due to the cardiac muscle damage occurring in DCM.

Treatment response was studied in six cases that survived for atleast 30 days. Clinical improvement was present in 62.5 % of the cases. Atrial fibrillation was absent on day 30 of treatment. Cough and skin rashes were the common side effects. Mean values of RBC and haemoglobin on day 30 showed a significant reduction indicating development of anemia due to direct effect of angiotensin on erythropoesis. Significant reduction in CPK on day 30 when compared to day 1 might be indicative of improvement in the coronary circulation following treatment.

Appendix - I

PROFORMA

Case No. /Sl. No. **Date:**

1. **Name and address of the owner:**
2. **Details of the animals**

Breed :
Age :
Sex :
Colour
If vaccinated :
If yes, details :

3. **Clinical history**

Date	Diseases encountered in the past	Treatment adopted

1. **General clinical examination:**
2. **Systemwise examination**

a) Digestive system :
b) Respiratory system :
c) Cardiovascular system :
a) Auscaltation of cardiac region :
b) Pulse

- **Rate**
- **Rhythm**
- **Type**

c) CRT/Min
d) Venous distension
e) Hepatojugular reflex

3. **Clinical Observation**
   a) **Clinical data**
      1. **Respiration rate (per min)**
      2. **Pulse (rate per min)**
      3. **Temperature (F)**
      4. **mucous membrane**
      5. **lymph nodes**

b) Clinical signs

(present/absent)

1. **Lethargy**
2. **Dyspnoea**
3. **Cough**
4. **Syncope**
5. **Exercise intolerance**
6. **Ascites, peripheral oedema**

4. Results of Special examination:

1. **ECG findings**
2. **Echocardiography findings**
3. **Radiographic findings**
4. **Haemato – biochemical findings**

Sl no.	Parameters	Result
1.	Hb (gm/dl)	
2.	VPRC (%)	
3.	RBC (millions/cu. mm)	
4.	TLC (Thousands/cu.mm)	
5.	DLC	
	Neutrophils (%)	
	Lymphocytes (%)	
	Eosnophils (%)	
	Monocytes (%)	
	Basophils (%)	
	Serum analysis	
1.	Sodium (mEq/L)	
2.	Pottasium (mEq/L)	
3.	Creatinine (mg/dl)	
4.	CPK (U/L)	

6. Diagnosis

7. Treatment

Signature of the chairperson **Signature of the student**