Chapter

Left Ventricle Arrhythmogenic Cardiomyopathy in Canines and Felines

Guillermo Belerenian, Cristian Daniel Rodríguez, Víctor Castillo and Gustavo Abuin

Abstract

This chapter describes pathological, electrocardiographic, echocardiographic, and clinical findings of two cases, one in a canine and the other in a feline, which suggest the presence of Left Ventricle Arrhythmogenic Cardiomyopathy. It is considered to be of interest for comparative medicine. To the authors' knowledge, it's the first ever description of the pathology carried out in companion animals. The canine patient arrived at the clinic with arrhythmias. After 48 hours, he had a sudden death and the heart was studied, finding a partial replacement of the free wall and septum of the left ventricle with fatty tissue. The feline patient also had a sudden death, and the heart was studied, where transmural replacement of the myocardium from the free wall of the left ventricle was found, which was replaced by adipose tissue.

Keywords: arrhythmogenic cardiomyopathy, feline, canine, adipose replacement, arrhythmia

1. Introduction

Arrhythmogenic Cardiomyopathy is a genetic disease of the heart muscle characterized by the replacement of the myocardium with fibroadipose tissue [1]. The onset of the substitution begins in the epicardium and progresses over time toward the mesomyocardium. The disease was originally called Right Ventricle Arrhythmogenic Dysplasia because that was the phenotype which was first discovered. The new knowledge about it highlights a genotype-phenotype correlation, and the characterization of the myocardial tissue through cardiac magnetic resonance in the human species demonstrated the involvement of the left ventricle. Nowadays, it is called Arrhythmogenic Cardiomyopathy because it can involve both ventricles, or predominantly the right ventricle or predominantly the left ventricle.

In this chapter, we report two cases of left ventricle predominant Arrhythmogenic Cardiomyopathy in companion animals. The existing evidence suggests that it could be more prevalent in the Boxer and in the English Bulldog breeds, when speaking of canines, even though the authors found it in a Fila Brasilero dog [2]. This form of Arrhythmogenic Cardiomyopathy may resemble dilated

cardiomyopathy or myocarditis, and it appears that there is a genetic basis for these two different phenotypes [3].

To summarize, nowadays we can find the right-predominant phenotype, the left-predominant phenotype, and the biventricular phenotypic variant of the disease [4].

2. Phenotype

Studies of anatomic pathology in human beings who presented right ventricle Arrhythmogenic Cardiomyopathy showed evidence of macroscopic and histological involvement of the left ventricle in up to 76% of the cases. It was affecting the free wall and the septum, most often regionally, and the most involved areas were the posteroseptal and posterolateral. The lesion was located in the outer layer, which had areas of replacement fibrosis or subepicardial fibrofatty change [5].

The phenotypic features of Left Ventricle Arrhythmogenic Cardiomyopathy in humans include electrocardiogram (ECG) abnormalities, such as low-amplitude Quality Rating System (QRS), in the limb's derivations or t-wave inversion or flattening in the inferolateral derivations, as well as ventricular arrhythmias with right bundle branch block morphology (a ventricular conduction disorder that can happen in any of the two ventricles), which denotes its origin at the left ventricle.

Echocardiogram (Echo) shows a normal or mildly depressed left ventricle's systolic function, without or with mild dilation. When performing a cardiac magnetic resonance imaging with contrast, fibrosis in the subepicardial layers at the inferior or inferolateral regions is evidenced. The subendocardial layer is conserved, so regional contractility may be at a normal state. Therefore, echocardiography is sometimes not as useful for diagnosis as magnetic resonance imaging (MRI), which is a limitation for animal cardiology since this diagnostic method is not so easily available in companion animals [6].

3. Genotype

In Arrhythmogenic Cardiomyopathy, most pathological mutations affect genes that encode proteins that are structural for the intercellular binding of myocytes. Among these proteins, the most found at a mutated state are: Plakophylin, Desmoplakin, Desmoglein, and Desmocollin. Rarer are those mutations affecting Alpha-T-Catenin and N-cadherin. Mutations were also found in nondesmosomic genes, such as Phospholamban, Mylamin, Desmin, Titin, and Lamina A and C.1. These latter mutations are also associated with dilated cardiomyopathy and, therefore, may have overlapping phenotypes [7]. There also exist mutations in transmembrane proteins, such as Transmembrane Protein 43 or the Transforming Growth Factor Beta-3 (TGF-β3).

Genotype-phenotype correlation studies on human medicine showed that the mutations in genes that synthesize proteins, such as Desmoplakin, Phospholamban, Filamin C, Lamina A and C, Desmin, and Transmembrane Protein 43, specifically affect the left ventricle primarily before affecting the right ventricle [8]; while the mutations of Plakophylin C, Desmoglein, Desmocollin, and Plakoglobin affect the right ventricle primarily. Phospholamban inhibits the calcium transport of adenosine phosphatase (ATPase) of the sarcoplasmic reticulum (SR), so mutations dysregulate calcium flow predisposing to arrhythmia and ventricular dysfunction. Phospholamban mutations were found in boxer dog family groups [9].

4. Diagnosis

In human medicine, the Padua criteria are used to diagnose and phenotypically categorize Arrhythmogenic Cardiomyopathy, using major and minor criteria for each method and for each region.

For predominantly right affectation (that's to say, when the right ventricle is predominantly affected), the major criteria by echocardiography are right ventricular morphofunctional anomalies, akinesia, dyskinesia or regional dilation of the right ventricle, and dilation or global systolic dysfunction of the right ventricle. And the minor criteria are regional right ventricle akinesia or aneurysm of the right ventricle free wall.

On the other hand, for predominantly left affectation, the major criteria are global systolic dysfunction of the left ventricle with depression of the shortening fraction, with or without dilation of the left ventricle; and a minor criterion would be left regional hypokinesia or akinesia of the free wall or septum.

The major criteria for cardiac magnetic resonance imaging for each sector are transmural anomalies that suggest a fibrous replacement of the myocardium in the septum or in the free wall, while the minor criteria would be very restricted fibrous replacement lesions, either in the septum or in the free wall [10]. Major and minor criteria are also applied with the use of the electrocardiogram as a diagnostic method. Respecting the repolarization abnormalities, a major criterion for the right ventricle would be inverted t-waves in the right precordial leads V1 V2 V3; and a major criterion for the left ventricle would be inverted waves in the left precordial leads V4 V5 V6, always in the absence of left bundle branch block. Minor criteria would be inverted t-waves in two precordial derivations for both ventricles.

About the depolarization anomalies, a major criterion would be the appearance of epsilon waves, which would be low-amplitude signals between the end of the QRS complex and the beginning of the t-wave in right precordial derivations from V1 to V3. In the left ventricle, a major criterion would also be the appearance of low QRS voltages lesser than 0.1 millivolt in the limb leads [11]. Another major criterion for the right-predominant condition is the emergence of frequent ventricular extrasystoles, greater than 500 in 24 hours, or a sustained or nonsustained ventricular tachycardia with left bundle branch block morphology. In the case of the left-predominant condition, it would be the same but with a sustained or nonsustained ventricular tachycardia with right bundle branch block morphology. A minor criterion for both ventricles would be ventricular extrasystoles minor to 500 in 24 hours. Lastly, genetic family history (whether there are known mutations for the disease in the family research) is important. In veterinary medicine, these criteria are not established [12].

The studies carried out on animals have been done mainly on canines from the Boxer and English Bulldog breeds, but they have not been able to establish any diagnostic criteria, although it is allowed to suspect the disease when a 24/48-hour rhythm Holter is done and more than 1000 premature ventricular complexes appear daily with morphology of left bundle branch block (in the case of suspected involvement of the right ventricle) and with morphology of right bundle branch block (if left ventricle involvement is suspected) [13]. It is also important to correlate it with echocardiographic changes, in addition to the criteria detailed above. If right ventricle Arrhythmogenic Cardiomyopathy is suspected, the right ventricular cavity may be dilated, the wall may be very thin, or there may also be regional or global motility alterations; the TAPSE (Tricuspid Annular Plane Systolic Excursion) and the right ventricle ejection fraction may be decreased. In the case of the left ventricle, ejection fraction, shortening fraction, and MAPSE (Mitral Annular Plane Systolic Excursion)

may be decreased. There may also be regional or global motility alterations and the wall may be thinner, which is less frequent in canines.

In the case of felines, we will see that a wall of the left ventricle was found completely replaced by fat and it became thinner. Clinically, syncope or sudden death predominates. Alterations in biomarkers, such as ventricular natriuretic peptide and troponin, may appear [14].

5. Description of the canine case

A 2-year-old male Brazilian Fila canine with a history of syncope during exercise was presented to the cardiology clinic. On clinical examination, the auscultation revealed an irregular rhythm, and no murmurs were detected. The weight of the animal was 20 kg. The blood chemistry and hemogram parameters were within normal limits.

A six-lead electrocardiogram showed the presence of isolated premature ventricular complexes with right bundle branch block morphology. Then, the echocardiogram showed an increase in the diameter of the left ventricle diastole ending part (62 mm) normalized to body weight, with a shortening fraction of 41% and an ejection fraction of 71% (preserved). A 24-hour Holter monitoring was indicated, which was performed the next day, and a complete blood test was also indicated, the results of which were normal [15]. The patient remained at home during the Holter study. A three-channel study was performed, and the recording showed baseline sinus rhythm during 95% of the study time. The maximum heart rate was 231 beats per minute and the minimum was 54 beats. There were 11 episodes of supraventricular tachycardia lasting 3 seconds on average. A total of 93 complexes of ventricular origin were detected, approximately 50% of which were escape beats. All ventricular escape complexes had left bundle branch block morphology, while premature ventricular complexes had right bundle branch block morphology (**Figures 1** and **2**). During the study, an increase in the QT interval was observed, corrected by Basset's formula (**Figure 3**). After 24 hours of performing the rhythm Holter, the patient died suddenly while performing physical activity. After the animal's death, authorization was obtained to perform the necropsy.

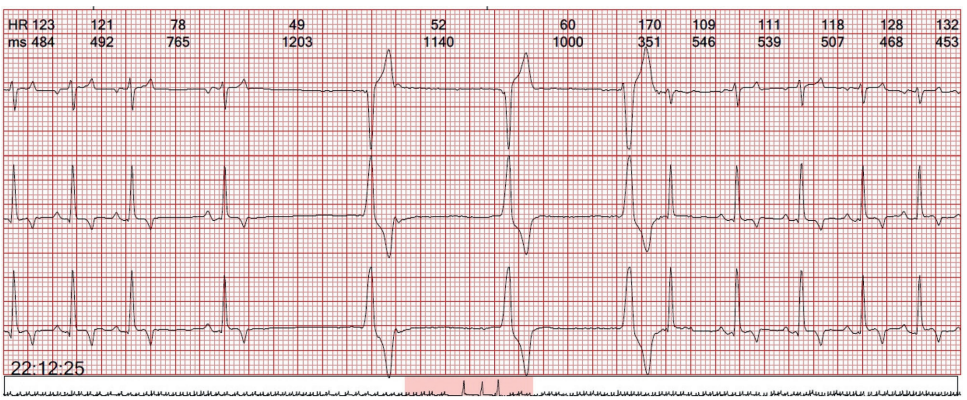

Figure 1.
Idioventricular rhythm in the canine patient.

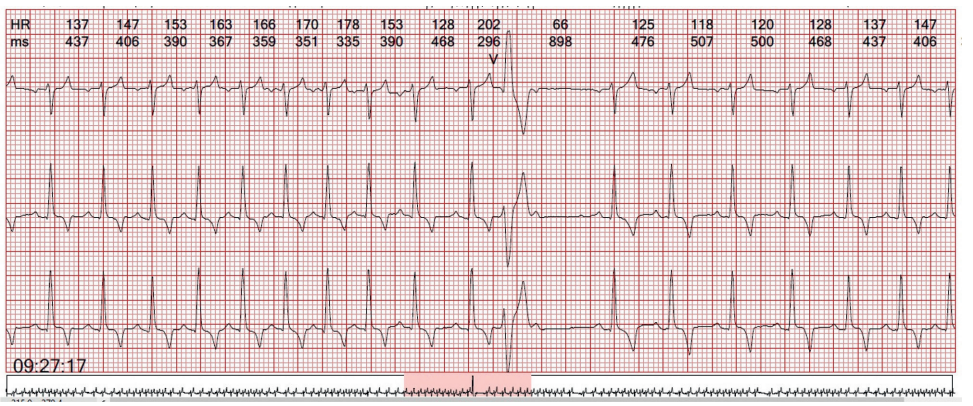

Figure 2.
Ventricular premature complexes with right bundle branch block morphology in the canine.

Fc	91	111	130	150	170	213	125
QT	0,2	0,2	0,2	0,2	0,2	0,2	0,22
rr	0,64	0,52	0,38	0,4	0,36	0,28	0,46
raíz de rr	0,8	0,72	0,61	0,63	0,6	0,52	0,67
QTc	0,25	0,27777778	0,32786885	0,38461538	0,38461538	0,38461538	0,32835821

Figure 3.
QT corrected by Basset's formula.

During the study, a clear cardiomegaly was evidenced, the weight of the heart was greater than 13 grams of cardiac tissue for every kilogram of body weight. No pulmonary edema, pleural effusion, or ascites were observed. The heart was exposed, preserved in 10% formaldehyde, and sent for study to the pathology service of the Hospital Santojani in the Ciudad Autónoma de Buenos Aires. Slices were made with hematoxylin–eosin staining, after including the paraffin samples. In the free wall of the left ventricle, a predominantly subepicardial fat replacement was observed and the septum on the left side was affected (**Figure 4**) [16]. The base of implantation of the papillary muscles was also affected, where replacement by adipose tissue was found (**Figure 5**). Perivascular fibrosis and replacement fibrosis also coexisted in some areas of the left ventricle, suggesting a lesion that led to necrosis and fibrosis. Myocardial wavy fibers were also found in both ventricles, and preserved myocardial muscle fibers were found within the fibrofat replacement islets (**Figures 6** and 7). This led to the finding of a suggestive left-predominant arrhythmogenic cardiomyopathy. There were no signs of congestive heart failure. No signs of myocarditis were observed. Fat replacement of up to 50% of the free wall was also found in some areas of the right ventricle, but this was very localized. There is a possibility that physical activity may have triggered the hot phase of the disease, and mechanical stress may have caused the decoupling of more myocytes, with the consequent secondary injury with predisposition to ventricular arrhythmias and sudden death [17].

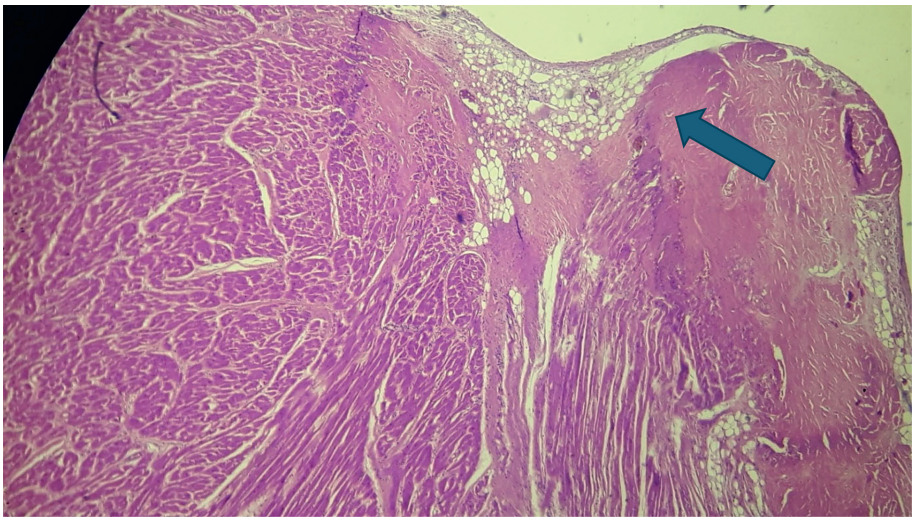

Figure 4.
Histopathological image of the interventricular septum with fat replacement. The arrow points to the fatty replacement area in the interventricular septum.

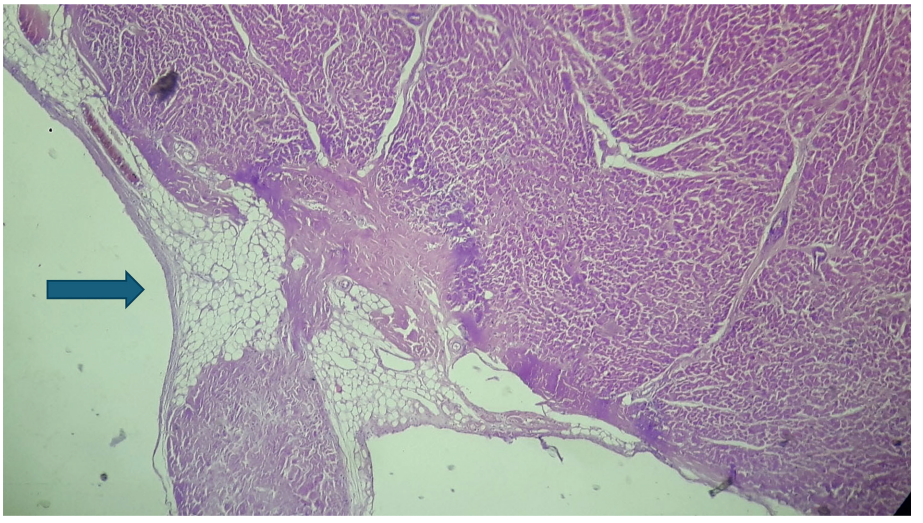

Figure 5.
Histopathological image. Staining with hematoxylin and eosin. Canine left ventricle. Papillary muscle base fat replacement. The arrow points to the fatty replacement at the papillary muscle implantation site.

6. Feline case description

A 3-year-old male European common cat was presented to the emergency room. It was neutered and had had syncope. Routine auscultation revealed an arrhythmia. An electrocardiogram was performed, in which ventricular tachycardia with right bundle branch block morphology was observed in the tachycardia beats (**Figure 8**). The blood analysis were within normal parameters.

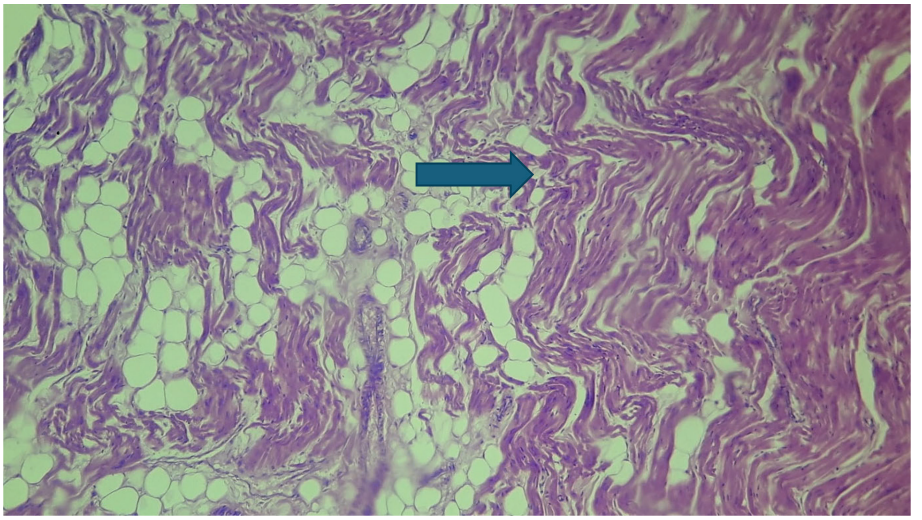

Figure 6.
The arrow points to the myocardial wavy fibers in areas of fat replacement.

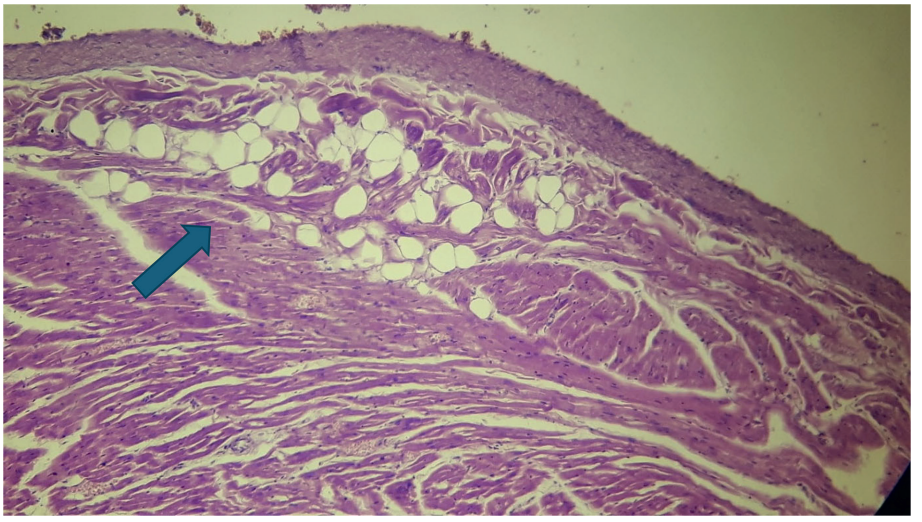

Figure 7.
The arrow points to the subepicardial fibrofatty replacement in the canine left ventricular wall.

The patient is scheduled the next day for an echocardiogram, but it faces a sudden death at home. Permission is obtained from the owners to perform the necropsy. The anterolateral free wall of the left ventricle was completely replaced by fat and there were no abnormalities in the epicardial coronary arteries that ran through the entire wall, even in the segment where the fat replacement was located. The histopathological study did not reveal coronary artery disease nor was there any thromboembolism or atheromatous plaques along the coronary artery branches that crossed the segment replaced by fat. However, a virtually total replacement of the free wall of the left ventricle was found, with very little subendocardial tissue preserved and the entire epicardium, subepicardium, and mesomyocardium replaced by fatty tissue (**Figure 9**). This also led

to the suspicion that the arrhythmia originated in the left ventricle, given the morphology of the complexes and that the fatty replacement of that segment of the free wall of the left ventricle was the origin of the arrhythmia that produced the sudden death. In this case, the staining was also performed with hematoxylin–eosin (**Figures 10–12**).

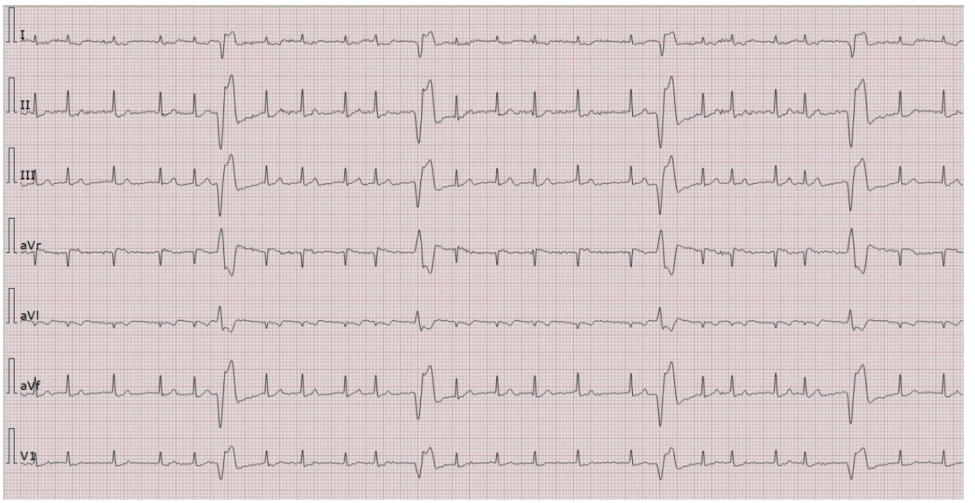

Figure 8.
Ventricular extrasystoles with right bundle branch block morphology in the feline patient.

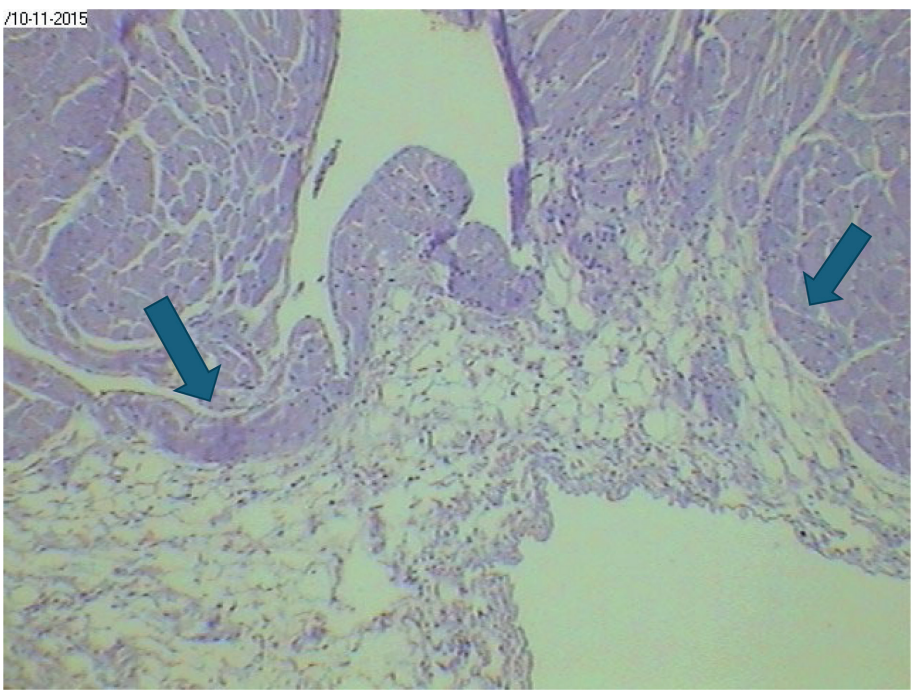

Figure 9.
Histopathological image of the feline patient. Fat replacement of the free wall of the left ventricle with preserved subendocardium. The arrow points to the fatty replacement in the epicardium.

To the knowledge of the authors, left ventricle Arrhythmogenic Cardiomyopathy in companion animals has not yet been described. It should be noted that in these two cases, there were no signs of heart failure prior to death, so it is estimated that death was due to arrhythmia [12].

7. Discussion

In the classic form of right ventricle Arrhythmogenic Dysplasia, now called Arrhythmogenic Heart Disease, the overall function of the left ventricle is usually not affected. The involvement of both ventricles usually occurs in the outer third of the

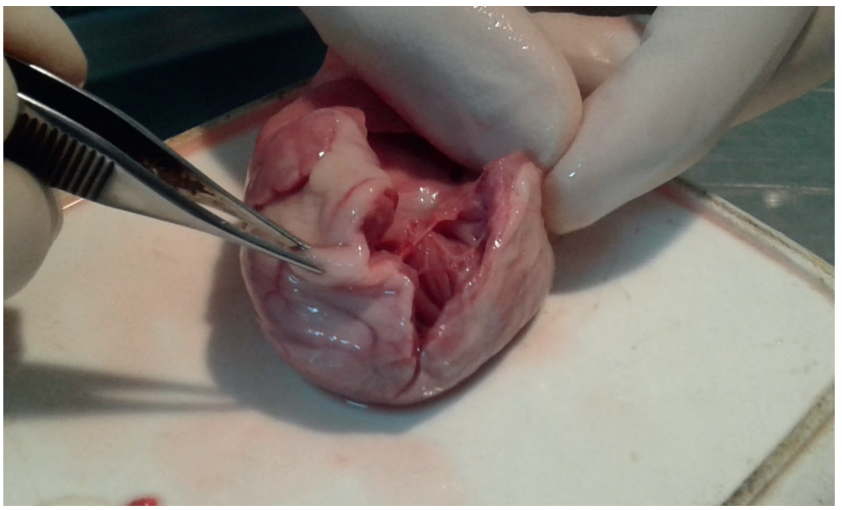

Figure 10.
The forceps take the free wall of the feline patient's left ventricle replaced by fat.

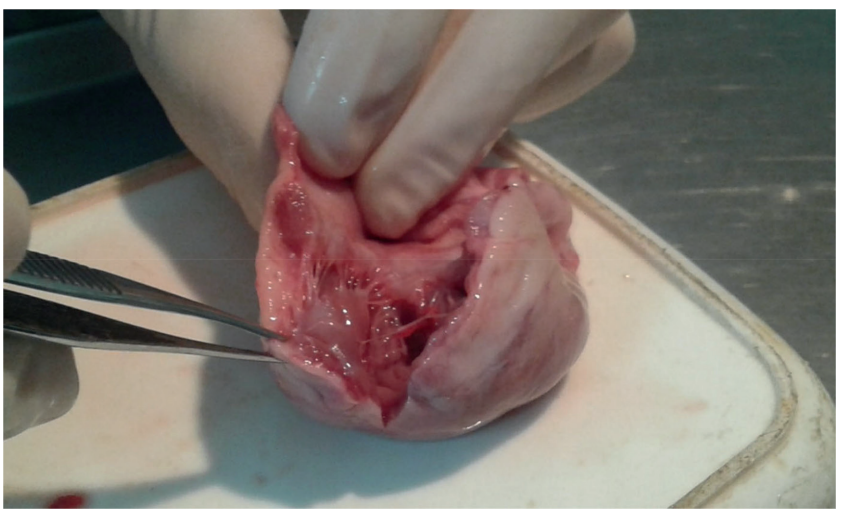

Figure 11.
Preserved myocardium is observed above below the fatty replacement of the ventricle wall.

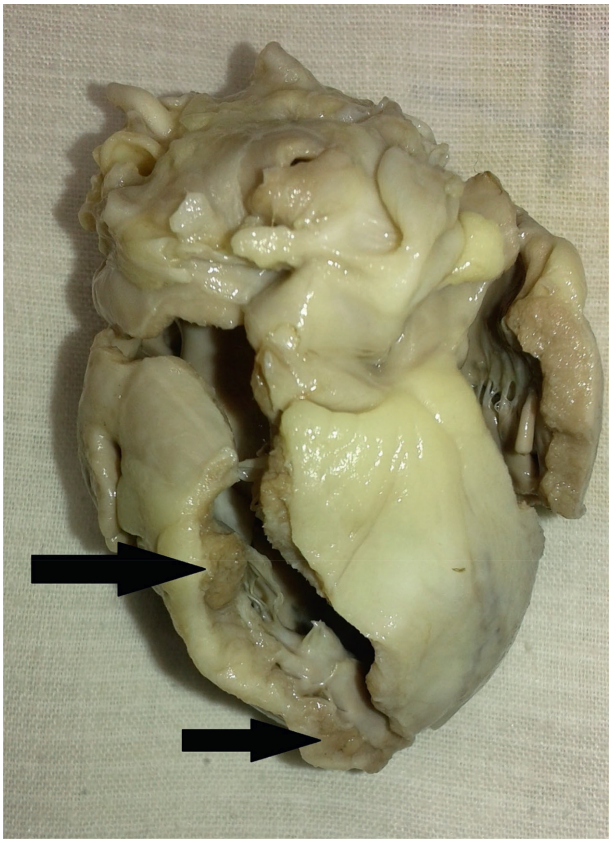

Figure 12.
Formaldehyde piece from the previous case. The arrows show the remnant of myocardium preserved in the free wall replaced by fat.

myocardium and, in general, on the right side of the interventricular septum. In the present canine case, the structural abnormalities found during the echocardiographic study corresponded to an increase in diastolic diameter, preserving the shortening fraction without evidence of alterations in the thickness of the free wall of the left ventricle or septum.

In the left dominant form of Arrhythmogenic Cardiomyopathy, the distribution of fibrosis usually predominates in the outer third, that's to say, in the epicardium and subepicardium, and progresses to the endocardium. This lesion may have a circumferential shape or may be patchy. The left form of Arrhythmogenic Cardiomyopathy may or may not be associated with dilation of the right ventricle. In the classic form of the disease, ventricular tachycardia with left bundle branch block morphology can be observed, while in the left ventricular form, ventricular tachycardia will present right bundle branch block morphology.

In human medicine reports of the left-predominant form, the interventricular septum was affected in more than 50%. These findings coincide with what was observed in the present canine case and with what was found in the feline, where the fat replacement took place in the free wall of the left ventricle [18]. On the other hand, the difference observed in the present case differs with respect to the biventricular form, because in this case there is right and left dilation, and in our canine and feline

cases, the dilation was only on the left side. The right ventricle in both cases was normal. In human medicine, before the disease is in a highly advanced stage, it is difficult to differentiate the left form from the biventricular presentation. It's the same when distinguishing dilated cardiomyopathy of the left form from Arrhythmogenic Heart Disease, because the subepicardial distribution of the lesion must be taken into account, which is more frequent in the left form of the disease than in the dilated one [19].

Another differential feature that supports the diagnosis of the left dominant form over the dilated form is the presence of severe ventricular arrhythmia in the arrhythmogenic form, which is disproportionately high for the degree of systolic involvement of the left ventricle. The same happens with the appearance of congestive heart failure. That is a final event in Arrhythmogenic Cardiomyopathy, whereas in dilated cardiomyopathy, it is an initial event. Cases with classic Arrhythmogenic Heart Disease arrive with arrhythmia with normal left ventricular systolic function. Additionally, in predominantly right-sided Arrhythmogenic Cardiomyopathy, the left-sided septum is much less affected than the right-sided septum. In our canine case, septal involvement was a distinguishing feature to suspect a left form of the disease, while in our feline case the septum was preserved. Another differential diagnosis in the findings observed in this report is the ischemic heart disease.

When speaking of ischemic heart disease, fibrosis with subendocardial disposition is usually observed, which can be transmural after progressing. In our report of the canine case, there was an epicardial and midventricular lesion but without dysfunction or dilation of the left ventricle and without coronary involvement [20]. This also shows that, between the studies by imaging, the echocardiogram has low sensitivity to detect this type of lesion and it is very important to consider the use of magnetic resonance imaging (MRI) with gadolinium as contrast to further improve the diagnosis [21]. On the other hand, the mutations discovered (both in humans and animals) of the genes encoding desmosomic and extradesmosomic proteins demonstrate an overlap between dilated heart disease, arrhythmogenic cardiomyopathy, and channelopathies, with expressions of different phenotypes.

Mutations affecting compound area genes are now considered to be important in the pathogenesis of these diseases, which could represent a continuum between them from a purely arrhythmogenic phenotype to one with left ventricular dilation and congestive failure.

The canine patient in this report had conditions that suggested the presence of a canalopathy, given that the corrected QT interval was prolonged and had structural alterations suggestive of Arrhythmogenic Cardiomyopathy, such as fibroadipose replacement [22]. It also presented signs that are frequently seen in dilated cardiomyopathy such as undulating myocardial fibers. This indicates that further studies are required to differentiate between these different phenotypic presentations.

In the case presented in the feline, the changes were totally limited to the free wall of the left ventricle, but although the damage was transmural, a small layer of the subendocardial was preserved. Since transmural heart attack of epicardial coronary origin has not been described and no coronary pathology has been found in the arteries that supplied the fibrofatty replacement segment in the feline left ventricle, the hypothesis that it is an ischemic pathology would be discarded. It is also important to note that in the rest of the feline heart that was preserved without injury, there was no hypertrophy, which suggests that we can also rule out the terminal phase of feline hypertrophic cardiomyopathy, where there may be thinning of the wall due to microvascular injury. In the latter case, in the final stage of hypertrophic heart disease

with abnormal remodeling, there is usually a lot of fibrosis. In our feline case, this is not true because there was a notorious fat replacement, which makes us think of an Arrhythmogenic Cardiomyopathy of the left ventricle.

8. Conclusion

In both of the presented cases, the lesions by fatty tissue replacement of the cardiac muscle in the left ventricular wall, without evidence of coronary ischemic lesion or of microvascular lesion, allow us to conclude that the compatible diagnosis is Arrhythmogenic Cardiomyopathy. The clinical course of the canine, which did not present heart failure but did present severe arrhythmias, also speaks in favor of Arrhythmogenic Cardiomyopathy. In the case of the feline patient, it was similar to the canine patient and the histopathological findings of fatty replacement in the ventricle were similar in both animals.

To the authors' knowledge, this report is the first one made about Left Ventricle Arrythmogenic Cardiomyopathy in companion animals, and future studies are required to better understand the disease in these species.

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