A Case Study and Literature Review of Arrhythmogenic Right Ventricular Cardiomyopathy in the Horse

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1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heart muscle disease characterized by the progressive degeneration of cardiac myocytes, which are replaced by fibrofatty tissue (Marcus et al., 2010; Pilichou et al., 2016). As the name of the disease would suggest, it is usually the right ventricle that is more severely affected, with more extensive replacement of myocardium with fatty or fibrofatty tissue (Corrado et al., 1997). However, the histological manifestation of the disease may progress to reach the ventricular septum, encroach into the left ventricle and even the atria (Meurs, 2017). Some studies have suggested that the spread of the infiltration has a wave front pattern, from epicardium to endocardium (Basso et al., 2004; Oxford et al., 2011; Gandjbakhch et al., 2018).

Arrhythmogenic right ventricular cardiomyopathy is a disease reported in humans and Boxer dogs. Other domestic species, such as the cat and horse, are less commonly affected, with very few reported cases in these species. The clinical characteristics of ARVC are very similar in humans and dogs; including monomorphic left bundle branch block ventricular arrhythmias, heart failure and sudden cardiac death (SCD) (Basso et al., 2004; Sen-Chowdhry et al., 2010). Clinical signs include dizziness, syncope and heart palpitations (Nava et al., 2000). However, some cases of ARVC have no previous clinical symptoms, with sudden death being the first indication of the disease. The typical clinical feature of ARVC is a life-threatening ventricular arrhythmia that may, or may not, be associated with structural changes to the myocardium (Meurs et al., 2014).

The disease is familial in humans and the Boxer dog (Basso et al., 2004; Sen-Chowdhry et al., 2010). The heritability of the disease in humans has been linked to mutations in genes encoding for the cardiac desmosome proteins (Gandjbakhch et al., 2018). However, studies have shown that desmosome mutations are not responsible for ARVC in Boxer dogs. The aetiology and inheritance of the disease in other domestic species is unknown. Arrhythmogenic right ventricular cardiomyopathy has only been reported in three horses in the United Kingdom (UK), with two published papers to date. These papers have suggested a diagnosis of ARVC or ARVC-like disease in the three horses as a result of post-mortem examination. The aim of this review is to outline an unreported suspected case of ARVC in a horse who died suddenly and unexpectedly in the United States of America (USA). The review will also compare the suspected case of ARVC in this horse to those reported in the previous two published papers and to ARVC cases in humans and dogs.

2. Case Report

2.1. Signalment and History

A 25-year-old, Clydesdale gelding was presented for post-mortem examination at the Department of Biomedical Sciences, Section of Pathology, Cummings School of Veterinary Medicine, USA. The horse had previously been used as a patrol horse by the Boston Park Rangers. After developing arthritis, the horse had been retired for three years. Sudden death with no previous clinical signs was reported by the owner.

2.2. Pathology Report

Case number: N10-188

A 625 kg 25 years old Clydesdale gelding is examined at 1:00pm on May 21, 2010 (post-mortem interval of 22 hours) by Ildiko Erdelyi DVM, PhD. The animal is in good nutritional status with adequate subcutaneous, omental, and perirenal adipose tissues. The right mandibular incisor one is cracked. There is mild calculus on all teeth.

There is approximately 100 ml of dark red haemorrhagic pericardial fluid. The subendocardial myocardium throughout the right ventricular septum and free wall is replaced by a poorly demarcated, 1 – 5cm thick area of homogenously pale tan tissue. This is most prominent (and nearly transmural) below the tricuspid valve along the right ventricular free wall. The right atrium is less affected. The right ventricular free wall is 2.0 – 3.2 cm thick, the interventricular septum is 3.5 – 6.0cm thick and the left ventricle is 2 – 3.5cm thick.

There are irregularly shaped segmental transmural haemorrhages (up to 7.0 x 6.0 cm) throughout the mid to distal jejunum. There is multifocal to coalescing dark red/black discoloration throughout the fundus of the stomach. There is a 2.0 x 2.0 x 1.0 cm lipoma at the mid ileal mesenteric root. There is a 3.0 x 4.0 x 2.0 cm mesenteric lipoma at the base of the cecum. The stomach contains 5kg soft dry fibrous green ingesta. The small intestines contain approximately 4 litres of green-brown fluid. The cecum contains 8kg, the large colon 6kg, small colon 7kg of semi-soft to dry fibrous green.

Summary of gross findings

Regionally extensive discoloration is seen in the heart, affecting the interventricular septum, right ventricle and atrium. In the jejunum, mild multifocal segmental transmural haemorrhage is noted.

Histology

Heart: approximately 30-50% of the myocardium is replaced by variable sized, multifocal to coalescing sheets of well-differentiated adipocytes which are separated by moderate amounts of collagenous connective tissue (Figure 1A). The adjacent myofibers and the remaining entrapped myofibers are fragmented, shrunken with loss of nuclear staining and cytoplasmic cross striation. The Pukinje fibers are disrupted by the fibrofatty tissue (Figure 1B) and exhibit mild cytoplasmic swelling and vacuolation.

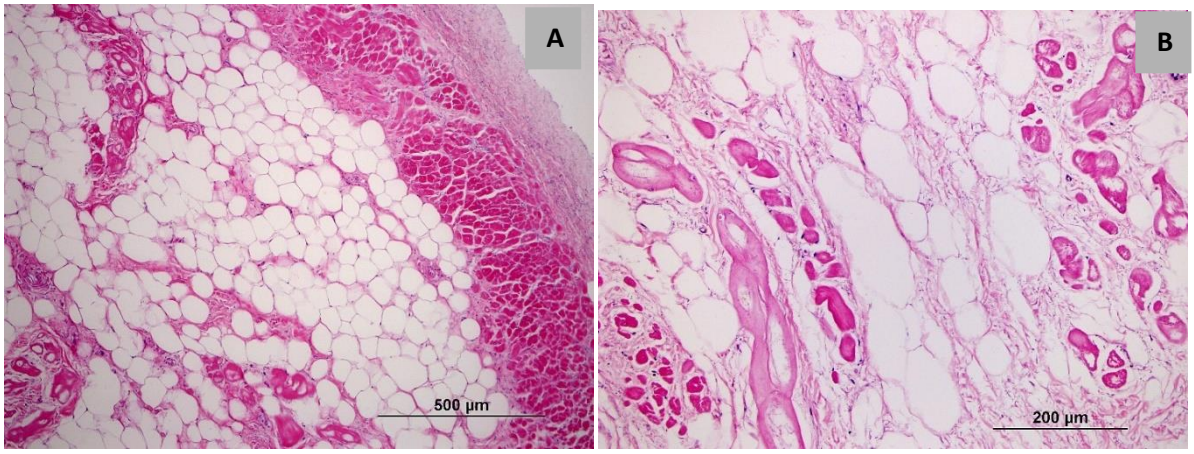

Figure 1: Histopathology Slide (A) right ventricle showing adipocytes with haematoxylin and eosin stain, Bar 500 micrometers (B) disrupted Purkinje fibres with haematoxylin and eosin stain, Bar 200 micrometres

Brain: the large motoric and sensory neurons in the brain stem, midbrain and thalamus, the Pukinje cell in the cerebellum, neurons and fewer glial cells throughout the cerebral grey matter contain abundant cytoplasmic golden-brown pigment (lipofuscin). Few similar pigment-rich macrophages are multifocally present in the peri-, and intravascular spaces.

Pituitary gland: the pars intermedia is expanded and effaced by a regionally extensive, non-encapsulated, well-demarcated expansile mass that compresses the adjacent pars nervosa and pars distalis. The mass is composed of small nests of polyhedral to pyriform neoplastic cells that are separated by fine fibrovascular septa with numerous thin walled congested capillaries. The neoplastic mass is surrounded by small aggregates of pigment-rich macrophages.

Adrenal glands: the medulla of the right adrenal is focally expanded and effaced by a non-encapsulated, moderately well demarcated mass. The mass contains polyhedral neoplastic cells separated by well vascularized fine fibrovascular stroma. Nodules of zona fasciculata cells exhibit marked swelling, abundant clear cytoplasmic vacuoles that replaces the nuclei to the periphery. There is marked atrophy/loss or cytoplasmic vacuolation of the cells in the zona reticularis associated with mild diffuse fibrosis and small numbers of pigment-rich macrophages.

Morphological diagnosis

The heart showed marked subendocardial fibrofatty infiltration of the right ventricle, atrium and septum and subepicardial fibrofatty infiltration of the left ventricle and atrium. There was also multifocal to coalescing extensive myofiber necrosis/loss. Both of which are consistent with Arrhythmogenic Right Ventricular Cardiomyopathy. There was a mass in the pituitary gland pars intermedia, likely to be an adenoma. The right adrenal gland contained a non-capsulated mass, assumed pheochromocytoma (unilateral). The cause of sudden death in this gelding is likely the result of arrhythmia associated with the marked fibrofatty infiltration with extensive myofiber necrosis and Purkinje fibre disruption. However, the pheochromocytoma may have contributed to cause of death if tachycardia was present.

3. Review of Literature

3.1. Arrhythmogenic Right Ventricular Cardiomyopathy in Humans

Arrhythmogenic right ventricular cardiomyopathy is a rare (1:2000–1:5000) inherited cardiac condition in humans (Pilichou et al., 2016). It was first described in 1982 as a dysplasia because it was thought to be a congenital defect in the development of the right ventricular myocardium (Marcus et al., 1982). However, subsequent research into the disease revealed that it may be caused by a genetic defect in the cardiac desmosomes and, it is therefore, classified as a cardiomyopathy (Maron et al., 2006). Arrhythmogenic right ventricular cardiomyopathy predominantly occurs in individuals between adolescence and early adulthood. Rarely is it found in children or those over sixty years old (Dalal et al., 2005), with 80% of cases being diagnosed before the age of 40 years (Gemayel et al., 2001). Some studies suggest that men are more commonly affected than women (Camm et al., 2013). However, other studies have recorded no difference in prevalence of ARVC between the sexes. The reason for the over-representation of males in some studies has been attributed to male hormones and their possible role in the pathogenesis of ARVC, however, there has been little evidence of this. It may be more likely due to social or cultural differences between geographical locations.

3.1.1. Clinical Presentation of ARVC in Humans

Arrhythmogenic right ventricular cardiomyopathy has been described as a progressive disease, with varying stages of disease corresponding to typical presentation types. There have been four main clinical presentations of disease described (Corrado et al., 1990); the earliest of which may be asymptomatic or concealed disease. Although structural changes in the heart may not be present in this phase (Muthappan & Calkins, 2008), the risk of sudden cardiac death (SCD), particularly during exercise, is significant. Arrhythmogenic right ventricular cardiomyopathy has been reported the second most common cause of sudden death in the young (Thiene et al., 1988) and the main cause of sudden death in competitive athletes in the Veneto Region of Italy (Corrado et al., 1990).

The second phase of ARVC, described by described by Corrado et al., (1990), is characterised by symptomatic ventricular arrhythmias. These arrythmias are usually seen in patients in their thirtieth to fortieth years of life and are commonly triggered by effort/work. Ventricular arrythmias in ARVC patients usually have left bundle branch block morphology (LBBB), reflecting a right ventricular origin of the arrhythmia (Muthappan & Calkins,

2008). These arrhythmias range from isolated premature ventricular beats to sustained ventricular tachycardia (VT) with LBBB morphology, up to ventricular fibrillation leading to cardiac arrest (Thiene et al., 2007). The milder arrhythmias may cause palpitations and syncope, or they may even be asymptomatic. The typical electrocardiography (ECG) findings in this phase are described later in this review.

Patients may present with right heart failure in the fifth decade of life and beyond (Prior & La Gerche, 2020). This represents the third presentation type described by Corrado et al., (1990) and usually occurs in the later phase of disease. The progressive loss of the right ventricular myocardium may impair the mechanical function of the RV and account for severe pump failure (Thiene et al., 2007). The fourth presentation type is biventricular heart failure, which occurs when the disease involves the ventricular septum and the LV, resulting in congestive heart failure. This phase often has a similar presentation as dilated cardiomyopathy and it is important to differentiate between the two diseases. In this stage, ventricular arrythmias may be pleomorphic, originating from different cardiac regions. The involvement of the ventricular septum and LV worsen the prognosis of these patients and the formation of endocavitary mural thrombi is common. In such conditions, contractile dysfunction may be so severe, the patient will require cardiac transplantation (Thiene et al., 2007).

Despite some evidence of ARVC being a progressive disease with clear clinical phases, phenotype and clinical presentation of the disease tends to vary significantly between individuals. Some patients may remain completely free of disease throughout their life, despite being genotypically positive for ARVC. This variability is yet to be fully explained and the mechanisms behind it are likely complicated. Heterogenicity and reduced penetrance of the genetic mutations causing the disease are likely to account for some variation in course of disease and presentation types. However, exercise has repeatedly been implicated in the early presentation of ARVC in patients and is, therefore, a likely factor in the variability of phenotypic presentation of ARVC. Other environmental factors such as inflammation, viral and bacteriological infections or apoptosis may facilitate disease progression and presentation. All of these factors need further investigation.

3.1.2. Pathological Presentation of ARVC in Humans

The pathological features of ARVC have been well documented in humans. The hallmark histological feature of ARVC is the loss of right ventricular myocardium with substitution of fibrous and fatty tissue (Sen-Chowdhry et al., 2005). Macroscopically, ARVC may look like a "fatty heart" (*adipositas cordis*), but to make a differential diagnosis, there are two important histological features that will provide a clear diagnosis of ARVC: significant fibrosis (replacement-type) and/or degenerated changes of the myocytes entrapped within the area of fibrous/fatty tissue (Basso & Thiene, 2005). Inflammation and apoptosis are also common pathological mechanisms reported in ARVC cases, but their presence is variable. It remains unclear if inflammation and apoptosis are primary triggers of ARVC or if they are consequences of the disease.

The replacement of myocytes with fibrofatty scar tissue has been shown to progress from the epicardium toward the endocardium and extend to become transmural. The disease predominantly involves the right ventricular free wall, however, progression into the ventricular septum, left ventricle and atria have also been described (Meurs, 2017), with 50% of cases involving the left ventricle (Basso et al., 2009). The result of the fibrofatty infiltration is a thinning of the ventricular wall and aneurysmal dilation. These changes are typically seen in a region termed the "Triangle of Dysplasia"; the inflow tract (sub-tricuspid region), outflow tract (infundibular region) and apex (Marcus et al., 1982; Basso et al., 1996). These locations are particularly vulnerable to aneurysm formation due to continuous cycles of mechanical stress.

The fibro-fatty replacement of myocardial tissue seen in ARVC has two distinct patterns; a predominantly fatty infiltration (fatty or lipomatous pattern) and a fibrous and fatty infiltration (fibrofatty or fibrolipomatous pattern) (Thiene et al., 1988). These two patterns show differences in their pathological presentation. In the fatty variant, the adipose tissue reaches the endocardium (transmural infiltration) and the heart may even show an increase in wall thickness ("pseudo-hypertrophy") (Basso et al., 1996; Thiene & Basso, 2001). There may be small, focal areas of fibrous tissue, but these are only detected with higher magnification power. This pattern is usually confined to the right ventricle and aneurysms are only seen occasionally. In the fibrofatty variant, the wall is thinner and translucent, which results in aneurysms in approximately 50% of cases. The septum and left ventricle are commonly affected (20% and 47% respectively) (Basso & Thiene, 2005).

These two patterns of ARVC may not be distinct disease forms but rather, states of progression of the disease. The fatty variant is thought to be an earlier, milder form of ARVC, with lower occurrence of aneurysms seen in this variant than the fibrofatty form. The fibrofatty infiltration is thought to occur in an attempt to repair the initial damage to the heart by the predominantly fatty infiltration, as evident by the extensive replacement-type fibrosis and myocyte death degeneration, and is therefore considered to be a more progressed form of the disease. Inflammation is also commonly involved in this pattern type, with two thirds of cases having inflammatory cell infiltrates (CD43-positive T-lymphocytes) associated with focal myocyte necrosis. Some studies report that the fibrofatty replacement of the myocardium occurs as a healing process in response to the inflammatory disease such as chronic myocarditis (Thiene et al., 1991). However, the role of inflammation in the pathogenesis of ARVC is still undetermined and there is no conclusive evidence of disease progression or different pathomechanisms of ARVC.

3.1.3. Diagnosis of ARVC in Humans

The diagnosis of ARVC is often challenging, especially during the early phase of the disease, due to the non-specific nature of the clinical findings. There is no single gold standard test, the best strategy involves combining information from several diagnostic tests. Currently, the diagnosis of ARVC in humans is based on the presence of major and minor standardised Task Force Criteria (Table 1), including ECG, ventricular arrhythmias, right ventricular function and morphology, histopathology and family history. The Diagnosis is established when two major, one major plus two minor, or four minor criteria from different groups are fulfilled.

Table 1: Task Force Criteria for ARVC Diagnosis (adapted from McKenna et al., 1994)

Criteria	Major	Minor
I. Global and/or regional dysfunction and structural alterations	Severe dilatation and reduction of right ventricular ejection fraction with no/mild left ventricular impairment Localised right ventricular aneurysms Severe segmental dilatation of the right ventricle	Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle Mild segmental dilatation of the right ventricle Regional right ventricular hypokinesia
II. Tissue characterisation of wall	Fibrofatty replacement of myocardium on endomyocardial biopsy	
III. Repolarisation abnormalities		Inverted T waves in right precordial leads (V2 and V3) (>12yrs old, in absence of right bundle branch block)
IV. Depolarisation/conduction abnormalities	Epsilon waves or localised prolongation (>110 ms) of the QRS complex in right precordial leads	Late potentials (signal-averaged ECG)
V. Arrhythmias	Arrhythmias plus T-wave abnormalities (see III)	Left bundle branch block type ventricular tachycardia (ECG, Holter, exercise testing) Frequent ventricular extrasystoles (>1000/24-h) (Holter).
VI. Family history	Familial disease confirmed at necropsy or surgery	Family history of premature sudden death (<35yrs) due to suspected ARVC Family history of ARVC (clinical diagnosis based on present criteria)

Electrocardiogram abnormalities are detected in more than 90% of patients with ARVC (Nasir et al., 2004; Dalal et al., 2005). Typical ECG features include presence of precordial T wave inversions (TWI) beyond lead V2, an epsilon wave in leads V1 to V3 and a widened QRS complex in leads V1 toV3 (parietal block). The T-wave inversion in leads V1 to V3 are present in 87% of patients with ARVC and are considered a minor diagnostic criterion in the absence of a right bundle branch block. The "epsilon waves," are "postexcitation" electrical potentials of small amplitude that occur in the ST segment after the end of the QRS complex (Muthappan & Calkins, 2008) and are a strongly indicative of intraventricular impulse conduction delay (Fontaine, 1995). They are considered a major diagnostic criterion for ARVC and are present in 33% of patients with ARVC (Nasir, et al., 2004). Late potentials at the end of the QRS complex may be seen on signal average ECG (wide amplitude superficial ECG). They correspond to the epsilon wave on surface ECG and reflect areas of slow intraventricular conduction due to islands of surviving myocardium interspersed with fatty and fibrous tissue. The slow the electrical conduction in the right ventricle may also cause localized widening of the QRS complex (≥110 milliseconds) in the right precordial leads, which is seen in 64% of the patients with ARVC.

Cardiac imaging with echocardiography, angiography or magnetic resonance imaging (MRI) is used to assess the structural and functional abnormalities of the right ventricle. Major criteria consist of severe dilatation and reduction in systolic function of the RV, with no/mild impairment of the LV; localized RV aneurysms; and severe segmental dilatation of the RV. Minor criteria are mild global RV dilatation and/or reduction in ejection fraction with normal LV, mild segmental dilatation of the RV free wall and regional RV hypokinesia. Although angiography is often the most specific tool for revealing aneurysms localized in infundibular, apical and sub-tricuspid regions (specificity >90%), it is an invasive technique and may not be the first choice of diagnostic tool in all cases (Muthappan & Calkins, 2008).

Echocardiography is a less invasive and easily available, which makes it a first line method in patients with suspected ARVC or in family screening. It also allows serial examinations and is commonly used in follow-up examinations to assess disease progression. Common structural changes in more progressed disease states include right ventricle wall motion abnormalities (79%), trabecular derangement (54%), and sacculations (17%) (Basso et al., 2009). These are identifiable when using echocardiography, however, identifying structural and functional changes in the earlier, milder phases of the disease is

more challenging as the changes may only be very subtle. Magnetic resonance imaging is an attractive tool because it is non-invasive and has the ability to distinguish fat tissue from muscle. A potential advantage of using MRI lies in its ability to detect early signs of ARVC, such as regional and diastolic ventricular dysfunction, which could otherwise escape diagnosis by Task Force Criteria. Magnetic resonance imaging with gadolinium enhancement can detect intramyocardial fibrosis, which is important because this finding can precede functional abnormalities, thus allowing early disease detection and management (Sen-Chowdhry & Syrris, 2006; Sen-Chowdhry et al., 2007).

Transvenous endomyocardial biopsy of the right ventricular free wall can assist diagnosis by indicating fibrofatty replacement. This technique is preferably guided by using echocardiography, MRI, or electroanatomic mapping. Myocardial atrophy due to fibrofatty replacement, with a residual amount of myocardium of less than 60% should be regarded as a major diagnostic criterion, whereas an amount of 60–75% is a minor diagnostic criterion (Basso et al., 2009). There is a potential role of endomyocardial biopsy in the early diagnosis of ARVC as preliminary data indicates that changes in the various intercalated disk proteins are detectable with immunohistochemical staining. However, further studies are needed to confirm the use of this method in early diagnosis (Saffitz, 2005; Fidler et al., 2008).

Finally, diagnosis of ARVC through information of family history is used by the Task Force Criteria. Familial disease confirmed at necropsy or surgery is a major criterion, whereas family history of premature sudden death (<35 years) or a family history of clinical diagnosis based on the present criteria, are considered minor criteria.

3.1.4. Genetic Background of ARVC in Humans

The familial characteristic of ARVC in humans is thought to be a consequence of a mutation in a gene encoding cardiac desmosomal proteins. Desmosomes are intercellular junctions found in cardiac muscle, epithelia, and some other tissues. They are located at the cell membrane where they act as anchors for intermediate filaments of the cell cytoskeleton. By linking intermediate filaments of adjacent cells, desmosomes form a network of adhesive bonds, providing structural support and mechanical strength throughout a tissue (Al-Jassar et al., 2013). The desmosomes in the cardiac muscle reside within intercalated disks of the cardiac myocytes (Saffitz et al., 2010).

As seen in Table 2 below, desmosome proteins are coded for by three gene families: the cahedrin, armadillo and planktin families (Delmar & McKenna, 2010). The cahedrin family is responsible for producing desmoglein (Dsg) and desmocollin (Dsc) proteins, which act as adhesion molecules. The armadillo family produces plankoglobin (Pg) and plankophilin (PKP) and the plankin family produces desmoplankin (DP), which all act as linker proteins. Although desmosomes are also found in other tissues around the body, myocardial desmosomes have cardiac specific isoforms of the proteins which are limited to PKP2, Dsg2 and Dsc2. Along with Dp and Pg, these three cardiac isoforms anchor the intermediate filament desmin to the cardiac myocyte plasma membrane (Bolling & Jonkman, 2009). Studies over the past 15 years have identified mutations in DP, Pg, PKP2, Dsg2 and Dsc2 as being responsible for the vast majority ARVC cases, with PKP2 mutations appearing most frequently (Basso et al., 2009; Cox et al., 2011).

Table 2: Gene Families Coding for Desmosome Proteins (adapted from *Patel & Green, 2014*)

Gene Family	Proteins	Abbreviation	Role
Cadherin	Desmoglein Desmocollin	Dsg Dsc	Adhesion molecules
Armadillo	Plankoglobin Plankophilin	Pg PKP	Linker proteins
Planktin	Desmoplankin	Dp	Linker proteins

Arrhythmogenic Right Ventricular Cardiomyopathy is hereditary in up to 50% of human patients. The disease is typically transmitted with an autosomal dominant pattern of inheritance, although, rare autosomal recessive forms have been described (Marcus et al., 2013). Typically, 50% of off-spring of an affected individual will carry the gene mutation and be at risk of developing the ARVC phenotype, although penetrance is incomplete, and expression is variable. Approximately 40-50% of patients with ARVC have been shown to have one or more mutations in genes encoding desmosomal proteins (Sen-Chowdhry et al., 2005), thus, ARVC is often referred to as a disease of the desmosome (Basso et al., 2009; Herren et al., 2009; Rickelt & Pieperhoff, 2012). Some studies suggest that this figure is actually higher and both incomplete penetrance and limited phenotypic expression are responsible for the underestimation of the prevalence of familial disease (Corrado et al., 2017). It should be mentioned that there have been non-desmosomal gene mutations described which also give rise to inherited arrhythmogenic cardiomyopathies.

3.1.5. Pathogenesis of ARVC Disease in Humans

The hallmark histological feature of ARVC is the loss of myocytes with an infiltration of fibro-fatty tissue in the heart, however, the mechanisms by which these changes occur are poorly understood. Degeneration of the myocytes is thought to play a major role in the pathogenesis of ARVC (Patel & Green, 2014). Desmosomes, located in the intercalated discs (ICD), link the adjoining myocytes in the heart tissue and any disruption in the desmosome function will result in a disruption of the linking myocytes and loss of adhesion between myocytes. This impaired cell adhesion could lead to accelerated apoptosis of myocardial cells and degeneration of the myocardium, resulting in areas susceptible to replacement with fibrous and fatty infiltrate as a result of healing processes.

Transdifferentiation of tissue may be another pathway of fibrofatty infiltration of the heart. People with ARVC have an increased activity of adipo-fibrogenesis in their heart tissue, which is thought to involve the canonical Wnt–β-catenin signalling pathway (Corrado, et al., 2017). This pathway plays a vital role in myocyte differentiation and normal myocardial architecture. The β-catenin is involved in preventing the differentiation of mesodermal precursors into adipocytes and fibrocytes by suppressing the expression of adipogenic and fibrogenic genes. Genetically defective desmosomal proteins cause the translocation of plakoglobin from the sarcolemma to the nucleus (Lombardi et al., 2011), where it may antagonize the effects of β-catenin. By competing with β-catenin, intranuclear plakoglobin suppresses Wnt–β-catenin signalling and induces a gene transcriptional switch from myogenesis to adipogenesis and fibrogenesis (Garcia-Gras et al., 2006).

Inflammatory processes have also been postulated to initiate ARVC changes in the heart, possibly irrespective of desmosome mutations. Therefore, inflammation may play a larger role in non-familial ARVC cases. Inflammatory infiltrates are commonly seen in ARVC patients (Asimaki et al., 2011) but it is still unclear whether the inflammation is a cause of ARVC, a result of ARVC or an incidental finding. The fact remains that there is no clear cause of the fibrofatty replacement and none of the pathways mentioned above are mutually exclusive. It may be the case that all three are involved, to some extent, in the development of ARVC disease. However, it is evident that the fibro-fatty replacement of myocytes in the heart plays a major role in the disease and contributes to the development of ventricular arrhythmias, typically seen in people with ARVC, through slowing intraventricular conduction.

Fontain et al., (1984) suggested that the pathophysiology of ventricular arrythmias in ARVC is similar to the macro-entry mechanism seen in the case of ventricular scaring. The heart tissue contains areas of dense fibrosis with regions of surviving myocyte bundles (Soejima et al., 2002), thus, the fibrosis separates the myocyte bundles and causes conduction blocks (forming the boarders of the so-called re-entry circuits). This forces the excitation wave to take a circuitous course through the bundles (Stevenson, 2009). Furthermore, conductivity between cells can be diminished. This uncoupling of myocyte bundles slows conduction, although action potentials and ion channels in the myocytes can be relatively normal.

In some cases of ARVC, fatal ventricular arrythmia occurs with no previous clinical signs and with little or no fibrofatty infiltration of the heart. Therefore, it is likely that there are additional alterations to the heart tissue, other than fibrofatty infiltration, that contribute to the ventricular arrhythmias seen in ARVC patients. Remodelling of the ICD is thought to be one such alteration. Desmosomes, adherens junctions and gap junctions are the 3 main components of the ICD; gap junctions facilitate cell-to-cell propagation of the electrical impulse between cardiac myocytes (Delmar et al., 2009; Gutstein et al., 2001), whilst desmosomes and adherens junctions are essential for the mechanical coupling between neighbouring cells. Unlike in epithelial tissue, myocardial desmosomes and adherens junctions are not morphologically distinguishable at the ICD, they intermingle to form one electron-dense structure termed the “area composita”, which stabilises adjacent gap junctions (Bolling & Jonkman, 2009).

The components of the ICD act synergistically to regulate adhesion, excitability, and coupling of myocytes. It is, therefore, not surprising that mutations in desmosome genes have been shown to lead to changes in gap junctions, which, in turn, results in disruption of electrical impulse in the heart. Gap junctions comprise clusters of transmembrane channels, which play key roles in electrical impulse propagation and conduction velocity (Spach et al., 2000). Connexin 43 (Cx43) is the most predominant gap junction protein of the ventricular muscle and it ensures the free passage of ions and small molecules through the cells, synchronises electrical conduction and keeps the heartbeats in rhythm. Abnormal expression of Cx43 can affect the voltage-gated sodium ion channels at the cell junction, thus affecting the speed of sodium ion flow and action potential and further leading to arrhythmias (Sato et al., 2011).

There have been conflicting reports in the level of Cx43 expression in ARVC patients. Asimaki & Saffitz, (2012) and Yoshida et al., (2015) both described a decreased expression of Cx43 in patients with ARVC, whereas others found no difference in expression of Cx43 in patients with ARVC and healthy individuals (Paul et al., 2013; Kwon et al., 2013). This controversy in findings could be attributed to the lack of differentiation between severe and mild cases of ARVC. A study by Chen et al., (2017) divided ARVC patients into subgroups according to their different degrees of arrhythmia and found that patients with severe malignant arrhythmias showed significant abnormalities of Cx43 expression, while patients with less severe arrhythmias did not. These results suggest some correlation between reduced expression of Cx43 in ARVC patients and malignant ventricular arrhythmia. Furthermore, the study found that the remodelling of Cx43 had already occurred in early stages of ARVC, rather than a compensative alteration in end-stage patients (Chen et al., 2017). The findings of Chen et al., (2017) are supported by some animal models, which have confirmed that mice with cardiac-specific inhibition of Cx43 were moribund due to spontaneous ventricular arrhythmias but had preserved normal cardiac structure and systolic function (Gutstein et al., 2001). These findings suggest that decreased Cx43 expression may indicate a more malignant form of ARVC, regardless of the level of fibrofatty infiltration of the heart and may provide a useful marker for early identification of people more at risk of developing malignant arrhythmias in the future.

Although the exact consequences of desmosome gene mutations have not been concluded, it is clear that a single mutation in a desmosome gene not only affects the myocyte adhesion and structure of the myocardium, it also has several knock-on effects on the surrounding structures in the intercalated disc. Studies have demonstrated a linkage effect between mutations in a single protein and its expression, and a typical concomitant decrease in other desmosomal proteins (Zhang et al., 2010). Early immunoreactive studies found that a mutation in JUP, the gene encoding plakoglobin, lead to a decrease in plakoglobin, desmoplakin, and connexin-43 (Asimaki et al., 2007). In 2010, Xu et al. reported immunohistochemical staining in a patient with a PKP2 mutation that showed decrease in PKP-2, plakoglobin, desmin, connexin-43, N-cadherin and desmocollin 2/3 (Xu et al., 2010). It is evident that the pathophysiology and the pathways in which desmosome mutations cause disease, is complicated and yet to be fully understood. However, it seems likely that desmosome mutations play a major role in the development of familial ARVC in humans, possibly through many different pathways.

3.1.6. The Role of Exercise in ARVC

3.1.6.1. The Role of Exercise in ARVC in Patients with Desmosome Mutations

Prior & La Gerche, (2020) suggested three possible mechanisms of ARVC; a) genetic mutations of the desmosomes, leading to weak myocyte junctions; b) high mechanical force on the desmosomes (intense exercise); c) a combination of weak desmosomes and high mechanical force on the desmosomes. Individuals with desmosome gene mutations, who regularly undertake high intensity exercise, fall into the last category of ARVC mechanism. Dysfunction of desmosomal proteins predisposes the myocyte junctions to pathogenic remodelling when exposed to mechanical load (Delmar & McKenna, 2010; Saffitz et al., 2010). The dysfunctional desmosome can be mechanically torn apart when exposed to shear stress, leading to cell membrane damage and direct cell death, accompanied by inflammation and repair by fibrofatty replacement. Thus, the extra mechanical burden on the heart, which occurs during intense exercise, will accelerate and/or exacerbate the disruption of the cell-to-cell adhesion and stability (Prior & La Gerche, 2020). Cell adhesion defects are most likely to reach a critical point at places where the ventricular wall is thinnest, in part explaining why ARVC preferentially impacts the right ventricle.

There have been many studies into the effect of exercise on disease progression in individuals with known desmosome mutations. Animal model studies investigating heterozygous plakoglobin-deficient mice found that the sedentary plakoglobin-deficient mice developed gradual enlargement of the right ventricle over 10 months, when compared to wild-type mice, with no plakoglobin gene mutation (Kirchhof et al., 2006). Thus, providing evidence that gene mutations alone (without exercise) can cause ARVC symptoms. However, trained mice developed more severe RV enlargement after only 6 months, and this was associated with a high rate of spontaneous ventricular tachycardia of right ventricular origin. Thus, providing evidence that exercise will cause earlier onset and more severe clinical disease in individuals with gene mutations. In another mouse model of ARVC, phenotypic expression of a PKP2 mutation was only seen in animals who were subjected to an eight-week endurance swim training protocol and not in sedentary mice (Cruz et al., 2015). These animal studies support the concept that exercise is a trigger associated with phenotypic expression and more rapid progression of the ARVC phenotype in individuals with ARVC-associated gene mutations. However, there are no systemic human studies to confirm that the findings in the animal models can be directly extrapolated to human patients.

In a study conducted by La Gerche et al., (2010) a cohort of endurance athletes with right ventricular arrhythmias were examined, those with recognised ARVC gene mutations had worse RV function, but had engaged in less exercise than those without mutations, thereby supporting a role for exercise in progression of ARVC in gene positive athletes. Further human studies of patients with desmosome gene mutations observed that symptoms of ARVC occurred at a younger age (around 10 years earlier) in those undertaking endurance exercise when compared to sedentary individuals. The individuals that undertook endurance exercise were also more likely to have ventricular arrhythmias and heart failure than those who did the least amount of exercise (James et al., 2013; Ruwald et al., 2015). Similarly, in a cohort of patients with arrhythmogenic cardiomyopathy and mutation positive family members, a history of high intensity exercise was a strong predictor of life-threatening arrhythmias, with an eight-fold increase in risk over a median of 4.2 years follow-up (Lie et al., 2018). The evidence above, along with the sharp decline in ARVC-associated deaths after implementation of a pre-participation screening program for athletes (Corrado et al., 2006), support the theory that exercise is a contributing factor to acceleration and acerbation of ARVC in patients with gene mutations. Individuals with a confirmed gene mutation should avoid moderate to intense exercise with the aim to prevent or slow the phenotypic disease and this is reflected in recent European guidelines (Pelliccia et al., 2019).

3.1.6.1. The Role of Exercise in ARVC in Patients Without Desmosome Mutations

Desmosome gene mutations are found in approximately 50% of ARVC patients, it is therefore possible that some cases of ARVC develop due to non-genetic causes. Prior & La Gerche, (2020), stated that high mechanical force applied to the heart during intense exercise, with normal desmosome function, can lead to structural changes in the heart associated with ARVC. Similarly, it was postulated that excessive, repetitive wall stress causes disruption of normal desmosomes, eventually result in ARVC (Christiaans et al., 2012). Research into the consequences of high mechanical burden on the heart during exercise has found that the right ventricle (RV) dilates during exercise, leading to increased wall stress, whereas the left ventricle (LV) hypertrophies (La Gerche et al., 2010; La Gerche et al., 2012). Furthermore, RV wall stress at peak exercise in athletes rises by 170% compared to rest, whereas the LV wall stress only increases by 23% compared to rest (Heidbuchel et al., 2012). These findings not only show the high mechanical burden of exercise on the heart, but further explain why the RV may be particularly susceptible to

exercise-induced injury (Brosnan et al., 2014). Although RV changes are typically reversible, they can be persistent with frequent training (de Noronha et al., 2009).

Animal models have shown that exercise leads to fibrosis after long-term intensive exercise training (Benito et al., 2011). Some human studies have also found that fibrosis of parts of RV myocardium is possible over long training years. It is also evident that ventricular tachycardia can occur in athletes with regional RV fibrosis (Venlet et al., 2017). In veteran athletes, myocardial fibrosis is strongly associated with the number of marathons (>50 miles per event) (Wilson et al., 2011). All of these studies support the role of intense exercise in the pathophysiology of ARVC in athletes without confirmed desmosome gene mutations and suggest that it may be fibrosis in the myocardium, as a result of remodelling due to high mechanical burden on the heart, that is responsible for initiating the disease process. A fibrotic replacement of myocardium in hypertension or myocarditis is a well-known phenomenon, and we may see similar effects on cardiac tissue after repetitive bouts of extreme load (Mewton et al., 2011).

The term “exercise-induced ARVC” has been used to describe cases of ARVC in athletes without detectable gene mutations. Sawant et al., (2014) compared exercise history of atheletes diagnosed with ARVC, comparing those with and those without desmosomal mutations. They found that, although all the atheletes had done a similar duration of annual exercise, the altheletes with no detected mutation had done significantly more intense exercise before ARVC presentation than those with no detected mutation. In addition, top intensity exercise was associated with significantly earlier age of onset, worse structural disease at clinical presentation and shorter freedom of ventricular arrhythmia in follow up. This evidence suggests that intesnse exercise can be a cause of ARVC presentation in individuals without desmosome mutations. Furthermore, the group with no recognised desmosomal mutation had a lower rate of positive family history and were more likely to present below and up to the age of 25 years, particularly those with greatest amount of pre-symptom exercise. Thus, suggesting that there may be an “exercise-induced” ARVC form which is independent of the familial form.

However, ARVC only affects a minorty of atheletes despite similar exercise training exposure. It is, therefore, likley that the phenotypic expression of ARVC in athletes is multifacotrial, involving both genetic predisposition and environmental factors (such as intense exercise). For example, athletes with ARVC could have mutations of a gene which is not expressed phenotypically, unless subjected to an environmental trigger (such as endurance exercise). There may also be other gene mutations or defects that are not yet recognised in these athletes. It is possible that a subset of athletes with ARVC have a unique or pathologic hemodynamic response to exercise, which in turn leads to higher right ventricular load and eventually right ventricular dilatation and dysfunction. Genes involved in regulating these responses may also merit study (Sawant et al., 2014). Further investigation into genetic and non-genetic causes of ARVC are needed before conclusions are drawn about the pathomechanisms involved in ARVC in athletes without detected gene mutations.

Given the close strucutral and functional relationship between the desmosomes and the adherens junction in the intercalated disc, focus on investigating mutations in the genes encoding for the adherens junctions in athletes has began. One such mutation has been identifed in two ARVC paitents, a mutation in the adherens junction gene CTNNA2 (van Henge et al., 2013). This gene encodes the protein αT-catenin, a protein of adherens junctions in the area composita of the intercalated disc. van Henge et al., (2013) reported that the two individuals with mutations in the CTNNA2 gene fulfilled the current ARVC diagnostic criteria and their clinical phenotype was identical to that reported in ARVC patients carrying typical desmosomal gene mutations. van Henge et al., (2013) postulated that mutant αT-catenins might lead to weakened junctions between adjacent cardiomyocytes and to disruption of tissue integrity, particularly in response to excessive mechanical stress. The identification of a mutation in the adherens junction suggests that ARCV should be refered to as a disease of the intercalated disc rather than that of the desmosomes. However, futher research is required into the prevelance of mutations in the CTNNA2 gene and their role in ARVC. Interestingly, both of these individuals were diagnosed with ARVC at an early age (14 and 15 years respectively) which could be significant, however further research with larger cohort numbers are needed to conclued any relevance of age or exercise in these mutations.

3.2. Arrhythmogenic Right Ventricular Cardiomyopathy in Dogs

Arrhythmogenic right ventricular cardiomyopathy was first described in the Boxer dog in the 1980s by Harptser, who characterised the disease by fatty or fibrofatty replacement of the right ventricular myocardium (Harpster, 1983). Harpster termed this disease 'Boxer dog cardiomyopathy' but since then, careful evaluation of the disease has demonstrated striking similarities to ARVC in humans, and therefore it has been reclassified as 'Boxer ARVC' (Meurs, 2004). Although cases of ARVC have been reported as single cases in some other dog breeds, it is most commonly reported in Boxers (Meurs, 2004).

3.2.1. Clinical and Pathological Presentation of ARVC in Dogs

Boxer dog ARVC is a disease primarily of dysrhythmia rather than systolic dysfunction (Meurs, 2004) and therefore, most dogs present with ventricular arrhythmia (VA). However, the variability in presentation ranges from asymptomatic to sudden cardiac death (as is the case in humans with ARVC). In 1983, Harpster described three categories of the disease in dogs; Category 1, showing no clinical signs but having VA, Category 2 showing arrhythmias associated with clinical signs (e.g. syncope) and Category 3, showing evidence of congestive heart failure. Dogs with Category 3 disease may have biventricular heart failure and often show symptoms such as coughing, lethargy and ascites, arrhythmias and/or syncopal episodes (Harpster, 1983). These categories are similar to those seen in human patients, as described by Corrado et al (1990), and are now refered to as concealed, overt and myocardial dysfunction. The concealed form is characterized by an asymptomatic dog with occasional VPCs with LBBB morphology, which may lead to syncope or sudden cardiac death (Basso et al., 2004). The overt form is characterized by a dog with tachyarrhythmias and syncope or exercise intolerance. Myocardial dusfunction is diagnosed least frequently and is characterized by a dog that has developed myocardial systolic dysfunction, sometimes with evidence of congestive heart failure (Meurs, 2004).

Although Boxer ARVC is a familial disease and many dogs will have the causative gene mutation at birth, phenotypic presentation of ARVC appears as an adult-onset myocardial disease (Meurs et al., 2014). Dogs are most commonly diagnosed between 5 and 7 years of age (Meurs, 2017). This is consistent with the age-related penetrance of ARVC observed in human beings, where it has been suggested that age related penetrance may be because of progressive exposure of the abnormal myocardium to mechanical stress (Sen-Chowdhry et al., 2007; Sen-Chowdhry et al., 2010).

The histopathology hallmark in human ARVC of fibrofatty infiltration and loss of myocytes remains the hallmark for ARVC in dogs. This fibrofatty infiltration can be localised in the RV or generalised, as is the case in human ARVC cases. Studies into boxer dog ARVC have reported right and left ventricular and interventricular septal tissue involvement, displaying myocyte loss, vacuolization, and infiltration with adipose tissue. It is now widely accepted that left ventricular involvement is frequently recognized in people and dogs (Norman et al., 2005).

It has not been clearly established whether the categories of Boxer ARVC, described by Harpster, (1983), represent disease progression or if they have different aetiologies. This is also true of ARVC in humans, but the evidence in both humans and dogs suggests that the extent of fibrosis may correlate with the progression and severity of the disease. Predominantly fatty infiltration of the heart tissue may be considered the early phase of the disease, resulting in milder symptoms, whereas fibrofatty infiltration may develop later and cause more severe clinical signs (Basso et al., 1996). A study into ARVC in boxer dogs as an animal model, conducted by Basso et al., (2004), reported that purely fatty replacement of right ventricle represented the predominant morphological variant in two thirds of the boxer dogs in the study. In these dogs, the RV wall thickness remained normal and RV aneurysms were uncommon, thus suggesting an earlier, milder phase of disease. According to Basso et al., (2004), both forms of the disease occur in dogs but the the fatty form is more common in dogs.

Inflammation and cell death have been implicated in modulating ARVC disease, both in humans and dogs. Some investigations have hypothesised that myocarditis may be a possible cause of the progression of fatty infiltration to fibrofatty infiltration, suggesting that fibrofatty repair results from myocarditis-induced injury (Nava et al., 1997; Boffa et al., 1991). Although the precise role of myocarditis and apoptosis in the pathogenesis of ARVC is unresolved, the findings of Basso et al., (2004) support this hypothesis. Right ventricular inflammatory infiltrates were pronounced in Boxer dogs with the fibrofatty form, whereas areas of myocarditis were small and uncommon when associated with purely fatty replacement (Basso et al., 2004). A more recent study conducted by Vila et al., (2017), three out of five Boxers (60%) with fibro-fatty replacement within the right atrium had inflammatory infiltrates suggestive of myocarditis, whereas only two out of seven Boxers (28.5%) with fatty replacement had such infiltrates.

3.2.2. Diagnosis of ARVC in Dogs

Diagnosis of ARVC in dogs is as complex as it is in humans, with no one gold standard test. It is often diagnosed post-mortem with pathology and histopathology, as not all dogs show clinical signs of the disease. Symptoms of Boxer ARVC may include syncope, congestive heart failure, or sudden cardiac death (Basso et al., 2004). The disease is typically recognised and diagnosed based on the identification of ventricular tachyarrhythmia if clinical signs are present (Basso et al., 2004; Meurs 2004). A history of clinical symptoms, such as syncope or exercise intolerance, as well as the signalment of an adult to middle aged Boxer dog are indicative of ARVC. Signs may or may not be detected during a physical examination. In some cases, an occasional ventricular premature beat may be detected, heart murmurs are infrequently heard and, in rare cases, signs of right heart failure (ascites and jugular venous distention) may be observed (Meurs, 2017).

Holter ECG is the main ante-mortem diagnostic tool used in dogs. VPCs are detected using a Holter ECG; they may be present singly, in pairs, and in runs of paroxysmal ventricular tachycardia (Meurs, 2017). It is uncommon for normal healthy adult dogs to have any VPCs on a 24-hour Holter monitor. One study concluded that a healthy adult large-breed dogs had a median number of two VPCs in 24 hours (Meurs et al., 2001). Another study evaluated more than three-hundred asymptomatic adult boxers and found that 75% of the population had less than 75 VPCs in 24 hours (Stern et al., 2010). Therefore, the identification of frequent ventricular ectopy (>100 VPCs per 24 hours) in an adult Boxer is strongly suggestive of a diagnosis of ARVC, particularly if there is no other underlying systemic or cardiac disease that could cause a ventricular arrhythmia (Meurs, 2017). The Holter ECG may also detect supraventricular premature complexes, particularly in Boxers with ventricular dilation and systolic dysfunction.

A Holter ECG is recommended rather than a short-term ECG because the arrythmia may be intermittent and the VPCs may not always be detectable on the ECG. Holter ECG also serves as an important guide for monitoring treatment and following case progression. An additional advantage of using the Holter ECG is its potential prognostic significance; for dogs with structurally normal hearts, the presence of more than 50 VPCs per 24 hours, polymorphic VPCs, and the presence of ventricular tachycardia have all been associated with shorter survival (Motskula et al., 2013).

Some studies have researched the possibility of using time-domain signal-averaged electrocardiogram (SAECG) as a non-invasive diagnostic technique. This method detects late potentials (LP), high frequency and low amplitude signals that occur at the end of the QRS complex (Chamas et al., 2014). These signals are considered markers of slow and heterogeneous cardiac conduction between myocardial cells interspersed with fibrous tissue, therefore, the identification of LP can be used to predict risks for future arrhythmic events and sudden cardiac death (Spier & Meurs, 2004; Bernadic et al., 2005). Although there are few reference values for SAECG in healthy dogs, the detection of LP in the SAECG of Boxer dogs with ARVC was associated with high sensitivity and specificity in predicting cardiac-related deaths (sudden death or congestive heart failure) in those animals (Spier & Meurs, 2004).

Echocardiography has limited diagnostic value in most cases of Boxer ARVC because most of the myocardial changes occur at a histological level rather than a macroscopic level. Therefore, most affected dogs have apparently normal echocardiograms, particularly with regard to the size and function of the left ventricle. In some cases, thorough evaluation of the right ventricle may detect right ventricular enlargement and, possibly, right ventricular dysfunction. A small percentage of affected Boxers have left ventricular dilation, with median survival shown to be significantly shorter in these dogs compared to dogs with normal ventricular size (Motskula et al., 2013).

As in humans, there is a genetic screening process involved in the diagnosis of Boxer ARVC, which identifies if the dog has the deletion in the striatin gene (STRN). Screening allows informed decisions to be made about breeding and should be performed on all dogs used for breeding and Boxer puppies purchased as pets. The genetic screening can have three possible results: no deletion in STRN gene, positive heterozygous or positive homozygous. A negative result indicates that there is no deletion in the STRN gene and the dog is not at risk of developing ARVC due to the STRN gene deletion. This does not, however, rule out the risk of developing ARVC due to another genetic or environmental cause that may yet be undetected in dogs. If the dog is positive heterozygous, the dog has one copy of the normal gene (wild-type) and one copy of the STRN deletion. The low penetrance and variability in expression means that only about 40% to 60% of dogs with this genotype will ever actually develop the disease (Meurs, 2017). The third possible result of positive homozygous indicates that the dog has two copies of the STRN deletion. These dogs are more likely to develop the disease and to develop the disease at a younger age.

3.2.3. Genetic Background and Inheritability of ARVC in Dogs

Arrhythmogenic right ventricular cardiomyopathy is an autosomal dominant inherited disease in humans, with approximately 40-50% of cases linked to mutations of genes coding for proteins of the cardiac desmosomes. Canine ARVC is also thought to be a familial disease with autosomal dominant inheritance with reduced penetrance (Meurs et al., 1999; Cattanach et al., 2015). However, despite the clinical and pathological similarities between human ARVC and Boxer dog ARVC, the genetic mutations in desmosomal proteins which are linked to the disease in humans, do not appear to be responsible for the disease in dogs (Meurs et al., 2007). A study into the genetic alterations associated with the development of canine ARVC was conducted by Meurs et al., (2010) and found a novel sequence variant on chromosome 17 at the 3' UTR of the gene Striatin (STRN). Striatin is a 780-amino acid intracellular protein which functions as a scaffolding protein (Benoist et al., 2006). It is expressed in a wide range of tissues, primarily nervous tissue but also heart, digestive organs and kidney tissue. It is thought to play a major role in protein to protein interactions and has binding domains to caveolin and calmodulin, both of which are regulators of myocardial function (Nader et al., 2017).

In the study conducted by Meurs et al., (2010), Boxer dogs homozygous for the novel variant STRN were all affected by ARVC. On average, these dogs were more severely affected than dogs heterozygous for the variant. Forty-one out of the fifty-nine affected Boxers were heterozygous for the variant, which is consistent with a co-dominant inheritance. Penetrance was 100% in homozygotes in this study, but only about 82% in heterozygous dogs. However, four dogs that were diagnosed with canine AVRC did not show any mutation in STRN. The study suggested that this was due to the dogs being incorrectly diagnosed with ARVC based on phenotype. As none of the four dogs were examined with MRI or histopathology, it was impossible to confirm the diagnosis of ARVC. Eleven out of the thirty-five control dogs were found to be heterozygous for the STRN mutation. These dogs may have asymptomatic or concealed disease, with no visible clinical signs yet. Another possible explanation is the reduced penetrance of ARVC in dogs. Cattanach et al., (2015) disputed the eighty percent penetrance previously described in Meurs et al., (2010), suggesting that the penetrance might be closer to the 20–30 percent estimate for ARVC dominant inheritance in humans (Sen-Chowdhry et al., 2005). This low penetrance would account for the lack of disease in some dogs that were positive for the STRN gene mutation, however, more evidence is needed to support this.

In a similar study, forty-three Boxer dogs diagnosed with ARVC based on the results of the Holter ECG (at least 300 ventricular premature complexes per day, in the absence of other systemic or cardiovascular disease) were genotyped for the striatin deletion (Meurs et al., 2014). Thirty-six (84%) of the dogs were positive for the mutation, but seven (16%) dogs did not carry the mutation. These seven dogs could have been mis-diagnosed with ARVC based on VPCs but they could also represent a group of patients with ARVC not caused by deletion in the striatin gene. Further research into other possible causes of ARVC in Boxer dogs is necessary to gain further information about this. Five of the control dogs in this study were heterozygous for the striatin deletion but did not demonstrate the ARVC phenotype. This is suggestive of reduced penetrance of the gene mutations, with some dogs carrying the mutation but showing no phenotypic disease.

A pedigree-based appraisal of Boxer dog ARVC and the role of STRN mutation looked at three linages of Boxer dog pedigrees (Cattanach et al., 2015). Although there seemed to be a clear association between ARVC and STRN mutations in line one, with all affected dogs being homozygous or heterozygous for the STRN mutation, there was no similar link in line two. Some of the dogs in line two were heterozygous or homozygous for the STRN mutation, but others carried the wild type for the allele of STRN. These results show similarity to those recorded by Meurs et al., (2010) and Meurs et al., (2014). They suggest a complicated and, possible multifactorial aetiology of canine ARVC with no one simple genetic cause

Parallels may be drawn between the desmosome mutations found in humans, which only account for approximately 50% of human ARVC cases, and the STRN deletion in canine ARVC. There is evidence that these mutations account for some ARVC cases but there seems to be other, undetected causes of ARVC, both in humans and dogs. These causes may be genetic or environmental and both require further investigation. Cattanach et al., (2015) reported that canine ARVC is a homogenous disorder in Boxer dogs and those diseased dogs not carrying the STRN mutation cannot be explained by heterogenicity. They also suggested that a mutation in another gene laying close to the STRN on the same chromosome may be responsible for canine ARVC, which warrants further investigation. As is the case in humans, it remains unclear as to why some patient develop phenotypic ARVC disease and others do not.

3.2.4. Pathogenesis of ARVC in Dogs

As previously mentioned, striatin is a protein located in the heart and has binding domains to caveolin and calmodulin, both of which are regulators of myocardial function. In-vitro studies into the interactions of cardiac STRN with caveolin and calmodulin found that an increased expression of STRN resulted in an increased rate of spontaneous contraction of cultured myocytes, whereas a knockdown of STRN resulted in a decreased contraction rate by 40% (Nader et al., 2017). There are limited in-vivo studies to support this finding, but it is likely that STRN is involved in the contraction of myocytes in-vivo and it would be a reasonable assumption that a mutation or under-expression of the STRN could lead to poor contraction of the myocardium and play a role in the aetiology of ARVC in Boxer dogs.

Studies have demonstrated that striatin localizes to the cardiac intercalated disc and co-localizes to desmosomal proteins previously documented as being involved in the pathogenesis of human ARVC (Plakophilin-2, Desmoplakin and Plakoglobin) (Meurs et al., 2010). Striatin may provide mechanical stability to the myocardium via its expression at the intercalated discs and its interaction with desmosomal proteins (Breitman et al., 2008; Meurs et al., 2010). Ultrastructural examination of hearts from ARVC-diagnosed dogs, conducted by Oxford et al., (2011), reported a significant reduction in number of gap junctions, desmosomes, and adherens junctions within the intercalated disc in RV samples, compared to those from non-ARVC dogs. They also found a significant reduction in number of gap junctions and adherens junctions in LV samples of ARVC dogs, compared to those from non-ARVC dogs. Interestingly, a significant decrease in length, but not number, of desmosomal plaques was detected in the LV samples from ARVC dogs, compared to samples from non-ARVC dogs. These structural changes in the intercalated discs of dogs diagnosed with ARVC are similar to the changes seen in human cases of ARVC.

Although it is not possible to tell whether the STRN mutations cause the structural changes in the intercalated disc, the close association of striatin protein and the components of the intercalated disc may suggest involvement of the STRN mutations in the structural changes seen in ARVC cases. As previously mentioned in this review, the cardiac intercalated disc is a functional unit, the components of which function synergistically. A mutation in the STRN gene may lead to mechanical instability of the intercalated disc and, indirectly, cause changes in the numbers of desmosomes, gap and adherens junctions.

Although there has been no mutation identified in the desmosome proteins of dogs with ARVC, there is a disruption to the desmosome complexes in affected dogs, which may be explained by mutations in the STRN gene. This is an area for further research, to identify a clear link between STRN mutations, desmosome function and ARVC. The cause of the fibrofatty infiltration seen in Boxer dog ARVC remains unclear, as is the case in human ARVC. However, the cause of the VA is likely to be the remodelling of the intercalated disc that takes place and the consequential mechanical instability leading to interrupted conduction of impulses.

3.3. Arrhythmogenic Right Ventricular Cardiomyopathy in Horses

In general, horses do not suffer with myocardial diseases very commonly compared to other species. This is thought to be due to specific breeding selection of horses over many years, aimed at performance traits. Genome-wide sequencing demonstrated that the cardiac system was a key domestication target, with evidence for positive selection for multiple genes for which defects are associated with cardiomyopathy (Schubert et al., 2014). The clinical signs of myocardial disease in horses are variable as they depend on the underlying cause and the impact on myocardial function. In many horses, myocardial disease is subclinical (Decloedt, 2019), but in others, myocardial dysfunction may lead to poor performance, exercise intolerance, weakness, ataxia, syncope, respiratory distress, congestive heart failure, or sudden death (Decloedt et al., 2012; Tirosh-Levy et al., 2017).

3.3.1. Previous Reported Cases of ARVC in Horses

To date, ARVC has only been reported in horses in two published papers, the earliest of which reported ARVC as the cause of SCD in two horses (Freel et al., 2010). The first horse in the study was a five-year-old Clydesdale gelding, diagnosed with elevated heart rate and respiratory rate after its first bout of strenuous exercise. The horse was referred to the Royal (Dick) School of Veterinary Studies in Edinburgh, Scotland, where a Holter ECG revealed sustained ventricular tachycardia and occasional VPCs. Overnight, the horse experienced more frequent VPCs and the next day, ventricular fibrillation and cardiac arrest. The second horse in this study was a fifteen-year-old Cob gelding, presented for post-mortem examination at the University of Glasgow Faculty of Veterinary Medicine, Scotland, after being found dead in the field. This horse had no previous clinical signs.

The post-mortem macroscopic lesions of the hearts were consistent with those found in human and dog ARVC cases. Case One had a distended RV and showed multifocal, pale cream/yellow, irregular areas in the epicardium of the right ventricular free wall, which extended into the myocardium. The entire endocardial surface of the right ventricular free wall and the interventricular septum showed similar gelatinous, fibrous-like cream/yellow tissue. Similarly, in Case Two, the free wall of the right ventricle and the intraventricular septum on the right side were infiltrated by a gelatinous cream/yellow, fat-like tissue. This tissue was also seen, to a lesser extent, on the left ventricle. There were no other macroscopic abnormalities seen in either of the hearts. This fatty tissue seen macroscopically in both hearts is characteristic of ARVC and has been described extensively in humans and dogs diagnosed with ARVC.

The histopathological findings of the two hearts were also consistent with those of human and dog ARVC cases. Freel et al., (2010) described similar findings in the right ventricles of each heart, there was a patchy to diffuse loss of cardiac myocytes and replacement with a combination of adipose and fibrous tissue. There were large islands of adipose tissue embedded in a loose collagenous stroma and fine streams of fibroblasts, which had formed thick bundles. Small islands of surviving cardiac myocyte were interspersed between the adipose tissue and fibroblasts, some of which showed loss of myofibrils and occasional small vacuoles (degeneration). The left ventricle was also affected in the second case, with mild changes in focal areas similar to those described above. There were no remarkable changes in the heart valves of either heart and sections of heart muscle from the unaffected areas had no significant pathological changes. Freel et al., (2010) concluded that both horses died from fatal dysrhythmia, secondary to a distruption of the conducting system. A post-mortem diagnosis of ARVC was recorded for both horses.

The presentation of the two horses described in Freel et al., (2010) differ slightly from each other as Case One presented with clinical signs prior to SCD, whereas Case Two did not. However, both horses died suddenly and unexpectedly, which is common in human and canine ARVC, either with or without preceding clinical signs. Case One presented with VPCs, a useful diagnostic tool for ARVC in Boxer dogs (more than 100 VPCs per 24 hours on a Holter ECG). Unsurprisingly, there are no threshold figures reported for VPCs and ARVC in horses, further research into this area may provide some insight into the similarities between equine ARVC and canine ARVC and the development of a potential diagnostic tool for ARVC in horses.

Both horses described in Freel et al., (2010) were heavy, work-type horses. Although it is impossible to draw any conclusions from the very small number of cases, there may be a predisposition for ARVC in these types of breeds. As mentioned above, breeding selection has focused on performance traits of the athletic breeds of horses. Performance horses, such as Thoroughbreds and Arabians (race-horses) may have had a better selection programme in the last fifty years compared to work-type horses, due to their popularity and the nature of the equine industry today. Heavy, work-horses are not required in every-day life, as they once were and therefore, they may not have been selected for as intensively as the athletic breeds. There may also be other factors influenced by breed that are involved in the development of ARVC in horses, such as body weight and body fat percentage. Further investigation into ARVC in horses and the breeds affected is required to gain more knowledge about breed predilection of ARVC in horses.

Similar to ARVC in dogs and humans, the disease in horses may also be a familial disease, with specific breeds or genetic lines of horses being affected. This could be compared to the disease in dogs, where is predominantly affects certain linages of the Boxer dog Breed. Perhaps inheritance studies in horses could help determine if ARVC is a familial disease in horses, looking into genetic lines and causes of deaths. It is worth mentioning that both horses were geldings (castrated males). Although there seems to be a male predilection for ARVC in humans, there is no such predilection described in dogs. However, it cannot be determined if there is a predilection based on sex in horses due to the very small number of cases. Higher case numbers are needed to form any trend of sex predilection.

Strenuous exercise has been shown to be an influential factor in the rapid progression of ARVC in humans and some animal models. The first bout of strenuous exercise may have been an important factor in the acute onset of clinical signs and consequential SCD in Case One. However, it is the strenuous training regimes of the human athletes which is thought to significantly contribute to the remodelling of the heart over time and therefore, the onset of ARVC clinical signs. This was the first strenuous training of the horse, suggesting that remodelling of the heart in this horse was unlikely to be a result of a strenuous training programme. Furthermore, given that endurance and short distance race-horses undergo extremely strenuous training for years, without cases of ARVC being reported in these groups of horses, it is unlikely that intense training is responsible for development of ARVC in horses. Genetic predisposition may be a more influential factor in ARVC of equines. The horse in Case One may have had a genetic predilection for ARVC disease and maybe the

one strenuous exercise episode was enough to trigger the events that lead to phenotypic presentation of ARVC and SCD. As this is the first and only reported case of SCD due to ARVC after strenuous exercise in horses, further research and higher case numbers are required before any conclusion is drawn on the effect of exercise in equine ARVC. It may also be useful to examine hearts of race horses post-mortem to catalogue any histopathological changes in their hearts indicative of ARVC, even if they didn't exhibit any clinical signs of ARVC during their life. This may provide information on the effect of strenuous training programmes on equine hearts and the development of ARVC.

The second paper reporting ARVC in a horse was conducted by Raftery et al., (2015). A fifteen-year-old, Clydesdale cross, gelding (Case Three) was referred to Weipers Centre Equine hospital at the University of Glasgow, Scotland, after three observed episodes of collapse within the preceding nine months. The episodes were described as syncopal episodic collapse with presumed transient losses of consciousness and postural tone due to cerebral hypofunction (Raftery et al., 2015). Spontaneous recovery followed each episode, with no remarkable clinical findings. When the horse was examined on arrival to the hospital, Holter ECG findings reported frequent multiform VPCs (10 per hour) and several short bursts of spontaneous supraventricular tachycardia. Results of a neurological examination were unremarkable. The horse was placed on pasture rest and re-examined on three subsequent occasions, the first of which was two weeks later, with no remarkable findings. Four months later, the horse collapsed whilst eating in the stable and was examined but with no remarkable findings. On the third occasion, the horse had collapsed whilst eating. A Holter ECG showed multiple short periods of supraventricular tachycardia with no apparent external stimuli and some VPCs (4 in 15 hours). A decision was made to euthanise the horse based on the safety of handlers and a post-mortem examination was performed.

The macroscopic lesions and the histopathological findings of the heart were similar to those described in Freel et al., (2010). Macroscopically, the epicardium of the RV free wall and the endocardium were infiltrated by a yellow soft tissue, which expanded deep into the myocardium. In this case, the yellow tissue eliminated over sixty percent of myofibers in the RV, with similar, less severe lesions seen in the LV (20-30% myofibers destroyed). Small foci of the yellow tissue were observed multifocally in the left and right atria. Histopathology examination found a marked decrease in number of cardiomyocytes, replaced with adipose tissue intermixed with thickened bundles of fibrous connective tissue. The residule myocytes in or around the adipose tissue were highly vacuolated with loss of

myofibrils and nuclear detail (degeneration). The post-mortem results were indicative of ARVC and may provide evidence of the third reported case of ARVC in horses.

The presentation of syncopic episodes described by Rafferty, et al., (2015) were not previously reported in horses with ARVC (Freel et al., 2010). Although this presentation differs to the previous two equine ARVC cases, it is similar to that of humans and, especially Boxer dogs, where 52% of ARVC cases in Boxer dogs experience syncope (Basso et al., 2004). This may provide further evidence of similarities between ARVC in horses, dogs and humans. However, the variable presentation in all species makes it difficult to form a conclusive antemortem diagnosis of ARVC. In humans and dogs, phenotypic and clinical presentation of ARVC depend greatly on the genetic penetrance and heterogenicity of ARVC-causing mutations. There is no research into the aetiology or genetic cause of ARVC in horses and therefore, no evidence of heterogenicity or penetrance of the disease in horses. However, the variable clinical signs seen in the three reported equine cases may suggest a complicated aetiology with multiple influencing factors and variable penetrance of any genetic mutations.

Despite the different presentation of the horse described in Rafferty et al., (2015), the signalment was similar to the two horses reported in Freel et al., (2010). It was a fifteen-year-old, Clysedale-cross, gelding. As previously mentioned, there are not enough confirmed cases of ARVC in horses to draw any conclusions about the age, sex or breed predilection of ARVC in horses but it is interesting that all three horses are heavy breed, geldings and between the age of five and fifteen. Arrhythmogenic right ventricular cardiomyopathy is reported in postpubertal to middle aged humans and dogs, with practically no cases reported in the very young. By five years old, horses would be considered sexually mature and could be compared to a teenager of their human counterpart. This would correlate to ARVC cases not being described in the very young humans or dogs. There may be some correlation between severity of disease and age at which the three horses died. The younger horse of five years old suffered SCD after just one bout of strenuous exercise. Perhaps this indicates a more severe form of the disease in this horse, compared to the two that reached an older age of fifteen, with previous exercise.

Rafferty et al., (2015) reported that the horse was over-conditioned with a body condition score (BCS) of 4 out of 5. The excess body condition of the horse may also be pertinent to the development of the cardiac pathology. The relationship between obesity, a proinflammatory state and cardiac pathology is well documented in humans (Szczepaniak et al., 2007). This poses the question as to whether the histopathological changes described by Rafferty et al., (2015) are a direct consequence of obesity in horses or if obesity is a contributing factor to ARVC in horses? Fatty infiltration of the myocardium is regarded arrhythmogenic, it is therefore reasonable to explore the possibility that the clinical signs observed in this horse could be a result of arrythmia due to fatty infiltration of the heart due to excess fat deposits. However, obesity in horses is common in the UK (Stephenson et al., 2011), without the development of clinical signs seen in Case Three. Therefore, although it is unlikely to be the cause of death in Case Three, further research into the effect of obesity on the equine heart is needed to determine whether obesity causes arrhythmia in horses.

The common geographic location of these three cases may be significant when determining the aetiology of ARVC in horses. All of these cases were reported in the UK, more specifically, Scotland. The Clydesdale is a Scottish breed of horse and it is likely that most of the Clydesdale horses bred and transported in the UK have similar genetic lines. It would be interesting to perform a pedigree study of each of the horses reported in this review and of Clydesdale horses in general, to see if there was any history of SCD in specific, common genetic lines. Another explanation of the locality of the cases may be explained by environmental, climatic factors that are common to Scotland. Studies have suggested that environmental factors play a role in the phenotypic expression of the disease in humans and this is likely to be the case in horses too.

3.3.2. Comparison Between Case Study and Previous Reports of ARVC in Horses

The signalment of the horse described in this case study was similar in some respects to the previous four horses reported to have ARVC or ARVC-like disease. The horse was a Clydesdale gelding. Two of the previous horses reported are Clydesdales and one is a Clydesdale cross. The other three horses reported are also geldings. Although the very small number of representatives makes it impossible to confirm any breed or sex predisposition, it seems that Clydesdales and males are overrepresented in equine ARVC cases so far. Perhaps there is a male predilection in horses, as is the case in humans and there may be a breed predisposition similar to the Boxer dog. Again, higher case numbers and further research into the disease in horses is required to gain further knowledge about equine ARVC.

The horse in the current case study presented with sudden, unexpected death, as did the other three horses reported of suspected ARVC. Sudden, unexpected death is a common finding in ARVC cases in other species and is, therefore, likely to be common in horses with ARVC as well. This horse's history is comparable to the horse in Case Two, both horses led normal, active lives for many years and no clinical signs preceding SCD. However, this horse was slightly older than the other reported cases when sudden death occurred, at twenty-five years old, perhaps this was due to a milder disease or a slower progression of the disease.

Macroscopically, the heart showed fatty infiltration of the subendocardium. This was most prominent, and nearly transmural, below the tricuspid valve, along the RV free wall (Figure 2A). The location of this fatty tissue is similar to the previous three cases, all affecting the RV free wall (Figure 2B) and some affecting the right side of the interventricular septum.

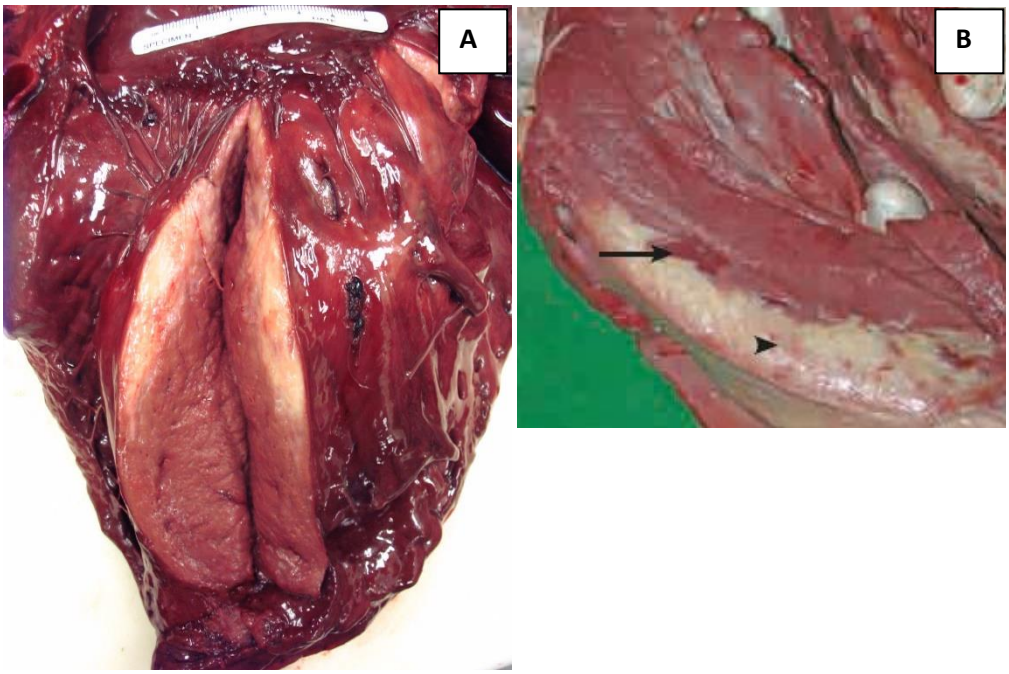

Figure 2: Macroscopic picture of heart (A) heart from Case Study, incision into wall of right ventricle under the tricuspid valve, showing fatty infiltration of myocardium (B) heart from Case 1, lesions extend into the underlying myocardium, giving the cut surface a 'marbled' appearance (arrowhead), also showing haemorrhages at boarder of abnormal tissue normal myocardium (arrow), image from Freel et al., (2010)

Thirty to fifty percent of the myocardium was replaced by adipocytes, which were separated by collagenous connective tissue. Similarly, Freel et al., (2010) reported over sixty percent myocyte loss in the RV of Case One and Case Two. The slightly lower percentage of myocyte loss in the current case may be attributed to a milder infiltration of fat and milder disease, which led to the longer lifespan of the horse (25yrs). The loss of myocyte number and the presence of fibrous and fatty tissue in the heart was a common finding in all four of the hearts. In addition, all four hearts demonstrate signs of myocyte/myofiber degeneration i.e. vacuolisation and loss of nuclear stain. The degeneration and loss of myocytes, with presence of fibrofatty tissue are characteristic of ARVC in humans and Boxer dogs.

Case One is the only heart out of the four to show dilation of the RV, this is a common finding in humans with ARVC and is thought to be associated with a more progressed, malignant form of the disease. The horse in Case One is the youngest horse reported with ARVC and died suddenly after the first bout of strenuous exercise. Perhaps this is further evidence of a more malignant form of disease in Case One, compared to the other three cases, which all lived for many years before phenotypic expression of ARVC.

Exercise may have played a role in the sudden onset clinical signs in Case One, this horse may have had a more severe disease form and the underlying disease was acerbated with this one bout of intense exercise. However, unlike human ARVC, there is no evidence of "exercise induced" form of ARVC in horses. None of the horses described above participated in regular, high level exercise and there have not been any reported cases of ARVC in endurance/race horses. Further investigation is warranted into the gross and histopathological changes in the hearts of endurance horses and race horses to gain insight into the effect of high level exercise on the equine heart. Perhaps cases of ARVC have previously gone undiagnosed in race-horses due to the limited knowledge of ARVC in horses. Or perhaps the cases of ARVC in horses are akin to Boxer dogs, where exercise is not consistent with the onset of clinical signs of ARVC (Basso et al., 2004).

It should be mentioned that the horse in the current case study was reported to have a pituitary gland adenoma and a bilateral pheochromocytoma. Pheochromocytoma is a rare finding in horses and most are clinically silent (Luethy et al., 2016). A retrospective study by Luethy et al., (2016) reported a post-mortem incidence of pheochromocytoma of 0.95%. The common clinical signs of functional pheochromoctyomas in horses are tachycardia, abdominal pain, sweating and muscle tremors (Buckingham, 1970; Yovich & Ducharme,

1983). As the pheochromocytoma was uncapsulated in this case, it may suggest that is was malignant in this horse. However, the lack of clinical signs previously reported in this horse is more consistent with a benign pheochromocytoma. As the heart rate of the horse was not measured ante-mortem, it is impossible to tell whether the horse was tachycardic. The pheochromocytoma may have contributed to the horse's death if tachycardia was present.

There is evidence that ARVC may have been the cause of death in this horse due to the fibrofatty tissue found in the heart. Pathology reports of the hearts of horses with pheochromocytoma have described either no abnormalities in the heart (Buckingham, 1970) or replacement of myocardium with fibrous and areolar tissue (described in one horse with pheochromocytoma) (Yovich & Ducharme, 1983). Therefore, the gross and histological changes in the heart of the horse in the current case study are unlikely to be linked to the pheochromocytoma.

4. Conclusion

There is still very little known about ARVC in horses, with only three horses previously suspected of the disease. There has been almost no research into the causes and pathophysiology of ARVC in horses, it is therefore impossible to compare genetic background and pathophysiology of ARVC in humans and dogs to that of horses. However, the signalment, history, clinical presentation, gross pathology and histopathology of the three previous reported cases in the horse are comparable to the current case and to humans and dogs. Thus, suggesting that there is an ARVC-like disease found in horses.

Genetic studies into possible causes of the disease in horses would be useful to establish the aetiology of the disease in horses. Investigation into the structure of the intercalated discs of horses diagnosed or suspected of ARVC may help in the identification of genetic causes of ARVC in horses. Genes encoding for desmosome proteins and adherens junctions should be examined in horses to identify any mutations that have previously been associated with ARVC in humans and dogs. Given that all four of the horses were either Clydesdale, Clydesdale cross or similar heavy breeds, it is likely that there is a genetic cause, perhaps with a breed or breed-type predisposition. The identification of a genetic cause of ARVC in horses may provide a possible candidate for a screening test that could be used in horses, similar to the human and Boxer dog screening protocols.

Further research is needed into the antemortem diagnosis of ARVC in horses. One possible method would be Holter ECG and number of VPCs. Determination of reference values of VPCs for both healthy horses and horses suspected of ARVC would be very useful in establishing this diagnosis tool in horses. History and signalment may also be useful in diagnosis of ARVC in horses, providing a profile of horses that may be at risk or suspected of having ARVC; for example, male horses between five and twenty-five years old, heavy breeds/Clydesdale, previous clinical signs of syncope, high heart rate and/or collapse.

A greater number of post-mortem examinations of hearts from horses that die suddenly is required to gain an insight into the prevalence of ARVC in horses. As previously mentioned, it is possible that ARVC cases have been undiagnosed due to the lack of knowledge or recognition of the disease in horses. Examination of hearts of horses from differed breeds and work-loads would be useful to identify any breed predilection or any correlation between exercise or bodyfat and ARVC. If more pathologists are aware that ARVC may be a differential diagnosis for horses that have died unexpectedly, with no other obvious cause of death, then ARVC may be correctly diagnosed more frequently in horses.

Higher case numbers are required to confirm characteristics of the disease in horses. There are similarities between this case study and the previous cases of ARVC reported in horses; all four horses died suddenly and unexpectedly, with similar macroscopic and histopathological lesions in the hearts. Although the presentation of disease varied in some of the cases, this is typical of ARVC in humans and dogs and may be typical of ARVC in horses. Given the similarities of all four cases, it seems that a post-mortem diagnosis of ARVC is reasonable and this case study seems to be the first diagnosed case of ARVC in a horse in the USA.

5. Summary

Arrhythmogenic right ventricular cardiomyopathy is a disease predominantly found in humans and Boxer dogs. It is an autosomal dominant inherited disease and affects approximately 50% of an affected individual's offspring. Genetic mutations in the genes coding for cardiac desmosome proteins have been found responsible in approximately 50% of human cases of ARVC. No such gene mutations have been found in dogs with ARVC, however, other mutations such as in the striatin gene have been indicated in the disease in dogs.

Arrhythmogenic right ventricular cardiomyopathy is a rare finding in other species, with only two published papers on ARVC in horses. Although there are similarities between the presentation, macroscopic lesions and histopathology for the reported cases of ARVC in horses and that of reported cases in humans and dogs, it is unclear whether the disease is accepted as a stand alone disease of horses. A recent pathology examination of a horse suspected of ARVC also showed similarities between that of the previously reported cases in horses and, therefore, this review was aimed at comparing the current case with previous cases in horses, humans and dogs.

The gross pathological findings in all four cases of equine ARVC were consistent with the macroscopic lesions found human and canine ARVC. Fat tissue infiltration of the RV free wall and right side of the interventricular septum was seen in all equine cases, with fatty infiltration affecting the left ventricles to a lesser extent. There were also common histopathological findings in all 4 horses with ARVC, including a marked decrease in number of cardiomyocytes, replaced with adipose tissue intermixed with thickened bundles of fibrous connective tissue. Thes findings are consistent with the hisopathology of human and dog ARVC cases, with the hallmark of ARVC being loss of right ventricular myocardium with substitution of fibrous and fatty tissue. From these findings, it would seem that ARVC in horses is the same disease as in humans and dogs and it may be considered a stand alone disease in horses.

6. Összefoglalás

Az arritmogén jobb kamrai cardiomyopathia (arrhythmogenic right ventricular cardiomyopathy, ARVC) gyakori betegség emberekben és boxer kutyákban. Ez a szívizombántalom autoszomális domináns öröklődésű betegség, amely a terhelt egyének utódainak kb. 50%-át érinti. Az emberi ARVC megbetegedések közel felében a szívizom desmozoma fehérjéit kódoló gének genetikai mutációját állapították meg. Hasonló dezmozóma mutációkat nem találtak a kutyákban leírt esetekben, de egyéb, pl. a striatin gén mutációját viszont megfigyelték a betegség kapcsán.

Az arritmogén jobb kamrai cardiomyopathia ritkán fordul elő más állatfajokban. Lovakban látott hasonló kórképről összesen két cikk jelent meg. Annak ellenére, hogy a bántalom megjelenésében, a makroszkópos és kórszövettani elváltozásokban akadnak az emberi és kutya esetekhez való hasonlóságok, még kérdéses, hogy a lovakban előforduló ARVC-re emlékeztető kórképek valóban önálló betegségként kezelhetők-e. Egy közelmúltban elvégzett kórbonctani vizsgálat a korábban lovakban leírt ARVC-hez hasonló elváltozásokat mutatott ki egy lóban, ezért jelen szakdolgozatban a mostani esetben talált elváltozásokat hasonlítom össze korábbi emberekben és kutyákban leírt esetekkel.

A boncolás során talált rendellenességek mind a négy, lóban talált esetben hasonlóak voltak az emberekben, illetve kutyákban talált makroszkópos elváltozásokhoz. A jobb kamra szabad falának és a kamrák közti sövény jobb oldalának zsíros infiltrációja mindegyik lóban vizsgált esetben felismerhető volt, míg a bal szívfélben a zsíros infiltráció kevésbé volt megfigyelhető. Emellett gyakori kórszövettani lelet volt ezekben a lovakban a szívizomsejtek számának jelentős csökkenése. Az elpusztult szívizomsejtek helyét szintén zsírsejtek, valamint kötőszövetes rostok foglalták el. Ezek a kórszövettani elváltozások megegyeznek a humán és kutya esetekben látottakkal, közülük a legjellegzetesebb a jobb kamraizomzat károsodása és zsírral és kötőszövettel való kevert pótlása.

A fentiek alapján valószínűsíthető, hogy a lovakban látott ARVC-re emlékeztető betegség valóban megegyezik az emberek és kutyák hasonló kórképével és önálló betegségként kezelendő ezentúl lovakban.

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