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Thesis

"Canine Cardiomyopathies: An Overview; Current Understanding and Perspectives for the Future"

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Budapest 2023

Contents

Abbreviations

Aa – Amino Acids

ACE – Angiotensin Converting Enzyme

AF – Atrial Fibrillation

AHA – American Heart Association

ANP – Atrial Natriuretic Peptide

ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy

BNP – B-type Natriuretic Peptide

CFA – Canine Chromosome

CM – Cardiomyopathies

CHF – Congestive Heart Failure

CO – Cardiac Output

cTnI – Cardiac Troponin-I

DCM – Dilated Cardiomyopathy

ECG – Electrocardiography

HCM – Hypertrophic Cardiomyopathy

ISFC – International Society and Federation of Cardiology

JDCM – Juvenile DCM

LV – Left Ventricle

NT-proBNP – N-terminal precursor to BNP

PDH – Pyruvate Dehydrogenase

PDK4 – Pyruvate Dehydrogenase Kinase 4

PLN - Phospholamban

PWD – Portuguese Water Dogs

RCM – Restrictive Cardiomyopathy

SCD – Sudden Cardiac Death

SR – Sarcoplasmic Reticulum

TTN – Titin

VPC – Ventricular Premature Complexes

WHO – World Health Organization

1 Abstract

Cardiomyopathies are an arduous spectrum of diseases of the heart muscle experienced by canines and may be of a growing concern within the expanding canine population. While the prevalence in many breeds is rather constant, new trends and changing breed popularity warrants an investigation and an overview of these complex conditions.

Of the various existing classifications of cardiomyopathies, derived from the evolution of human classifications, dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are the two most often encountered cardiomyopathic diseases in canine patients. Hypertrophic cardiomyopathy is a rarely diagnosed cardiomyopathy in dogs and hypertrophy of the left ventricle is often a result of another systemic disease. This review aims to provide an in-depth analysis of the major cardiomyopathies DCM and ARVC while giving a brief address and insight into HCM. DCM stands as the most commonly occurring of the two major myocardial diseases. ARVC may be less frequent but still poses as a life-threatening condition to the afflicted dogs.

This review gives an overview of the aetiological background and pathological mechanisms contributing to the development of these myocardial diseases. Genetic mutations found to be associated with specific breeds and these cardiomyopathies are explored, showing an importance for prompt and regular genetic screening. Nutritional deficiencies may be implicated in their pathogenesis and supplementation of these nutrients may show alleviation of clinical symptoms. The complex clinical forms and presentations of these cardiomyopathies make diagnosis challenging. Improvements in diagnostic methods such as advanced imaging, and accurate biomarker analysis, have improved our ability to detect and monitor these conditions. Once these cardiomyopathies are confirmed it is crucial to intervene to delay onset o or progression to more severe

The insights gained from the review highlight the need for ongoing research to further evolve our knowledge and undercover improved diagnostic and therapeutic strategies to battle and conquer these potentially fatal cardiac diseases.

2 Introduction

Cardiac diseases present quite a substantial cause of mortality in dogs as the fourth most common cause of death [1]. Canine cardiomyopathies are a specific collection of heterogenous myocardial diseases of dogs affecting the physiological structure and function of the myocardium. Frequent outcomes are contractile dysfunction, decrease of cardiac output (CO), and subsequent congestive heart failure (CHF) [2,3]. The American Heart Association (AHA) defines cardiomyopathies (CM) by 2 classifications; primary (genetic, nongenetic and acquired forms) and secondary (usually showing pathological changes resulting from multisystemic disorders) [4]. The AHA further divides these classifications into the major types usually identified in both humans and animals; dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), and unclassified cardiomyopathy [4]. It is interesting to note how the classification of these CM have evolved when compared to older categorisations. For example, in 1967, in a review by Jennings, I.W, she separated them strictly on a nutritional, infective, or neoplastic basis [5]. Since these earlier descriptions, the author of this review encountered an almost exponential growth in the volume of research published, in the latter half of the 20th century, leading to many advancements in our understanding of these diseases and thus significant developments in diagnostic and therapeutic modalities.

Among cardiomyopathies in canines, the most prevalent and most extensively studied forms are DCM and ARVC and will be discussed in more detail in this review. DCM is the second most prevalent cardiac disease in canine patients, following degenerative valvular disease, and accounts for 10% of cardiac-related diagnoses [6, 7]. DCM as a phenotype can affect many breeds. Primary idiopathic DCM, predominantly affecting large breed dogs is of great interest [2]. The breed most documented, and with the highest prevalence of DCM is the Dobermann pinscher, with a shown prevalence of 58.2% [8]. Great Danes, Irish Wolfhound and English cocker spaniels also represent breeds with a notably high occurrence of DCM [9]. ARVC is overrepresented in Boxer dogs as the most common acquired heart disease diagnosed in that breed, occurring in approx. 25% [2, 10]. HCM indeed manifests in canine patients but it is extremely rare [2] and is the more commonly occurring form of cardiomyopathies in domestic cats [11]. The complex interconnections between genetic and environmental factors of canine CM can make early diagnosis and effective management of these conditions quite challenging.

This review aims to serve as an update and analysis of the existing variety research undertaken on the specific cardiomyopathies in canine patients, to consolidate our current understanding of their aetiology, pathogenesis, clinical manifestations, diagnostic approaches, and treatment modalities. In parts it will discuss the evolution of our knowledge, possible because of numerous retrospective and randomised studies, and peer-reviews undertaken over the previous decades. Where applicable it will highlight gaps of knowledge and make suggestions for further research, with the desire to discover improved diagnostic measures and more specific targeted therapies.

3 Literature Review

3.1 Classification and Definition of Cardiomyopathies

Within the last 65 years, classifications and definitions of CM have evolved quite significantly, to better comprehend the overall manifestation and clinical presentation of these diseases. This development in understanding results from extensive research undertaken throughout these years. In 1957 Bridgen, W. conceived the term cardiomyopathies. This term was used to describe diseases directly affecting the myocardium, which could not be attributed to previous hypertension or coronary disease; “non-coronary cardiomyopathies”. Until this, sudden cardiac arrest not attributed to coronary disease was frequently diagnosed as myocarditis [12]. Goodwin, J. F. along with several other authors later studied and redefined cardiomyopathies, over a period of ten years, and categorically classified them in a way very similar to modern medical definitions; (1) congestive: characterised by cardiomegaly with poor systolic function (i.e., DCM), (2) hypertrophic (previously obstructive): characterised by increased thickness of the myocardial walls and obstruction of inflow (impaired diastolic compliance) (i.e. HCM), and (3) obliterative (constrictive): characterised by chamber enlargement and amyloid deposits within the myocardium (i.e. RCM) [13, 14]. The widely recognised medical definitions we refer to today were subsequently coined between 1980 and 1995 by the World Health Organisation (WHO) and International Society and Federation of Cardiology (ISFC). The earliest report described three categories: DCM, HCM, and RCM. In the later report, in 1995, they added ARVC and “Unclassified” to the previous three categorisations [15, 16].

3.2 Dilated Cardiomyopathy – DCM

3.2.1 Aetiology and Pathophysiology

DCM represents just the second most commonly occurring acquired heart disease in dogs. It is considerably less frequent than degenerative disease of the atrioventricular valves which account for 70-75% of canine cardiac diseases [2, 17, 18]. DCM is, however, the most prevalent heart disease in this species, initially affecting the structure of the myocardium itself. Most cases of DCM are understood to have a high genetic basis of occurrence. Many breeds, most notably Dobermann pinschers, carry strong familial inheritance of the primary form of this disease. These genes and the associated breeds are discussed in the next chapter.

Regardless of the initiating cause, be it of primary or secondary origin, the final DCM phenotype is characterized by eccentric ventricular hypertrophy and dilation, secondary to systolic dysfunction. In the event of this "pump-failure", the volume of blood ejected from the heart at the end of each cardiac cycle is decreased. This results in an increased end systolic volume (ESV) within the chambers. The excess volume of blood now present within the chambers, influences the subsequent remodelling and myocyte enlargement [4] and thus chamber dilation. The enlargement of the heart may be extensive and diffuse to all four chambers of the heart in significantly advanced cases (Fig. 1). Interestingly, in their 2018 review, Dutton, E. and López-Alvarez, J. highlighted the limitations of this "morphological" definition as it does not consider any of the electrical alterations detectable with electrocardiography (ECG), that result from the mechanical dysfunction. Their preference was to refer to DCM as a syndromic disease. The dilation and congestion may present with mechanical and/or electric abnormalities alongside multisystemic signs associated with congestive heart failure (CHF) such as oedema and effusions [7].

The precise aetiology of DCM varies. The contributing factors of its development are certainly multifactorial, with such genetic and acquired, and nutritional and toxicological factors. Idiopathic/primary DCM, with potential familial inheritance, attributes to most of the final diagnoses and the background of the "idiopathic" DCM phenotype, by definition, remains unclear. Secondary myocardial disease, including secondary DCM, or infective myocarditis are less frequently identified in canine patients [18].

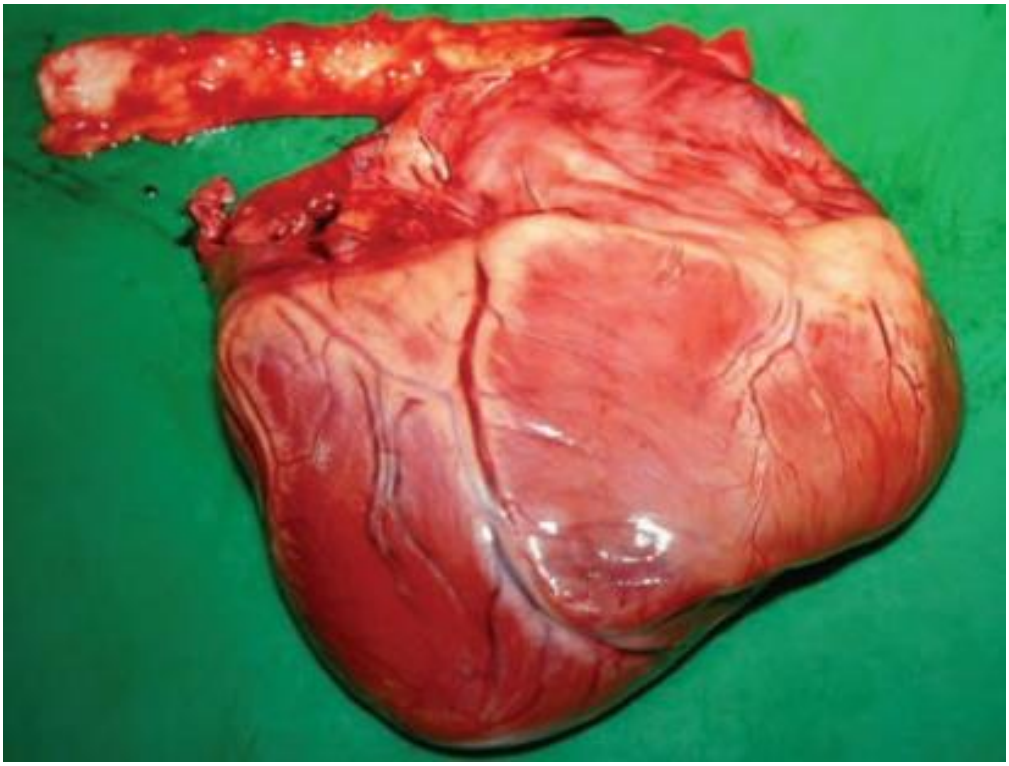


Fig.1: Cardiac specimen from 10y/o Newfoundland with DCM which was treated for CHF for 4 years and eventually had to be euthanized. All chambers are markedly dilated with flaccid myocardium. Image sourced from citation [50]

3.2.2 Genetic Factors and Inheritance Patterns

Today, genetic factors are known to contribute significantly to the development of DCM in humans and several species of animals [19]. In humans, mutations associated with over 50 genes can be identified to date and has an underestimated prevalence rate of 0.036% [20]. In dogs this number is vastly lower and compared to human genetics is still poorly understood but has shown significant progression in understanding over the years.

Prior to the sequencing of the human genome and the initiation of the 'Genomic Era', in an early 2001 review of canine idiopathic DCM by Tidholm et. al., they concluded that the available evidence to suggest a genetic basis for the development of the disease was lacking, but remained aware of its potential, as DCM is more prevalent in some breeds [21]. In this review just 2 cytoskeletal proteins were explored. They noted the demonstration of X-linked muscular dystrophy and DCM, linked to a deletion of the entire dystrophin gene in German short-haired pointers. They also highlighted that, although molecular analysis of the actin gene in Dobermann dogs with DCM proved unremarkable,

a heritable form of DCM due to an actin mutation was shown in humans and could be considered an underlying factor [21].

Current European population data demonstrates that 11 out of the 12 breeds with the highest cardiac mortality, were predisposed to develop DCM (e.g., Irish wolfhound, Great Dane, St. Bernard, Newfoundland, Leonberger, Dobermann, Finnish hound, Boxer, Giant schnauzer, English cocker spaniel, and Flat-coated retriever) [22].

The breeds with identified genes studied in detail, and in which this section will focus, are Dobermann, Welsh Springer Spaniel, Irish Wolfhound, and Portuguese Water Dogs. Several genes have been discussed as potential causatives involved in the disease process in these breeds [23]. These gene are responsible for encoding proteins, essential for the physiological structure and function of cardiac muscle cells. Mutations inevitably lead to abnormalities in the heart's structure and function, a critical underlying factor in the development of DCM. Although DCM has a high prevalence in Boxer dogs and is widely documented, this DCM phenotype also frequently results from the progression of a separate familial cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC) and will be discussed in more detail in the respective section.

Dobermann Pinschers appear to have the highest prevalence of DCM [8]. Genetic studies have shown it is primarily an inherited condition with an autosomal dominant pattern of inheritance, usually manifesting in middle to old-aged individuals. Meurs et. al. identified and discussed, in their original investigations, several causative genetic mutations in this breed, most notably, the pyruvate dehydrogenase kinase 4 (PDK4) and titin (TTN) genes. Both mutations were shown to both be of an autosomal dominant nature [24, 25].

The PDK4 gene encodes the PDK4 protein which has an important regulatory role in the glucose metabolism of cells, including the cardiac myocytes. This kinase protein is key in the modification of an important enzyme; pyruvate dehydrogenase (PDH), physiologically converting pyruvate into acetyl-CoA and producing energy through the citric acid or Krebs’s cycle. Using molecular methods such as polymerase chain reaction (PCR) and western blot, a 16-base pair deletion of PDK4 was detected in 86% of Dobermann with idiopathic DCM [24]. An increased rate of glucose oxidation results from the inability of PDK4 to negatively regulate PDH. The subsequent energy deficiency weakens the cardiac myocytes resulting in their structural alterations and impaired functions.

TTN, the largest mammalian gene, encodes the titin protein commonly known as connectin. This huge protein, found in the sarcomere of striated and cardiac myocytes, provides elasticity, allowing effective physiological stretch and contractility during the cardiac cycle. Pathologic missense variants of TTN cause the impaired integrity and elasticity of cardiac muscle, resulting in structural failure. [25]

Mutations in the transmembrane phosphoprotein; phospholamban (PLN), have been demonstrated and studied in human patients with DCM for several years. [26, 27]. PLN is crucial for cardiac contractility by regulation of the calcium adenosine triphosphatase pump (SERCA2a) of the sarcoplasmic reticulum (SR). When phosphorylated by protein kinase A, PLN modulates calcium reuptake into the SR. Mutations of PLN subsequently decrease the influx of Ca^{2+} into the cardiac myocytes during relaxation, ultimately disrupting the contractility rhythm of the cells [27]. A DCM-linked mutation of the phospholamban gene coined; R9H was identified in a recent study of a family of Welsh Springer Spaniels with echocardiographic and electrocardiographic evidence of DCM (e.g., systolic dysfunction and left ventricular dilation) [28]. Interestingly this study demonstrated that all dogs possessing the mutation developed the DCM phenotype, showing a significantly high penetrance. Unfortunately, 75% of the sample eventually succumbed to sudden death. Though this study was limited by the number of evaluated dogs, the association with the PLN mutation was determined based on the absence of the variant in 346 unaffected dogs. Further studies, with larger and random populations of this breed are warranted in the time ahead.

Though no definitive gene mutations have been identified in many other breeds, potential loci of interest currently linked to canine DCM have been described in Portuguese water dogs (PWD) and Irish Wolfhounds [29, 30]. A whole-genome study was performed of 119 PWD, of which 40 were afflicted with an autosomal recessive form of juvenile DCM (JDCM). The JDCM was linked to mutations of a previously unknown locus on canine chromosome (CFA) 8 [29]. Using similar techniques, a later genome-wide association study (GWAS) of Irish wolfhounds also identified up to six loci of interest with potential involvement in DCM cases. CFA 1,10,15,17,21 and 37 presented with evidence of association [30]. Only with continued genomic studies of these predisposed breeds, is it possible to discover novel genetic mutations and therapies to combat the disease.

3.2.3 Nutritional Background

A deficiency or imbalance of certain nutrients, though not a causative factor in the idiopathic form of the disease, can still play a role in the development of a final DCM phenotype. Deficiency-associated clinical cardiomyopathies, resulting from inadequate supply of dietary taurine, carnitine, and their sulphur-based amino acid precursors; methionine and cysteine, have already been identified and documented for a long time in cats and dogs [31, 32]. An investigation of American Cocker Spaniels with DCM demonstrated a favourable responsiveness to supplementation with taurine and carnitine, showing their ability to alleviate the disease. Though physiological myocardial function in these dogs did not fully return, it improved to a point where their cardiovascular drug treatment could be withdrawn safely from their treatment protocols [32].

In recent decades with the growth of vegetarianism/veganism and grain-free and home-prepared feeds, novel diets encountered now have shown reduced levels of taurine and other amino acids (Aa) and may be linked to taurine deficiency. [33, 34]. Home-cooking of some feeds significantly decreases the biological availability of the Aa due to thermal degradation, directly affecting taurine synthesis [33]. Novel plant-based diets are completely devoid of detectable taurine levels and very low in sulphur amino acids, and the increased fibre levels in these diets show the ability to reduce amino acid absorption thus further reducing taurine production [34]. Of the identified nutrient deficiencies, taurine attained popularity and traction because it is known directly to result in taurine responsive DCM in feline patients, and is an essential amino acid in this species, [31, 35, 36]. The discovery of this deficiency-related disease in feline studies, later influenced medical physicians to use these animal models to assess a similar relationship of taurine deficiency and clinical DCM in humans. While they could agree on the cardioprotective effects of the amino acid they could not confirm its direct involvement in the background of DCM [37].

In canines, taurine is not considered an essential amino acid, because usually it is sufficiently produced endogenously. Taurine is physiologically synthesised from the amino acid precursors; methionine and cysteine, by the rate limiting enzyme found endogenously in the liver; cysteine sulfonic acid decarboxylase [38]. Reasons for the contrast between cats and dogs and their requirements for taurine supplementation may be explained by various factors. Most obvious is the varying concentration levels of cysteine sulfonic acid decarboxylase in the tissues of different species. This enzyme has long been known to be significantly lower in the liver of cats versus dogs, reducing the rate of taurine synthesis.

[39]. These results were supported by the later investigations that confirmed a taurine deficient diet fed to cats [36], did not lead to the same taurine deficiency when fed to a sample of dogs [40]. This credence that DCM and taurine deficiency in canines had no association was only questioned when it was confirmed that DCM diagnosed in foxes was in fact a result of dietary taurine deficiency [41]. When taurine levels in canine patients were evaluated again in another study, it was demonstrated that 17% of these dogs, diagnosed with DCM, had low concentrations of the amino acid in their plasma. These were breeds that were previously not known to be susceptible to DCM (e.g., American Cocker Spaniels and Golden Retrievers). The authors could not conclude, however, that the occurring DCM was a direct result of the deficiency as the breeds who were predisposed showed normal plasma concentrations [42].

The relationship of taurine and DCM continues to be imperfectly understood. It is known that there are breeds more at risk of developing the disease, most notably Golden Retrievers [43, 44]. Larger breeds seem to represent most diet related secondary DCM cases, presumably due to differences in the rate of taurine synthesis [45]. Though it remains a multifactorial disease, the same taurine responsive DCM seen in cats [31, 36] has been demonstrated in dogs [32] showing it as a critical nutrient for cardiac health. More supplementary-based studies should be carried out to conclude the direct relationship.

The metabolically active levocarnitine (L-carnitine) is an essential compound which mediates transport of fatty acids across the mitochondrial membrane, where it undergoes beta-oxidation [35, 46]. In a physiologically oxygenated heart, the preferred substrate utilized by the cells as an energy source are fatty acids [47], thus making them an important nutrient for healthy metabolic functions. With its involvement in lipid metabolism and fatty acid transport, carnitine plays an important role in healthy heart function. It was demonstrated that clinical heart disease such as DCM was associated to a deficiency of this nutrient in a family of Boxers, where myocardial function was greatly improved in response to l-carnitine supplementation [48, 49]. Both sire and dam, and two littermates were diagnosed with DCM, and low myocardial concentrations of carnitine were detected in all the offspring. Following high-dose l-carnitine supplementation, fractional shortening increased, and the cardiac function improved, in both littermates afflicted with DCM. Both parents unfortunately expired a short time into l-carnitine treatment and could not be conclusively evaluated [49, 50]. Currently only small-scale reports are available on carnitine and DCM association. Most dogs affected with DCM

may not appear to have a taurine or carnitine deficiency. With many causatives in the background of this CM, nutritional deficiencies are just but one. Supplementation with these very safe nutrients can still prove very beneficial in promoting good cardiac health and should be considered alongside the primary treatment protocols.

3.2.4 Clinical Presentation and Diagnostics

DCM usually presents heterogeneous in nature. The complex variation of the causative genetic and nutritional factors in the aetiological and pathophysiological background can lead to differences in the form and time of manifestation of the disease. Most cases appear in middle-aged dogs with some breed dependent differences. Reports show Irish wolfhound present younger with a median age of 4.7 years old and Great Danes appear at an average of 5 years old [9]. The same reports show Boxers are oldest at time of presentation with peaks from 6 to 10 years [9].

Regardless of breed, the development appears slowly with a prolonged preclinical phase, termed; the ‘occult’ phase, advancing over several months to years, without noticeable clinical symptoms [2]. With the advancement of myocyte enlargement and contractile malfunction, canines usually progress into obvious overt DCM and present with signs of ongoing heart failure. The majority of cases actually present with advanced stages of CHF [9]. Failure to detect the condition in the occult phase or in the early overt phases Physical findings can differ slightly depending on the severity of this cardiac decompensation and some breed specific variations [2, 9, 50]. Dyspnoea, cough, exercise intolerance, and syncope are all observable commonalities. Great Danes tend to present with cough and weakness, Boxers most frequently experience collapse, and Golden retrievers are known to show reduced appetite [9]. Less obvious signs in all breeds may be discoverable upon physical exam. These include ascites, pleural effusion and adventitious respiratory sounds, arrhythmias and deficits in pulse quality, and even some soft murmurs [2, 50].

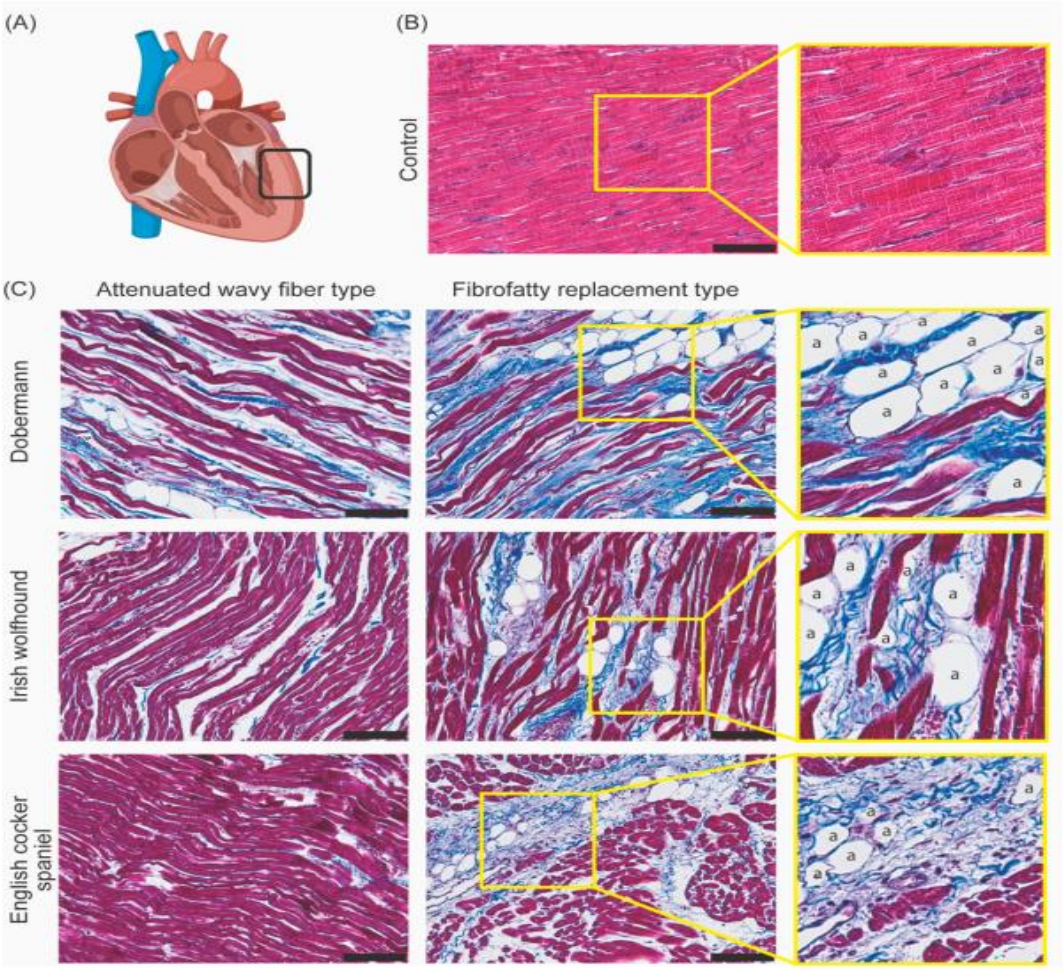
Severe cardiac impairment and poor perfusion may present with the signs of low output such as episodes of syncope and, more severely, sudden cardiac death (SCD). The systolic dysfunction may be accompanied by electrical impairment, and the resulting arrythmias can also manifest in these life-threatening symptoms. SCD can be quite common and even the earliest outcome in occult DCM. Syncope and SCD seems to widely occur in Dobermann [51]. This breed shows the highest risk of DCM-related SCD, occurring in approximately 20-30% of those with overt signs [50, 52, 53]. The high risk of

SCD is one of several breed specific variations in the clinical presentation. Irish wolfhounds seem to represent a lower risk of any symptoms and effective stabilisation can lead to a good prognosis in this breed [50]. One clinical aspect more detectable in Irish wolfhounds with idiopathic DCM is the occurrence of atrial fibrillation (AF) rather than ventricular arrythmias. Long term outcomes were reported for this breed with the presence of DCM, AF, or both [9, 54].

The lack of observable clinical evidence in the occult phase can make early diagnosis of the disease particularly challenging, and patients usually present with advanced forms and symptoms of concurrent CHF [22]. Despite this, the available diagnostic options still prove useful in identifying subtle cardiac changes, indicative of DCM. Sensitive diagnostic tools such as echocardiography and electrocardiography, and biomarker laboratory analysis can be particularly valuable for screening the disease and assessing the arrhythmia, ventricular dilation and systolic dysfunction before the onset of clinical signs [2, 50]. Histopathological examination also provides useful information in the definitive post-mortem diagnosis of DCM, but apparent microscopic changes can vary among myocardial samples depending on the underlying aetiologies [23, 55]. Though these evident histologic changes fluctuate, characterization has shown there are two distinct histopathological phenotypes [22]. The presence of wavy attenuated myofibrils or fatty infiltration are the two commonly presenting forms (Fig. 2). Many samples may also exhibit atrophy and necrosis, myocytolysis and extensive fibrosis, and lympho-plasmocytic infiltration [23, 55]. Fatty infiltration of the myocytes may be discovered in Dobermann and Boxer breeds with DCM. This histopathological feature is also consistent and usually represented in the samples presenting with ARVC or Boxer cardiomyopathy [18, 23].

Fig.2 (NEXT PAGE): (A) Cardiac Model depicting histological sample location; Black Box. (B) Healthy control sample of myocardium from a 3y/o Beagle with physiologically normal cardiomyocytes. (C) Histological samples of diseased myocardium of 3 dogs confirmed with DCM (4y/o Dobermann, 5y/o Irish Wolfhound, and 7y/o English Cocker) displaying the two major histopathological forms of DCM; Attenuated wavy fibre or fibrofatty infiltration (Red: Cardiomyocytes, Blue: Fibrotic tissue, a: adipocytes. Image sourced from citation [23]

Fig.2



Best practice in relation to DCM involves regular screening and accurate diagnosis. Imaging modalities, such as radiography and echocardiography, ECG, and detection of cardiac biomarkers continue to be the most effective screening and diagnostic methods widely used and described [2, 56].

Thoracic radiography is a likely first diagnostic method suggested for a patient presenting with respiratory signs resulting from cardiovascular disease such as DCM, and it is indicated to determine the presence of CHF [50]. While dogs during the early occult period may appear radiographically normal, those presenting with a more advanced form of the disease may show left-sided and/or generalized cardiomegaly, distended pulmonary veins and/or pleural effusion, and respiratory patterns consistent with pulmonary oedema (Fig. 3) [2, 50]. Radiographical findings in 369 dogs confirmed to have DCM, discovered up to 80% of dogs presented with cardiomegaly and up to 75% presented with pleural and pulmonary fluid accumulation [9].

ECG is a necessary diagnostic aid for detection of any arrhythmia. Sinus rhythm is usually detectable in patients with occult DCM but with progression arrhythmias can occur. AF and ventricular tachyarrhythmias are mostly seen, occurring most commonly in Irish Wolfhounds and Dobermann respectively [2, 9]. The use of 24-hour Holter ECG monitoring is a gold standard screening method providing 24-hour ambulatory readings. Detection of >50-100 ventricular ectopies, over the 24-hour period on Holter ECG, is indicative criteria for the presence of DCM in Dobermann [2, 50, 57]. The presence or absence of an abnormal ECG alone is not definitive in the diagnosis of DCM, or other cardiomyopathies, for that matter as most arrhythmias accompanying cardiomyopathies show daily spontaneous variability [58]. The arrhythmias can potentially be of extracardiac origin also and their detection does not conclusively signify heart disease. Extracardiac arrhythmias should be excluded by complete bloodwork and other supplementary diagnostic aids

Primary diagnostics necessary for the definitive diagnosis of overt DCM involve most importantly an echocardiography examination. In addition to echo, a detailed clinical history and cardiological examination, and exclusion of other cardiac diseases should be carried out [2, 50]. Echocardiographic findings characteristic in dogs with DCM include dilated chambers, with left-sided enlargement predominating, poor systolic motion of the ventricular walls, and fractional shortening [2, 9, 50].

Commonly coupled with these physical diagnostic tools, is the detection of circulating serum cardiac biomarkers. Haematology in patients with DCM is usually unremarkable but measurements of these biomarkers still provide valuable information about the cardiac stress and dysfunction, and the prognosis of the affected dogs [18, 50]. Natriuretic peptides contributing to the control of cardiovascular and renal function have been identified in investigations and reviews for many years [59, 60]. These peptide hormones are released by the myocardium in response to increased stress and stretch. Atrial natriuretic peptide (ANP) and its N-terminal precursor molecule are predominantly released by the muscle of atrial walls. Whereas B-type natriuretic peptide (BNP), and the N-terminal of its precursor; proBNP (NT-proBNP), are predominantly released by ventricular myocardium. NT-proBNP in canine patients proves the most studied and most sensitive natriuretic peptide to detect cardiac disease [2, 50, 61].

Another beneficial marker for cardiomyocyte damage is cardiac troponin-I (cTnI). Troponins are integral proteins for the physiologic function of muscles and are found in skeletal and cardiac muscle alike. Cardiac troponins are gold standard to detect acute

myocardial infarction in humans and can be reliable for assessment of myocardial injury in cats and dogs [62]. Considering that cTnI is highly specific and sensitive for injury to the cardiac muscle it may prove useful in the exclusion of the presence of other severe cardiac diseases such as extensive myocarditis or even pulmonary thromboembolism, as the concentration of this marker is significantly higher in these diseases compared to the concentrations detected in DCM. The measurement of cTnI alone it is not specific enough to definitively diagnosis DCM [50] and the interpretation of this and the previously mentioned biomarkers should be considered only alongside other clinical and diagnostic findings, to form a comprehensive understanding of the dog's cardiac health and the status of the disease.

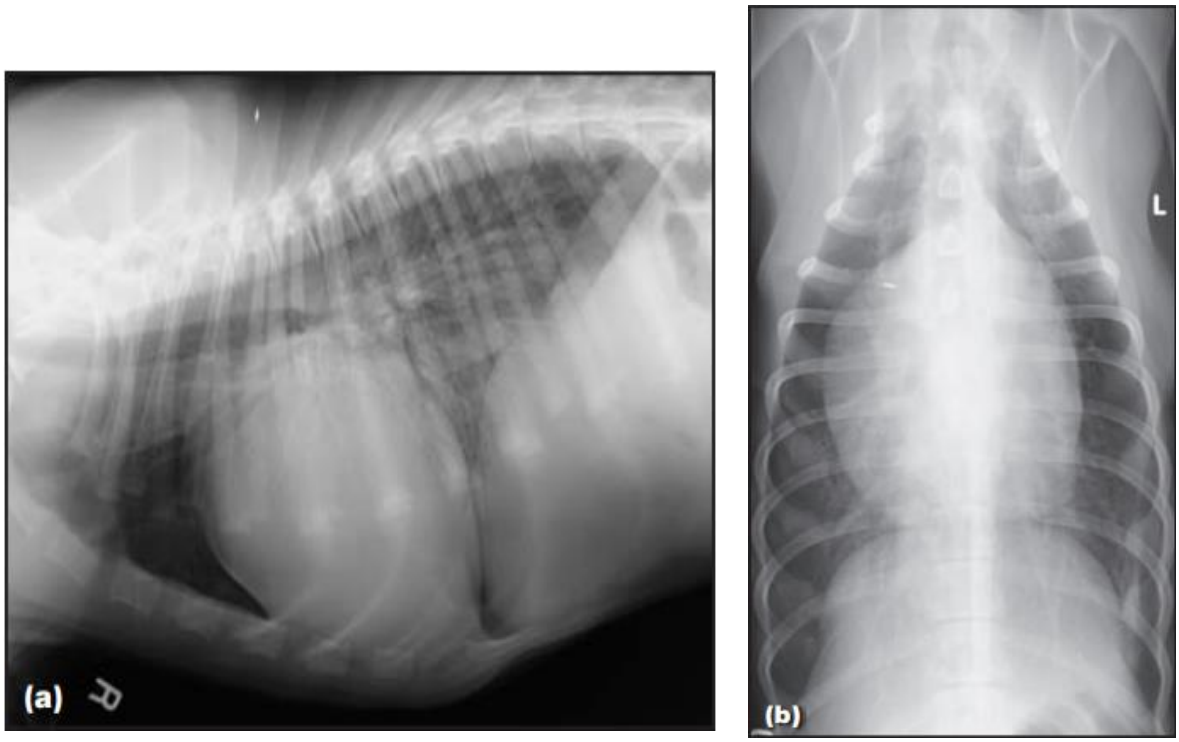


Fig 3: Thoracic radiographs from a 6m/o Great Dane with confirmed DCM after initial pulmonary oedema treatment. (a) Right lateral view displaying generalized cardiomegaly (confirmed by vertebral heart score) & an increase in interstitial patterns, consistent with pulmonary oedema (b) Dorsoventral view confirming cardiac silhouette enlargement & generalized increase in interstitial opacities. Images sourced from citation [50].

3.2.5 Therapy and Management Strategies

Early detection of occult DCM is crucial for implementing effective therapeutic and management measures to prevent or postpone the progression of the disease. Early interventions in the occult phase of the disease lead to a more favourable prognosis as inevitably this stage progresses to the overt clinical phase, cardiac failure, and death. Screening and diagnostic methods such as echocardiography, ECG and biomarker analysis are best in identifying subtle cardiac changes before clinical symptoms manifest. Screening yearly over the dog's life, especially in predisposed breeds, is recommended to detect subtle changes over time [56]. This value of occult DCM management was not highlighted and explained until 2004 [63]. Reviews prior to this did not discuss management guidelines in the pre-clinical phase separate from the overt form and focused only on therapeutic strategies of overt CHF such as rhythm and contractility control, and reduction of afterload and preload [60, 64].

Upon detection of the concealed occult form, preceeding any clinical manifestations, no medical management may be required [50]. Dietary modification and supplementation, and/or regular monitoring may slow the disease progression and allow for timely modifications. Diets supplemented with taurine, L-carnitine, and omega-3 fatty acids have shown to support and improve cardiac health in DCM and may prove beneficial in all stages of the disease [32, 65]. It is important to note that this dietary management alone will plateau in its ability to delay the onset of clinical signs, and additional medicinal agents must then be added to treatment protocols. The use of antiarrhythmics in patients with detectable tachyarrhythmias are decided by the frequency and severity of the arrhythmia of Holter ECG. Various antiarrhythmic protocols are available but the most effective is still unclear [2]. These agents will be explored in more detail in the description of the next cardiomyopathy.

We may include medication in our therapy of occult DCM, most notably pimobendan. Pimobendan is a positive inotropic medical agent and vasodilator that has been demonstrated to reduce morbidity and mortality in Dobermann with CHF, secondary to DCM [66, 67]. With an average difference of 182 days of increased survival time, pimobendan even showed positive results in preventing the onset of CHF in Dobermann with the occult form of the disease. This was achieved at a median dose of 0.453 mg/kg/day [68]. It also proved to reduce heart size in other breeds with cardiomegaly and degenerative valvular disease [69], but the full extent of its benefits in other breeds with occult DCM remains unclear and use prior to clinical manifestations should be approached

on an individual basis. Population samples of a more inclusive nature are required in future studies to assess the drug's full potential

Following progression to the clinically evident and overt DCM with co-existing signs of ongoing CHF, the goal of medical management is to prolong the survival time and improve the quality of life of the patient. Current recommendations mainly consist of the use of three medicinal agents. The afore mentioned pimobendan, now prescribed at a dose of 0.25 mg/kg orally BID is combined with the most effective diuretic; furosemide, at a dose of 1-2mg/kg orally BID in the case of mild CHF or 1-5mg/kg orally in chronic CHF. If required, an array of available angiotensin converting enzyme (ACE) inhibitors [50]. Diuresis alleviates the strain on the affected heart by reducing both preload and afterload. ACE inhibitors counteract the renin-angiotensin aldosterone system and provide vasodilation. They may also be paired with the aldosterone antagonist; Spironolactone, if required [50]. Various ACE-inhibitors are available with varying dosages based on formulations. Adequate antiarrhythmic therapy may also be required. The reader is referred the BSAVA drug formulary for current recommended dosages [70].

Novel genetic therapies, still in the research phase, also exist and continue to emerge with new developments in gene identification and gene transfer techniques. Most clinical trials underway are in human medicine, with an emphasis on cancer research [71]. Viral vectors serve as a primary delivery system for this gene transportation to introduce and express functional genetic material when the endogenous gene is defective. This process is named "insertional mutagenesis". This virus-mediated way of delivery can carry disadvantages though. Viral vectors can frequently elicit an immune response disrupting the expression of the exogenous gene [71]. Results in genetic research may appear promising, but there is still room for discovery of better and more efficient techniques with the continued growth of research in this field and it shows great potential for newer developments and applications.

3.3 Arrhythmogenic Right Ventricular Cardiomyopathy - ARVC

3.3.1 Aetiology and Pathophysiology

Arrhythmogenic right ventricular dysplasia (ARVD), now ARVC, is an intricate cardiomyopathy primarily characterised by sustained ventricular tachycardia and pathological ventricular changes. Fontaine et al. originally described ARVD in human patients in 1977. Their report demonstrated sustained ventricular tachyarrhythmias in six individuals that did not present with clinically overt heart disease. Cardiac evaluation in these individuals showed dilation of the right ventricle and structural fibrofatty infiltration of the myocytes [72]. Over the coming decades Fontaine and Marcus et. al. continued to extensively report and review ARVD/ARVC in humans, and thus the condition remains well-documented [73, 74]. While our complete understanding of ARVC in canine patients is still evolving, what is understood is that Boxer dogs continue to overrepresent this condition in dogs. It's the most commonly occurring primary CM in this breed and is recognised to have familial inheritance [2].

It was Harpster who first identified and detailed ARVC in Boxers. Clinical and histopathological features resembling ARVC in humans, but relatively specific to this breed were detailed in his report. He attributed the term; "Boxer cardiomyopathy", to this uniquely presenting myocardial disease [75, 76]. Inheritance factors are of particular interest in the background of this CM and the current emphasis is on the genetic deletion mutations of the striatin (STRN) gene on chromosome 17 [2, 77]. The aetiology, like other CMs, remains multifactorial and beyond the genetic background of the disease in this breed, such environmental or nutritional factors may also contribute to its secondary development. ARVC in Boxer dogs has demonstrated a response to omega-3 fatty acid supplementation, suggesting that a deficiency of these cardiac supportive nutrients may have a role in disease occurrence and supplementation may help to alleviate the condition [78]. The specific involvement of nutrient deficiencies in the pathophysiology of this CM is not clear but remains a promising area of interest for further evaluation.

ARVC has been documented and characterised in various breeds other than Boxers, such as Dachshund, Labrador, Bulldog, and Dalmatian [79, 80, 81]. These dogs were confirmed to have ARVC based on the similar clinical and histological pathology to that in humans and Boxers (e.g., fibrofatty infiltration, ventricular arrythmias and sudden death).

The prevalence and identification in these other breeds is not well documented and specific familial inheritance has not yet been widely described.

ARVC is predominantly defined by potentially life-threatening ventricular premature complexes (VPC), and progressive loss of systolic function, subsequent to extensive fibrofatty remodelling of the right ventricle's myocardium (Fig.4). The precise pathophysiology of the fatty infiltration is not fully understood, but is widely appreciated to originate from genetic mutations and defects of the adhesive cellular proteins at the gap junctions [2, 82]. The severity of these pathological changes, and indeed the inheritance factors of genetic mutations, play a very important role in the overall presentation and manifestation of the disease. Several genes are responsible and have been identified in humans [82] but the STRN mutation remains the one of most concern for Boxers [77]. Patients with ARVC are at a significantly high risk for sudden cardiac death and it can occur even before the onset of symptoms. This disease accounts for the second most common cause of SCD in young humans [82] and was the result of up to 40% of Boxers in a canine study [87].

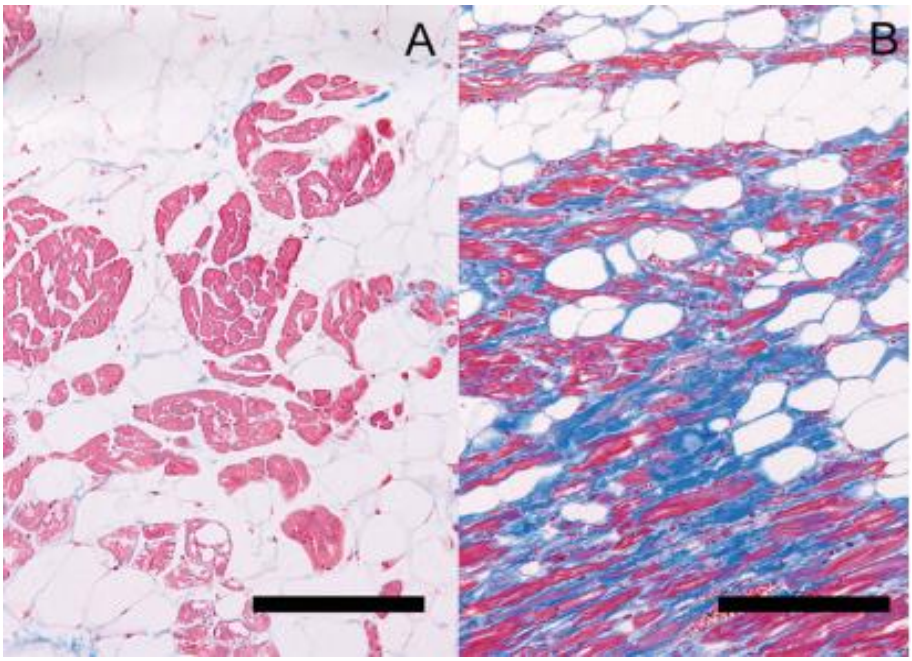


Fig 4: Myocardial tissue samples from patients with ARVC. Masson's trichome stain. Bar = 80 µm. (A) Sample of the right ventricle from a 4y/o Shetland sheepdog displaying fatty replacement, and entrapment of myocyte clusters by the adipocytes. (B) Sample of the right ventricle from a 5y/o Bulldog displaying fatty infiltration of the myocardium with interstitial fibrosis (blue fibres). Image sourced from citation [81].

3.3.2 Genetic Factors and Inheritance Patterns

When ARVC was first detailed in Boxers it was considered that hereditary origin was likely, but no definitive genes had been discovered in the background of the disease by this time [76]. It was not until their later reports that Meurs et. al. finally noted and documented a potential familial nature of the condition. Since this they have researched and reviewed ARVC in Boxers quite extensively over the previous decades leading to huge advances in the knowledge of the disease, particularly their discovery and description of the genetic mutations in the background [77, 83, 84]. Groups of Boxers were first evaluated for Familial Ventricular Arrythmias (FVA) by Meurs et. al. to prove the existence a familial inheritance of the disease. These Boxers were diagnosed with FVA, using Holter ECG, based on the presence of >50 ventricular ectopies within a 24-hour period. Given that a large portion of the dogs did not present with histopathological lesions of the myocardium, they did not refer to the FVA as a cardiomyopathy but rather focused on the electrical abnormalities present. Irrespective of this technicality, their data was highly suggestive that FVA was an inherited disease of an autosomal dominant nature [83].

The most significant advancement by these authors in the understanding of ARVC genetics, was their detection of a deletion mutation on the 3' untranslated region of STRN, which could be associated with the development of the myocardial disease [77]. As part of a canine model GWAS, in which all dogs were phenotyped for ARVC, fine mapping and DNA sequencing identified STRN as the strongest region of interest, located on chromosome 17. Definitive ARVC diagnosis in these Boxers was then concluded based on the presence of ≥500 ventricular ectopies on 24-hour ambulatory ECG, and if present syncope [77].

The STRN protein plays a major role in selected cellular processes, including cell signalling and structure. STRN is discoverable in the intercalated disc region of cardiac myocytes where it is co-localized with important desmosome proteins [77]. Desmosomes are the adhesive intracellular junctions maintaining normal connection and structural integrity of the cell [82]. Reductions of desmosome adherence may lead to myocyte death, inflammation, and fibrosis [85]. Following this cell inflammation and death, incomplete repair of the myocardium and replacement by fibrofatty material is one of the key features of the disease. Although the precise role of STRN in cardiac function has not yet been well described, its relationship with the integrity of cellular adherence can provide at least one explanation for its potential involvement in the pathological mechanisms of the disease.

Not all Boxers with the STRN mutation necessarily manifest with occult ARVC. Dogs that were genotyped as heterozygous for the deletion demonstrated just 82% penetrance. Heterozygous individuals were shown to have a less severe form of the disease or were not shown to have the disease at all [77]. This is highly supportive of the need for early genetic screening to isolate the dogs who could be at increased risk for developing the disease. Identifying affected carriers and intervening early is beneficial for a more favourable prognosis. Genetic testing, however, is not to be relied on alone for disease screening and should always be supplementary to other gold standard tools such as 24hr ECG.

3.3.3 Clinical Presentation and Diagnostics

ARVC is typically a disease of adult Boxers, with a median age of 6 years old at the time of diagnosis [2, 84, 86]. Harpster initially documented three distinct presentations of the cardiomyopathy and categorised them as follows; Category 1 or "Asymptomatic": Described a dog with detectable ventricular ectopies, but not displaying any associated clinical signs. Category 2 or "Collapsing Spells": Described dogs who experience episodes of syncope and collapse, usually following intense exercise or excitement. Category 3 or "Congestive Heart Failure": Described dogs, usually in a progressed state of CHF [75].

More recent descriptions of ARVC discuss and review the disease in an almost identical way to Harpster, in which three forms may be evident. Category 1, more recently referred to as 'concealed' or 'occult' ARVC, continues to account for asymptomatic dogs with detectable tachyarrhythmias or VPC. Category 2, or the 'overt' form, classifies dogs experiencing episodic weakness or syncope brought about by a detectable arrythmia. The occurrence of these episodes are exacerbated by, and usually detected following, strenuous work or exercise. The arrythmia must be detected in all categories to confirm the disease. Category 3 represents the smaller percentage of dogs presenting with systolic impairment of the ventricles and subsequent consequences of CHF. The classical symptoms of cardiac failure, previously described for dilated cardiomyopathy, occur with varying severity depending on the current stage being experienced by the patient [84, 86]. Given the significant involvement of the left ventricle in this progressive form of ARVC it can often mirror the symptoms of advanced idiopathic DCM. It may prove difficult to differentiate which CM was the initiating factor but nonetheless the approach to the cardiac failure is the same. This "DCM phenotype" is present in approximately 10% of Boxers [2, 86].

Findings of the physical exam in ARVC may be unremarkable depending on the presenting manifestation. Syncope is the most frequent complaint, with a history of exercise intolerance. A murmur may be detected, but in Boxers it's worth noting that a breed associated murmur, with underlying aortic dysfunction, is common [2]. The significant risk of sudden death for these dogs should not be forgotten [87].

Diagnostics for ARVC incorporates a combination of criteria because many of the findings are non-specific to the condition. Tachyarrhythmias, collapsing spells and myocardial failure can result from various CM. Boxers participating in ARVC clinical studies are generally diagnosed and allocated to one of the three categories of the disease based on an anamnesis of weakness and syncope, electrical abnormalities signifying arrythmia, and/or echocardiographic evidence of ventricular insufficiency and heart failure [84, 86, 88].

In the event of a sudden fatality, postmortem MRI and histological detection of fibrofatty replacement of the myocardium is widely accepted as definitive diagnosis of the disease. The absence of postmortem evaluation, however, tends to be a recurring limitation of many of the undertaken studies [86, 88]. The presence of syncopal episodes and weakness upon exercise may be highly suggestive of ARVC, but the defining feature of the CM, and that which is used for antemortem confirmation, are the consistent tachyarrhythmias and VPC discovered only upon ECG [10, 84, 86].

Frequently, a single ECG upon clinical examination may show no abnormalities in affected dogs, because the frequency of VPC can show up to 80% spontaneous variability [58]. Sustained ventricular tachycardia is the characteristic discovery (Fig. 5). Atrial fibrillation and other supraventricular arrythmias are less common and may be detected in dogs of the third presenting category or the 'DCM phenotype' [2]. The VPC variability means asymptomatic dogs may still have underlying ectopy which may only be detected upon 24-hour ambulatory ECG. Up to 25% of Boxers initially considered as 'clinically normal', were actually discovered to have > 91 VPC/24h using ambulatory Holter, and frequency of ectopy was correlated to the grade of the arrythmia [10]. Objective criteria for confirmation of ARVC by Holter is not completely standardised, and various cut off points for the number of VPC qualifying for diagnosis seem to exist. Older studies considered Boxers positive for ARVC with the detection of ≥500 VPC/24hr [58, 77, 92]. Since 2014, newer studies and more current recommendations identify affected dogs by the presence of ≥300 VPC/24hr [2, 83, 88]. The difference of 200 ectopies need not be of significant debate, and in fact between 50 to 300 VPC is already highly suggestive of the disease,

especially if other characteristic findings are present. Less than 50 VPC can be considered as normal and unaffected [2].

Thoracic X-ray may show various findings and radiology is not particularly sensitive or specific for ARVC. Boxers with syncope and/or VPC, and no myocardial dysfunction may display no radiographical abnormalities, and most ARVC dogs show a normal cardiac silhouette [2]. Cardiomegaly and pulmonary oedema are potentially only identified in Boxers with the DCM phenotype and/or apparent signs of heart failure [2]. In one of the groups of Boxers studied by Palermo et. al., those with ARVC and left ventricular dilation, up to 82.3% of the dogs showed cardiomegaly. Pulmonary oedema was consistent with 58.8% of the same group. Only 1 of the 20 dogs from the other group, those with normal ventricular size, showed any cardiomegaly [86]. If this cardiomegaly was truly present in the 'normal' group, another unrelated cardiac disease could have been in the background.

Echocardiography in ARVC may provide useful information but it is not always of high diagnostic value. Typical myocardial remodelling is histologic and may not be apparent on an ultrasound. Mild to moderate right ventricular enlargement may be revealed in most cases, potentially accompanied by right ventricular dysfunction [86, 89]. Dogs with impairment of the right ventricle may have a worse prognostic value, seen by a decrease in the mean survival time. Duration of survival was determined in a study using echocardiography to measure tricuspid annular plane systolic excursion (TAPSE). TAPSE is a quantitative estimate of the fractional shortening of the right ventricle and is a very useful scoring system to determine right ventricular function. Lower TAPSE was identified in dogs with ≥50 VPC/24 h on Holter examination and correlated with shorter survival time of cardiac function compared to those with <50 [89]. Echo studies typically classify dogs as having myocardial dysfunction by referring to standardised left ventricular measurements. An internal diastolic and systolic diameter of >4.8cm and >3.3cm respectively and a left ventricular fractional shortening of <21% are consistent [84]. It should be remembered that these readings and dimensions are not definitive for ARVC but are for the assessment of the presence of left sided enlargement and dysfunction. Left sided cardiac failure may manifest because of numerous cardiac conditions and these should be excluded as causative factors.

While the combination of the diagnostic tools mentioned above remain gold standard methods, supplementary examinations such as interpretation of cardiac biomarker levels in the blood can also complement a thorough diagnosis. Cardiac troponin-I and brain

natriuretic peptide serum concentrations were evaluated in Boxers with and without ARVC by Baumwart and Meurs. No correlation between BNP concentrations and the severity of the disease was detected, but cTnI evaluation proved otherwise. Boxers with ARVC had significantly higher levels of cTnI in their blood and there was a strong correlation between the high concentrations, number of VPC/24hr and the grade of arrythmia [90, 91]. Biomarker analysis still cannot accurately confirm the presence of the disease or distinguish between
other cardiac diseases but should be interpreted alongside other reliable methods and results.

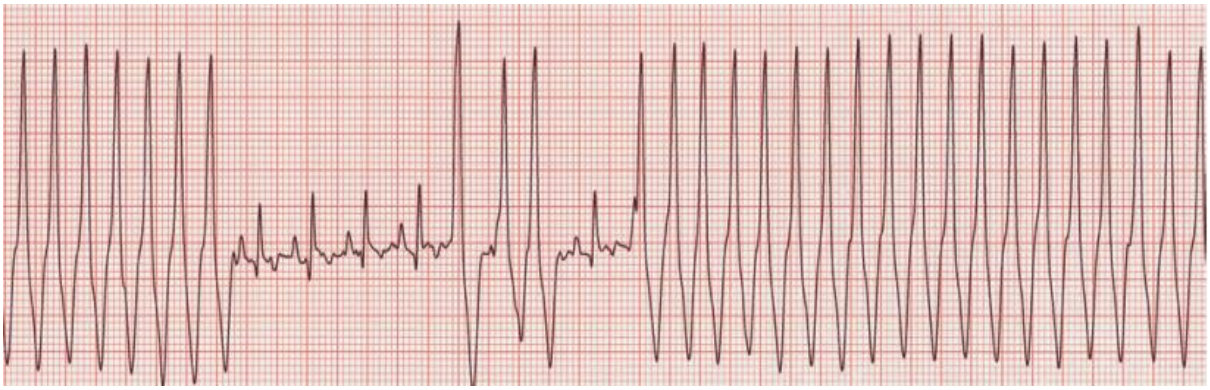


Fig.5: An ECG reading from a Boxer with ARVC displaying paroxysmal ventricular tachycardia of up to 300bpm. Image sourced from citation [2].

3.3.4 Therapy and Management Strategies

Effective treatment and optimal management of ARVC is achieved first by early and accurate diagnosis, and then the use of appropriate medicinal and supplementary therapeutic options. Treatment of choice depends on the form and severity of the disease and may require multimodal therapy. Descriptions of specific treatment protocols are minimal but are usually centred around reducing the number of VPC and the grade of arrythmia, and thus hopefully decreasing syncopal episodes and the risk of sudden death. Most ARVC cases are presented with these symptoms and the application of antiarrhythmic agents are most frequently indicated and discussed [2, 92]. Treatment of the less commonly occurring form, that with myocardial dysfunction, is approached with the aim of alleviating the coinciding signs of cardiac failure.

The ideal time to initiate the application of antiarrhythmic agents is not clearly standardised or established and clinicians should approach treatment modalities on an individual basis. With that in mind, there are commonly adhered to guidelines. Syncopal

patients are a clear indication for initiating pharmacological therapy. Boxers with sustained ventricular tachyarrhythmia or at least >1000 VPC/24hr on Holter ECG should also be considered as first choice for the application of antiarrhythmic agents [2]. Meurs et. al. compared four commonly applied antiarrhythmics (procainamide, atenolol, sotalol, and mexiletine), and confirmed the use of sotalol, or a mexiletine-atenolol combination, as the two most effective agents for reducing VPC and improving the grade of the arrhythmia [92]. Pre- and post-treatment ambulatory ECG demonstrated both drug protocols had the ability to reduce >85% of VPC in most dogs and decrease the severity and complexity of the arrhythmia also. No significant improvement was observed in dogs receiving treatment with either procainamide or atenolol alone [92]. It's worth noting that these same agents, who effectively tackled the rhythmic alterations, did not seem to have a worthy effect on the number of syncopal episodes. Theoretically, targeting the arrythmia should also influence the frequency of syncope. One likely explanation for this is due to individual manifestations of the disease or individual reactions to the medication. A proarrhythmic effect could be detected in some of these cases, further proving individual reactions. Most antiarrhythmics can possess a proarrhythmic effect and is considered proarrhythmic if the frequency of VPC increases by 85% [92].

For the smaller portion of Boxers that present with systolic impairment and signs CHF, pharmacological treatment is effectively identical to that previously described for dogs with CHF because of progressive DCM. Once LV systolic dysfunction is confirmed, pimobendan, diuretics, and ACE inhibitors are indicated to alleviate the signs of myocardial failure and improve the quality of life of these Boxers. The individual state of cardiac failure is assessed and treated appropriately.

The use of fish oils and L-carnitine can prove beneficial in the supplementary treatment of this CM. This review has already previously explored the cardioprotective effects of these supplements in the previous myocardial disease, and their application should be considered. Omega-3 fatty acids in fish oils has already proved to show an antiarrhythmic effect in a population of Boxers. Compared to flax oil and a control group, who showed no overall improvement, the fish oils demonstrated the ability to reduce the mean number of VPC/24hr from 397 to 162 [93].

Novel therapies for battling this condition are being widely investigated all the time and their importance cannot be overlooked. Implantable cardioverter defibrillators have demonstrated many benefits in the countless human trials and successful application in the treatment of a Boxer with ARVC has been described [94]. This management strategy is

understudied and requires research on a large-scale population basis. Human medicine is continuing to shed a lot of light on new therapeutic options, evident in the stem cell-based approaches being explored. Stem cells are proving beneficial in cardiac diseases to interpret the pathologic mechanisms in the background and to regenerate the damaged myocardium [95]. Emerging therapies offer hope for future advancements in our field, but currently, a multidisciplinary approach is required, and it is crucial that veterinarians and human physicians combine their expertise and collaborate to conquer these complex conditions.

3.4 Hypertrophic Cardiomyopathy – (HCM)

HCM is a very rare condition in canine patients compared to their feline counterparts, but it deserves brief acknowledgement and insight in the event of that rare occurrence. It was previously thought to be more prevalent in larger breeds but has since shown to have no predilection and can occur in any breed, regardless of size, sex, or age [96]. This cardiomyopathy is substantially detailed in humans and felines but the available body of research describing HCM in dogs is limited. There are small differing aspects, between species, of the dynamics and consistency of the hypertrophy, but regardless the final result is concentric thickening of the left ventricle [96]. Confirmation of LV hypertrophy in dogs is not automatically indicative of HCM and other causes should be excluded. Underlying conditions such as subaortic stenosis and systemic hypertension may increase the pressure within the ventricle, resulting in the consequential hypertrophy of the chamber wall [2], and these should be ruled out first. The recent retrospective study detailing the signalment, signs, diagnostics, and survival in dogs with HCM identified HCM as the initiating cause in just 20% (68/345) of dogs with LV hypertrophy. The final diagnosis was concluded through rigorous exclusion of numerous other potential causes of myocardial hypertrophy and other miscellaneous reasons (Fig.6) [96].

HCM cases are usually suspected after detection of an asymptomatic systolic murmur resulting from outflow obstruction. Syncope, sudden death and/or clinical signs of concurring CHF (e.g., lethargy and respiratory distress) may also be present [2]. Diagnostics may prove challenging due to the rarity of the CM and the diverse clinical presentations. ECG and thoracic radiography may show varying and unreliable arrythmias and cardiomegaly respectively [2]. The gold standard method for definitive diagnosis is discovery of concentric LV hypertrophy by echocardiogram, in the absence of another

known systemic disease [2, 96]. Confirmation of hypertrophy of the LV wall can be based on comparison to healthy control measurements and rigorous exclusion of other diseases [96].

Treatment of HCM shares some similarities and differences to that of other CM. Heart rate and arrythmias can be controlled, and ventricular filling can be encouraged, using beta-blockers. In the case of coexisting CHF, diuretics and ACE inhibitors are warranted, but in the case of an outflow obstruction the use of positive inotropes, such as pimobendan, can be contraindicated [2]. Through appropriate therapy and lifestyle modification, prognosis of HCM can be favourable. Though standardised therapies are still lacking due to the rare occurrence, we can still derive effective treatment from the protocols of other cardiac diseases and those used in other disciplines and species.

Reason	n
Systemic hypertension	104
Chronic kidney disease	78
Dehydration	24
Hyperadrenocorticism	17
Congenital heart disease	18
Blood pressure not recorded	12
Cancer	11
Poor echocardiographic image quality	11
Concurrent use of furosemide	10
Pheochromocytoma	10
Drugs possibly leading to LV hypertrophy	10
Hyperthyroidism or L-thyroxine supplementation	5
Subaortic stenosis	5
Severe systemic disease	5
Records not available	4
Diabetes mellitus	2
Severe pulmonary hypertension with LV underfilling	2
Polycythemia vera	2
Concurrent use of prednisone	2
Equivocal LV wall thickening	2
Amyloidosis	1
Severe arteriosclerosis	1

Fig.6: Listed reasons for exclusion from a HCM diagnosis. Note that many of these reasons (e.g., systemic hypertension, subaortic stenosis, and concurrent use drugs potentially leading to LV hypertrophy) could result in a degree of myocardial hypertrophy due to increased resistance. Conclusively ruling out HCM. n=277 dogs. Image sourced from citation [96].

4 Discussion and Conclusion

Evidently heart disease poses significant challenges in veterinary medicine. Of the frequently detected acquired cardiac diseases in canine patients, cardiomyopathies represent a complex collection that can frequently result in cardiac failure and death. Over the years a vast amount of research has continuously been undertaken in both human and veterinary medicine alike to acquire and evolve a better understanding of the pathophysiological mechanisms and the genetic and environmental factors contributing to these diseases.

Various classifications of cardiomyopathies have been established, defined, and redefined throughout the decades. Though these definitions are typically derived from the human field, we in veterinary medicine attribute the same classifications to our patients, given the striking similarities in the pathophysiology and physical manifestations. This review aimed to analyse and highlight the cardiomyopathies frequently encountered in canine patients. DCM and ARVC are the two most prevalent CM in this species with an array of available research and documentation. HCM occurrence in dogs is very rare but exists, and almost mirrors the manifestation of the disease in their feline counterparts.

DCM is a severe and prevalent cardiac disease in canines, representing the most common heart disease in which the myocardium is afflicted. DCM describes a phenotype, defined by eccentric dilation of the cardiac chambers. The final phenotype may result from a primary or secondary origin. Secondary DCM, of a nutritional nature for example, does not occur so frequently, and in fact it is the idiopathic or primary DCM which is attributed to most cases. This review explored the hereditary nature of idiopathic DCM and the genetic mutations linked to specific breeds. Dobermann pinscher currently stand as the breed most frequently presenting with idiopathic DCM [8]. The mostly identified causative genetic mutations in this breed are those of the pyruvate dehydrogenase kinase 4 (PDK4) and titin (TTN) genes [24, 25]. The proteins encoded by these genes are vital to physiological cellular processes of the myocytes and dysfunction in their regulatory role compromises cardiac function. Different genetic mutations associated with other breeds was also detailed (e.g., phospholamban gene in Welsh Springers), however large-scale genetic studies in these breeds are still lacking.

With so many multiplex elements in the background of DCM, the presentation and overall manifestation is rather heterogenous. Different breeds present at varying life stages with most appearing in middle-age. When cases do appear, they are usually in a

progressive stage of CHF [9]. Respiratory distress, coughing, and exercise intolerance are usually the initial observation, and even episodes of collapse. Less evident signs may only be detected after a detailed physical exam. The existing diagnostic tools to detect DCM are very capable and newer ancillary tools continue to emerge and show promise. Biomarker analysis, genetic screening and advanced imaging techniques, that was detailed in this piece, have made definitive diagnosis more achievable. With these diagnostic methods we can detect certain, subtle cardiac changes, before progression into overt cardiac failure and this emphasises the importance of early screening to achieve affective interventions.

ARVC, though less common than DCM, still presents a severe situation to afflicted dogs and this review aimed to bring to light the necessary knowledge needed to effectively manage these conditions. Life-threatening arrhythmias and structural fibrofatty remodelling of the myocardium are the characteristic features. Boxer dogs represent the most common breed with this CM and because of this it was originally coined ‘boxer cardiomyopathy’ by Harpster [75, 76]. As in DCM, ARVC also carries a familial inheritance and deletion mutations of striatin (STRN) have been widely identified as the gene of most concern [77].

Syncopal episodes, brought about by sustained VPCs, are the usual presenting complaints. The VPCs are detected using ECG. Potentially, a single reading may detect the sustained arrhythmia but typically we diagnose these dogs based on 24-hour ambulatory Holter. Contrary to DCM, advanced CHF only occurs in a smaller percentage of patients, but nonetheless is a possible risk [2, 86]. The available diagnostic modalities are similar to those mentioned for DCM. In ARVC, the pathognomic manifestation is that of the ventricular ectopies, making ECG reading the gold standard method for detection. The characteristic histological features are assessed postmortem. Biomarker analysis is also useful here for detection of myocardial injury and should be used as supplementary protocols.

To conclude, this literature review aimed to offer a detailed understanding of the common cardiomyopathies in canine patients. The insights gained from this review underscore the significance of early detection, risk assessment, and tailored therapeutic approaches, promising improved quality of life and longevity for dogs affected by these complex heart diseases. It also highlights the imperative need for ongoing research to elucidate the intricate genetic underpinnings and expand our knowledge of these conditions, ultimately improving diagnostic and therapeutic strategies for canine cardiomyopathies in the future.

5 Acknowledgments

I wish to extend my sincerest thanks to my thesis supervisor, Dr. Gergely Kiss DVM, for his constant support, guidance, and feedback. His comments and encouragement have been indispensable in the shaping of this work, and I am thoroughly grateful for his time, expertise, and patience.

I also wish to extend my thanks to the professors at the department of internal medicine for their informative lectures throughout the years. Lest not forgot, I wish to thank the dedicated library staff at Hutÿra Ferenc library for their constant efforts to aid students.

Lastly, I am grateful for the continuous support and motivation from family, friends, and colleagues during the composition of this review piece.

None of this work, or my studies at UVMB would have been possible without the collective efforts of these people. Thank you for everything.

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(Citations formatted according to UVMB "Guide to Creating References in Theses and TDK papers", (2021))

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