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Arrhythmogenic right ventricular cardiomyopathy in dogs☆

S.M. Cunningham, DVM*, L. Dos Santos, DVM, PhD

Department of Clinical Sciences, Cummings School of Veterinary Medicine at Tufts University, 200 Westboro Road, North Grafton, 01536, MA, USA

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Abstract Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disease seen in dogs, cats, and humans. A common entity in Boxers and the related English bulldog, the disease is characterized by fatty or fibrofatty replacement of the myocardium, ventricular arrhythmias, and the potential for syncope or sudden death. In some individuals, concomitant left ventricular involvement results in systolic dysfunction and a progression to congestive heart failure. The clinical and pathological characteristics of ARVC share many similarities in dogs and humans, and Boxers serve as an important spontaneous model of the disease.

Although multiple mechanisms have been implicated in the pathogenesis of ARVC, the disease is ultimately considered to be a disorder of the desmosome. Multiple causal genetic mutations have been identified in people, and over 50% of affected humans have an identifiable mutation in desmosomal proteins. To date, only a single genetic mutation has been associated with ARVC in Boxer dogs. Other as-yet-undiscovered genetic mutations and epigenetic modifiers of the disease are likely. Treatment of ARVC in dogs is focused on controlling ventricular arrhythmias and associated clinical signs. This article will review the pathophysiology, clinical diagnosis, treatment, and prognosis of ARVC in the dog.

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* Corresponding author.
E-mail address: suzanne.cunningham@tufts.edu (S.M. Cunningham).

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Abbreviations

ARVC	arrhythmogenic right ventricular cardiomyopathy
BNP	brain natriuretic peptide
CHF	congestive heart failure
cTnI	serum cardiac troponin-I
DCM	dilated cardiomyopathy
ECG	electrocardiogram
ICD	internal cardioverter defibrillator
LV	left ventricle
RV	right ventricle
TAPSE	tricuspid annular plane systolic excursion
VPC	ventricular premature complex
Wnt	wingless-related integration site

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an important cause of syncope and sudden cardiac death in people and Boxer dogs [1]. It has also been described in the related English bulldog [2—4] and in isolated reports in a Labrador Retriever, Dachshund, Bullmastiff, Siberian husky, Shetland sheepdog, Dalmatian, and Weimaraner [5—9].

The disease is a common entity in the Boxer breed manifested by malignant ventricular arrhythmias, cardiac dilation, and systolic dysfunction, or both. As such, the Boxer serves as an important animal model for the disease in people. The earliest clinically recognizable stage of ARVC is characterized by the development of asymptomatic ventricular arrhythmias originating from the right ventricle (RV). At this stage, routine electrocardiographic (ECG) monitoring may identify infrequent ventricular premature complexes (VPCs) and lead to clinical suspicion of disease, but a definitive diagnosis is established from a combination of family and clinical history signalment, 24-h ambulatory ECG (Holter) monitoring, and echocardiography.

Mutations in various desmosomal proteins are identified in approximately 50% of human patients with ARVC [10]. However, to date, only a single genetic mutation, an eight base pair deletion in the striatin gene, has been found in association with the disease in Boxer dogs [11,12]. The disease is characterized by incomplete penetrance and variable disease expressivity, and striatin genotype is inconsistently associated with disease phenotype. From nine to 16% of dogs with clinical ARVC do not carry the striatin mutation and other genetic causes and nongenetic modifiers of disease expression are likely [11—13].

The histopathologic changes associated with ARVC in Boxers bear a striking resemblance to those accompanying ARVC in people, being characterized by fibrofatty replacement of cardiomyocytes and varying degrees of myocarditis [1]. Replacement of normal cardiomyocytes by inflammatory cells, fibrosis, and adipocytes results in an arrhythmic substrate that sets the stage for the development of malignant re-entrant ventricular arrhythmias. Worsening ventricular arrhythmias can result in clinical signs of weakness, syncope, or sudden death. Some proportion of dogs and people with ARVC will go on to develop left ventricular (LV) involvement with cardiac dilation and reduced LV contractile function, often progressing to overt heart failure [14,15]. Current pharmacologic therapy for ARVC is aimed at palliative relief of clinical signs and malignant arrhythmias, and the search for novel therapeutic targets is ongoing. This article reviews the clinicopathological features, etiopathogenesis, and current screening and treatment options for dogs with ARVC.

Etiology and pathogenesis

Pathological features

The pathological characteristics of ARVC are remarkably similar in people and dogs, with the hallmark features consisting of fatty or fibrofatty replacement of the RV myocardium (Fig. 1). Gross changes may be difficult to detect in the early stages of the disease, but RV chamber dilation may be identified in approximately one-third of Boxer dogs with ARVC [1]. Infundibular aneurysms may also be seen less commonly. On cut-section, patchy or multifocal grayish-white tissue replacement of the atrial and ventricular walls may be noted, typically progressing from epicardium to endocardium [5].

Two main histopathological patterns of disease are noted, a fatty form and a fibrofatty form. The fatty form, seen in approximately two-thirds of Boxers with ARVC, is characterized by substantial replacement of the RV myocardium by mature adipocytes [1]. The distribution is typically diffuse, with multifocal regions of fatty replacement of the RV free wall and trabeculae extending from epicardium to endocardium and mild interstitial fibrosis. The fibrofatty form is characterized by multifocal or diffuse areas of replacement by adipose cells, along with more extensive areas of replacement fibrosis. Surviving cardiomyocytes are embedded within surrounding adipose and fibrous

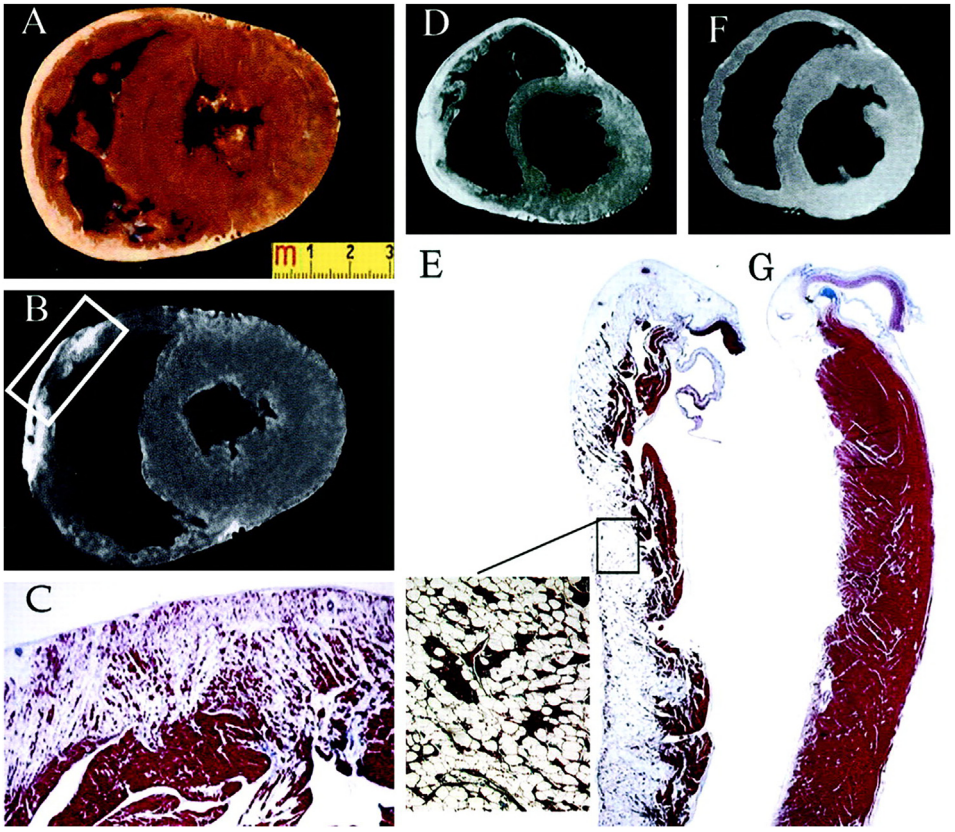

Fig. 1 Pathological findings in two Boxer dogs with a fatty pattern of arrhythmogenic right ventricular cardiomyopathy (ARVC) and a control dog. A, B, and C are from a nine-year-old female Boxer dog with ventricular tachycardia and sudden death during physical activity. A. Gross heart specimen cut in cross-section. B. T1-weighted postmortem magnetic resonance imaging (MRI) corresponding to the same cross—sectional plane as shown in A. Right ventricular (RV) cavity is dilated, but wall thickness is normal. C. Low-power histopathological section of RV wall from the region of bright MRI signals (delineated by the box in B); marked transmural fatty replacement is evident (magnification × 3). D and E are from a 12-year-old female Boxer dog with ventricular tachycardia and congestive heart failure. D. Cross-sectional MRI image showing bright, a high-intensity signal in RV infundibulum. E. Panoramic histopathological section from region of bright MRI signals demonstrating massive, diffuse fatty replacement of atrophic myocardium (magnification × 3). Inset shows small islands of a few surviving myocytes surrounded by fat (magnification × 10). F and G are from a normal control dog. F. Cross-sectional MRI showing absence of bright MRI signals in RV wall. G, Panoramic histopathological section demonstrating normal RV myocardial architecture (magnification × 3). Staining for C, E, and G is with trichrome Heidenhain (From Basso et al., 2014. Circulation 2004; 109 (9):1180—5 with permission).

tissue (Fig. 2B). These histopathological changes are typically most prevalent in the subepicardial and midmyocardial regions of the RV free wall (Fig. 2A). However, the disease is not restricted to the RV, and similar changes have also been documented in the LV and atrial myocardium of affected dogs [1,5,16].

Myocarditis is commonly identified in dogs, and people with ARVC and inflammation may be implicated in the pathogenesis of the disease [1,5,17]. Patchy lymphocytic infiltration is often associated with regions of myocyte death and fibrofatty replacement [1,5]. This fibrofatty myocardial replacement contributes to delayed conduction within the ventricular myocardium and gives rise to conditions favorable to re-entrant circuits and arrhythmogenesis. Both myocarditis and fibrofatty myocardial replacement have thus been associated with sudden death in dogs with ARVC [1,5]. It remains uncertain whether myocarditis accompanying ARVC is a primary phenomenon or a secondary reaction to spontaneous cardiomyocyte death. Although the RV is typically more severely affected, both myocarditis and fatty or fibrofatty myocardial replacement are also commonly noted in the left ventricular and atrial myocardium [1,5,16]. The recognition of these more diffuse changes has led some authors in the human and veterinary literature to adopt the broader term "arrhythmogenic cardiomyopathy" with classical RV dominant, LV dominant, or biventricular variants [18—21].

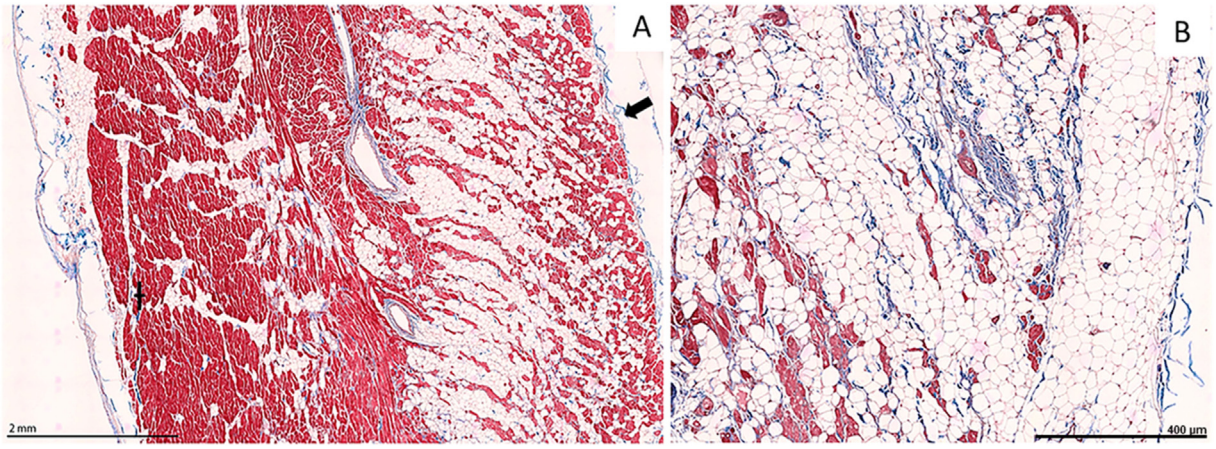

Fig. 2 Histopathology of the right ventricular (RV) myocardium from an eight-year-old female spayed Boxer dog with arrhythmogenic right ventricular cardiomyopathy that experienced sudden death (A) Low-power transmural section of the right ventricle showing marked diffuse fatty replacement of the RV myocardium progressing from epicardium (arrow) to endocardium (†). Fatty replacement is most severe in the subepicardial and midmyocardial regions. Masson's trichrome stain, 2 ×, Bar = 2 mm. (B) Higher power section showing severe fibrofatty replacement with few islands of surviving cardiomyocytes embedded in surrounding adipose and fibrous tissue. Masson's trichrome stain, 10 ×, Bar = 400 µm.

Ultrastructural features

Arrhythmogenic right ventricular cardiomyopathy is primarily considered to be a disease of the cardiac desmosome, and 12 of the 16 known genetic mutations that have been associated with ARVC in human patients at the time of this writing affect desmosomal proteins [10,15]. Desmosomes are integral components of the intercalated disk that play a crucial role in cell-to-cell adhesion and signal transduction of cardiomyocytes. Desmosomal abnormalities can result in weakening and disruption of intercellular junctions (Fig. 3), especially under conditions of mechanical stress, such as that posed by exercise [15,19,22].

Ultrastructural studies of myocardial samples from humans with ARVC have shown remodeling of the intercalated disks with desmosomal abnormalities and loss [23]. In myocardial tissue samples from affected Boxers (Fig. 4), evaluation of transmission electron microscopy has identified a reduced number of desmosomes, gap junctions, and adherens junctions, as well as alterations in sarcomeric structure [24].

Molecular mechanisms

Although the exact molecular pathogenesis of ARVC remains uncertain, studies suggest that aberrant translocation of plakoglobin from the cytoplasm to the nucleus (Fig. 3D) results in suppression of canonical (wingless-related integration site) Wnt signaling in the second heart field progenitor cells that control the development of the RV myocardium [19,25]. These altered progenitor cells are hypothesized to produce paracrine factors that provoke differentiation of non-cardiomyocytes (e.g., fibrocytes, pericytes or preadipocytes) to mature adipocytes, resulting in fibrofatty replacement of the ventricular myocardium. Changes in Wnt pathway proteins have similarly been identified in Boxers with ARVC [26], and a mutation has been identified in some affected dogs for the gene encoding for striatin, a protein in the intercalated disc that colocalizes with desmosomal proteins and is a known Wnt pathway component [11,26].

In addition to the re-entrant arrhythmias that arise from fibrofatty replacement of the myocardium, dysregulation of calcium handling by the sarcoplasmic reticulum has been shown to promote arrhythmogenesis in ARVC [19]. Reductions in mRNA and protein levels of both the cardiac ryanodine receptor [27] and calstabin 2 [28] have been documented in the myocardium of Boxers with ARVC and may serve as potential mechanisms of Ca^{2+} leak-induced ventricular arrhythmias. Additional molecular mechanisms that have been proposed to contribute to the pathogenesis of ARVC are shown in Fig. I (available in Supplemental Material online).

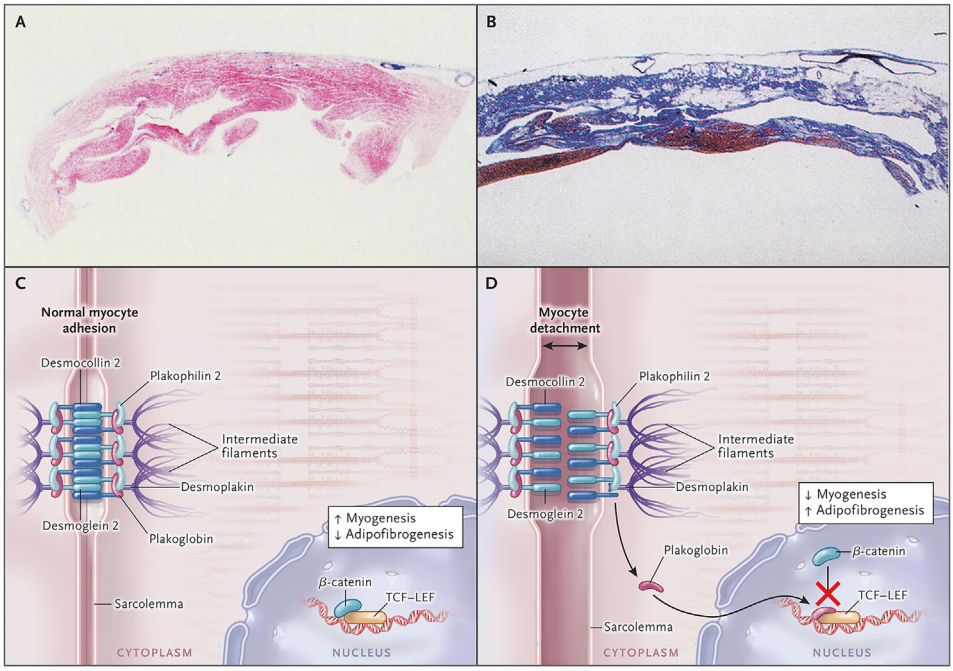

Fig. 3 Histopathological features and pathogenesis of arrhythmogenic right ventricular cardiomyopathy (ARVC). The distinctive histopathological feature of arrhythmogenic right ventricular cardiomyopathy is the loss of right ventricular myocardium and the substitution of fibrous and fatty tissue. Panel A shows a full-thickness histologic section (azan trichrome stain) of the anterior right ventricular wall in a normal human heart; Panel B shows a similar section from the heart of a patient with ARVC who died suddenly. With the azan trichrome stain, myocytes appear red, fibrous tissue appears blue, and fatty tissue appears white. Arrhythmogenic right ventricular cardiomyopathy is caused by genetically defective desmosomes, which are cell-to-cell adhesive structures. The desmosome contains three major components: desmoplakin, which binds to intermediate filaments (i.e., cardiac desmin); transmembrane proteins (i.e., desmosomal cadherins), including desmocollin 2 and desmoglein 2; and linker proteins (i.e., proteins of the armadillo family), including plakoglobin and plakophilin 2, which mediate interactions between the desmosomal cadherin tails and desmoplakin, as shown in Panel C. Abnormal desmosomes confer a predisposition over time to disruption of the intercellular junction, as shown in Panel D (double-headed arrow), mostly under conditions of increased mechanical stress, such as sports activity. A parallel pathogenic mechanism involves the canonical Wnt—β-catenin signaling pathway. This evolutionarily conserved pathway plays a pivotal role in cardiac development, myocyte differentiation, and normal myocardial architecture. During canonical Wnt—β-catenin signaling, β-catenin forms complexes with members of the TCF—LEF (T-cell factor—lymphocyte-enhancing factor) family of transcription factors in the nucleus to prevent the differentiation of mesodermal precursors into adipocytes and fibrocytes by suppressing the expression of adipogenic and fibrogenic genes (Panel C). Impairment of desmosomal assembly by genetically defective proteins causes the translocation of plakoglobin from the sarcolemma to the nucleus (arrows in Panel D), where it may antagonize the effects of β-catenin. By competing with β-catenin, intranuclear plakoglobin suppresses Wnt—β-catenin signaling and induces a gene transcriptional switch from myogenesis to adipogenesis and fibrogenesis (Panel D). Panels A and B are reprinted from Thiene et al. (From Corrado D et al. N Engl J Med 2017; 376: 61—72 with permission).

Genetics

In Boxers, ARVC is a familial disease inherited in an autosomal dominant pattern [29], with variable penetrance and expressivity. To date, only a single genetic mutation has been associated with ARVC in the Boxer. A genetic deletion in the 3' untranslated region of the gene encoding for striatin — a protein that colocalizes with three desmosomal proteins — is associated with the development of ARVC in some U.S. Boxers [11,12]. Dogs that are homozygous positive for the striatin mutation are more likely to develop the dilated cardiomyopathy (DCM) phenotype of the disease, may have a more severe ventricular arrhythmia, and may be more likely to develop the disease at a younger age [12]. However, ARVC is characterized by incomplete penetrance and variable disease expressivity, and striatin genotype is inconsistently associated with disease phenotype. From 9 to 16% of dogs with clinical ARVC do not carry the striatin mutation, and thus, other genetic causes and/or nongenetic modifiers of the disease are likely [11,12].

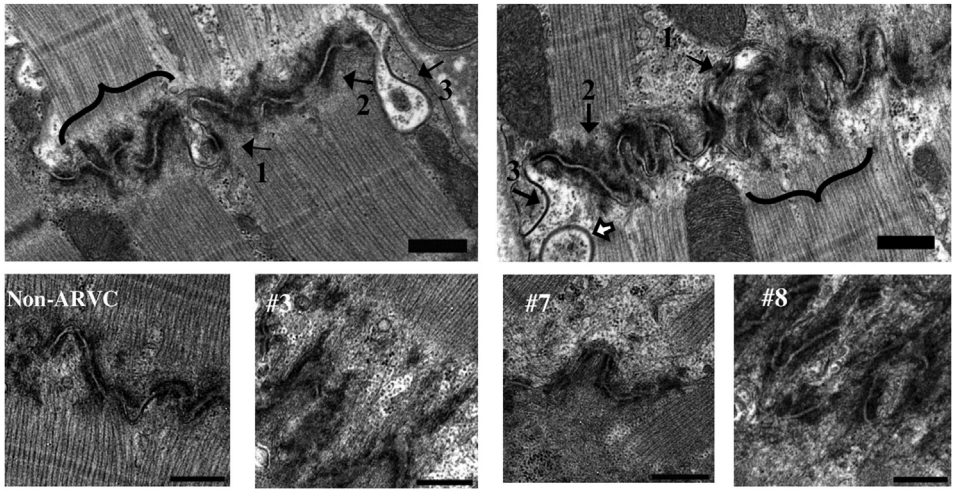

Fig. 4 Ultrastructural abnormalities in dogs with arrhythmogenic right ventricular cardiomyopathy (ARVC).13,000 × (scale bar denotes 500 nm) electron micrographs of intercalated discs from non-ARVC (left panel) and ARVC (right panel) afflicted tissue. Arrow 1: desmosome, arrow 2: adherens junctions, arrow 3: gap junction. White arrow, top right panel: Annular gap junction. Adjacent to the intercalated disc, pale areas lacking filaments are apparent in ARVC afflicted samples (bracket). Comparable areas in controls appeared more electron-dense and included filaments (bracket). Bottom panels show images of midmyocardial RV at 13,000 × magnification. One non-ARVC (left) and three ARVC dogs (#3, 7, 8) are included. Poorly organized, heterogeneous material, with actin filaments ending 0.25 to 1.5 microns away from the membrane of the cell, were present rarely in non-ARVC, and commonly in ARVC afflicted dogs. Dog #8 (lower, far right panel) revealed disorganized and folded intercalated discs (From Oxford et al. J Vet Cardiol 2011; 13 (2):101—13 with permission).

In humans, at least 16 different genetic mutations have been implicated in the development of ARVC. Most of these mutations are found in desmosome-related genes, and more than 50% of human patients with ARVC have an identified genetic mutation [10]. Despite the importance conferred to genetic screening in the diagnosis of ARVC in people [30], the penetrance of most pathogenic desmosome gene variants is only approximately 30%, suggesting that disease expression in humans is also influenced by other genetic or environmental factors [13,31].

Clinical features and natural history

Arrhythmogenic right ventricular cardiomyopathy is an adult-onset disease with age-related penetrance and a mean age of diagnosis of five to seven years in Boxer dogs. Although the disease is occasionally diagnosed in younger animals, the young Boxer with syncope is more commonly afflicted with neurocardiogenic syncope, and Holter monitoring is typically needed to differentiate. The disease was first described as "Boxer Cardiomyopathy" in U.S. Boxers by Neil Harpster in 1983 [32], before being re-classified as ARVC when the striking similarities between the clinical and pathological features of the disease in people and affected Boxers were described in 2004 [1]. The three clinical categories of the disease described by Harpster are still relevant to the classification of dogs with ARVC today.

I. The first category includes dogs with "concealed", or subclinical ventricular ectopy that is evident on ECG or Holter monitoring but not resulting in any discernible clinical signs. These dogs may have arrhythmia detected incidentally on routine physical examination or via screening with 24-h Holter monitoring. Genetic testing for the striatin mutation may identify at-risk individuals but cannot predict which animals will go on to develop the disease.
II. The second category includes dogs that present with ventricular tachyarrhythmias and associated clinical signs of syncope, collapse, weakness, or exercise intolerance. In some dogs, the first clinical sign of the disease is sudden cardiac death. Echocardiography in these dogs may reveal RV dilation or reduced RV systolic function, but the LV is grossly normal without obvious LV systolic dysfunction.
III. The final category describes dogs with arrhythmia and concomitant LV systolic dysfunction and possible progression to left-sided or biventricular congestive heart failure (CHF). These dogs are said to have a "DCM-phenotype", and

this manifestation of the disease can be difficult to differentiate from primary or nutritional DCM premortem. This form of the disease may be more prevalent in Boxers in the United Kingdom [33] and in English bulldogs [2].

Although the various clinical manifestations are thought to represent a continuum of the same disease, there is considerable variability in the severity and clinical course of the disease in individual animals, with some dogs exhibiting arrhythmias for years with no discernible cardiac enlargement developing, and other presenting with biventricular dilation and relatively mild associated arrhythmias. Left ventricular systolic dysfunction resulting in a DCM-like phenotype is also seen in a subset of human patients with ARVC and is typically associated with adverse outcomes [18]. The DCM-like phenotype of the disease is seen in a minority of U.S Boxers with ARVC [34], but when it does occur, it is associated with a poorer long-term prognosis, particularly if CHF has developed [33,35]. Syncope is seen in approximately one-third of Boxers with ARVC and has also been shown to confer a worse prognosis [33,34,36]. Despite the potential for sudden death, many dogs with ARVC without significant cardiac enlargement or CHF can have a good long-term prognosis and live for years with appropriate therapy [34].

Diagnosis

There is no single gold standard diagnostic test for the antemortem diagnosis of ARVC in dogs or people. In humans, the diagnosis is based on a qualitative scoring system comprised of major and minor task force criteria encompassing structural, electrocardiographic, and histological criteria [30]. Similar diagnostic criteria have not been defined in dogs, in whom the diagnosis is typically based on a combination of family history or clinical signs and the finding of ventricular ectopy in a predisposed breed with no other identifiable cause. Syncope or weakness in a middle-aged to older Boxer or English bulldog should prompt a diagnostic workup for ARVC, including a physical examination, minimum database, ECG, echocardiogram, and 24-h Holter monitor. An abdominal ultrasound may also be recommended in older animals to rule out the abdominal disease that can lead to ventricular arrhythmias (e.g., splenic lesions or adrenal mass). Unfortunately, many dogs affected with ARVC are asymptomatic until developing syncope or experiencing sudden death, hence the need for regular screening in predisposed animals [32,34].

Physical examination

Physical examination findings may be normal in dogs with ARVC, or affected dogs may have evidence of arrhythmia on auscultation, with pulse deficits noted. In dogs with left ventricular systolic dysfunction, a soft left apical murmur associated with mitral regurgitation, weak femoral pulses, or signs of CHF (jugular vein distension, dyspnea, cough, pulmonary crackles, abdominal distension) may be seen. A soft (Grade I-II/VI) systolic ejection murmur heard at the left heart base is a common finding in the Boxer breed that can be found in dogs with or without ARVC.

Electrocardiography

The hallmark ECG finding associated with ARVC is the presence of upright, left bundle branch block morphology VPCs originating from the RV [37]. These VPCs can be isolated or occur in a bigeminal pattern, in couplets, or in short paroxysms or sustained runs of ventricular tachycardia (Fig. 5). Polymorphic or LV origin VPCs are sometimes seen, mainly in dogs with significant LV involvement. Although structural and molecular changes have been demonstrated in the atrial myocardium of Boxers with ARVC, atrial arrhythmias are only common in dogs with concomitant atrial enlargement secondary to LV systolic dysfunction [14]. As arrhythmias may be intermittent, it is not unusual for some affected animals to have no arrhythmias over the course of a short diagnostic ECG.

In humans, several specific ECG criteria are considered in the diagnosis of ARVC, including localized prolonged depolarization, epsilon waves, T-wave inversion, and increased terminal activation [30]. Abnormal signal-averaged ECG findings, although nonspecific, fulfill a minor criterion for diagnosis of ARVC in human patients. Late potentials have been documented in signal-averaged ECG from some Boxers [38] and bulldogs [4] with ARVC; however, signal-averaged ECG is not widely available in veterinary medicine, and the clinical utility of this testing is limited.

Holter monitoring

Holter monitoring is the current screening method of choice for ARVC, and the results have diagnostic, prognostic, and therapeutic importance for the management of this arrhythmic disease

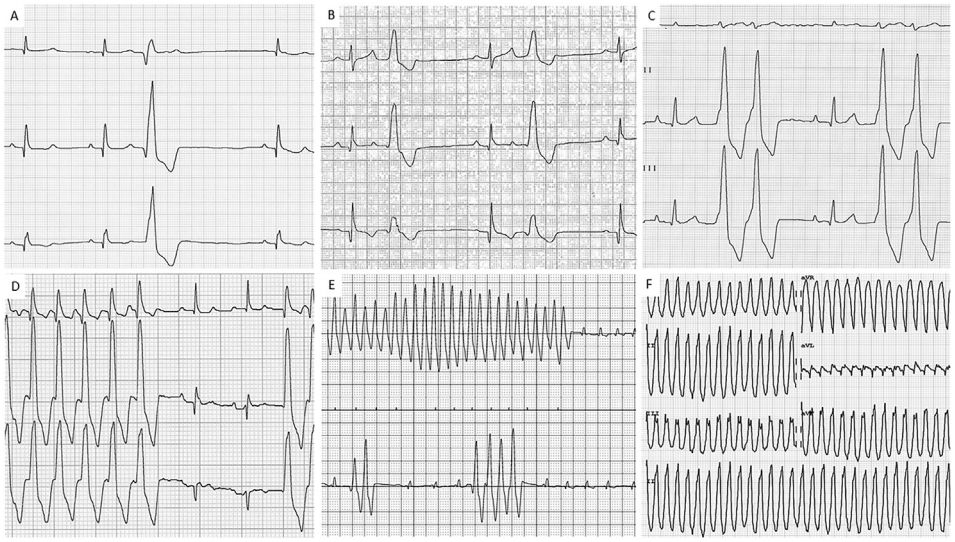

Fig. 5 Electrocardiographic (ECG) findings in dogs with arrhythmogenic right ventricular cardiomyopathy (ARVC). Normal sinus rhythm with isolated right ventricular origin ventricular premature complexes (VPC; A); ventricular bigeminy (B); ventricular couplets exhibiting R-on-T morphology (C); non-sustained paroxysms of ventricular tachycardia seen on a diagnostic multilead ECG (D) and on a Kardia mobile ECG device ([a] E); and sustained rapid R-on-T ventricular tachycardia that was refractory to medical therapy and required synchronized electrical cardioversion (F).

[33—36]. All Boxers should have a 24 or 48-h Holter monitor prior to being considered for breeding. However, it is important to note that given the age-related penetrance of ARVC (with worsened arrhythmia over time) and the variable arrhythmia frequency seen in affected dogs, normal results of a single Holter monitor cannot conclusively rule out the presence of disease [34]. Annual Holter monitoring is therefore recommended for breeding animals and dogs with a family history of ARVC. The authors recommend that potential breeding animals have at least two normal Holter monitor results prior to breeding. Table 1 details the Holter interpretation criteria that have been proposed for the screening of ARVC in Boxers [39].

Another simplified proposal for the diagnosis of ARVC in Boxers suggested to result in a more uniform disease phenotype similar to that described in people with arrhythmogenic cardiomyopathy is based on the presence of two out of the three following criteria: $\geq$ 100 VPCs, presence of couplets, or R-on-T phenomenon on a 24-h Holter [20]. The diagnosis of ARVC should not be based solely on an arbitrary number of VPCs, and the signalment and clinical signs of the dog, the complexity of the arrhythmia, and the presence or absence of other comorbidities that could contribute to ventricular ectopy should be all be considered. Additional screening tests that could predict the development of the disease prior to the development of Holter or echocardiographic abnormalities in affected individuals would have great utility in decreasing the prevalence of the disease in the Boxer breed.

Holter monitoring is also useful in the management of affected dogs to determine whether

Table 1 Proposed Holter criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy in Boxer dogs.

VPCs per 24 h	Interpretation
0—20	Normal
20—100	Equivocal
100—300	Suspicious/likely affected
100—300 with complexity (couplets, runs, or R-on-T); or 300—1000	Very likely affected
>1000	Affected; consider treatment

Modified from Meurs KM. Vet Clin North Am Small Anim Pract. 2017 Sep; 47(5):1103—1111.
VPC: ventricular premature complexes.

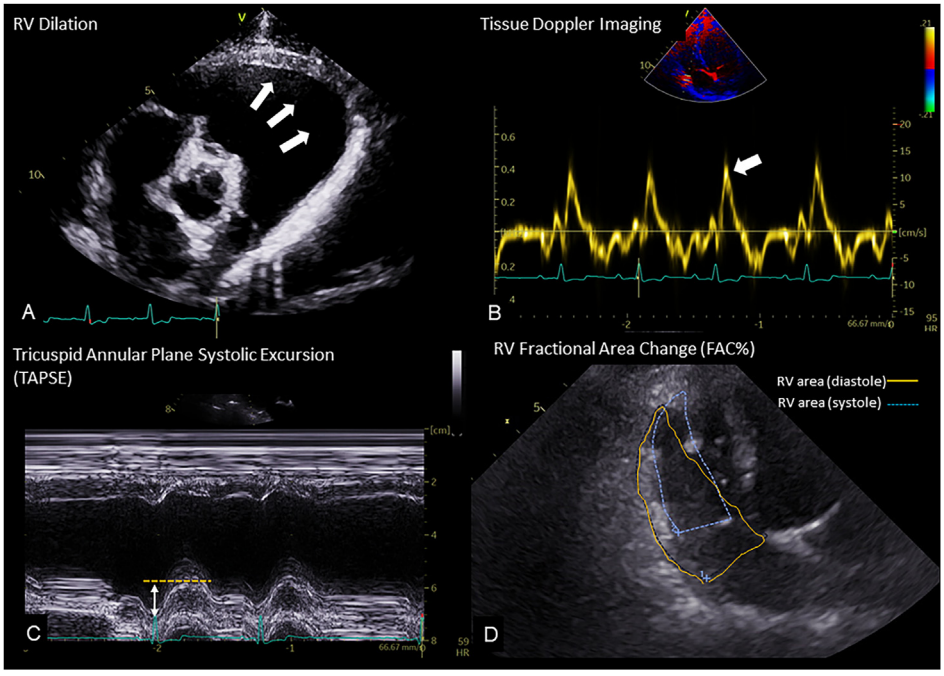

Fig. 6 Conventional echocardiographic assessment of right ventricular (RV) structure and function in dogs with arrhythmogenic right ventricular cardiomyopathy (ARVC). Panel A depicts a two-dimensional right parasternal short-axis image demonstrating RV dilation in a Boxer with ARVC (arrow). Right ventricular systolic function parameters that may be impaired in dogs with ARVC are demonstrated in panels B—D. Panel B shows pulsed wave tissue Doppler imaging-derived evaluation of the myocardial velocity of the lateral tricuspid annulus (S′ depicted by arrow). Measurement of tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC) are shown in panels C and D, respectively.

antiarrhythmic therapy is warranted and to monitor the efficacy of such treatment. When evaluating antiarrhythmic efficacy, it must be considered that a >80% day-to-day variability in VPC number has been documented in Boxers with significant arrhythmia (≥500 VPCs), so a >80% reduction in arrhythmia is needed to definitively suggest treatment efficacy [40].

In addition to Holter monitoring, implantable loop recorders or hand-held mobile ECG devices may be useful in allowing monitoring of the cardiac rhythm in the home environment. The authors regularly recommend home ECG monitoring (Fig. 5B) of dogs with ARVC with the Kardia mobile device.[a] Home ECG monitoring by owners allows for closer monitoring of patients between exams, and in some cases, these devices can supplant the need for an event monitor in animals with intermittent syncope. Further investigation is warranted to evaluate the potential utility of mobile ECG devices in the screening and management of dogs with ARVC and other arrhythmic diseases.

[a] Kardia Mobile, AliveCor Inc., San Francisco, CA, USA.

Echocardiography

Echocardiography plays an important role in the evaluation and prognostication of dogs with ARVC. The echocardiographic findings of some affected dogs may be normal. However, extensive fibrofatty replacement of the RV myocardium typically results in reduced RV systolic function and RV chamber dilation that can be detected on echocardiography (Fig. 6). Similarly, dogs with substantial LV involvement may develop LV dilation, wall thinning, and reduced LV systolic function that may appear indistinguishable from other causes of DCM-phenotype [14,33,41].

Reduced RV systolic function, as evidenced by decreased tricuspid annular plane systolic excursion (TAPSE; Fig. 6C) and pulsed wave tissue Doppler imaging derived systolic myocardial velocity of the lateral tricuspid annulus (S'; Fig. 6B), has been demonstrated in Boxers with ARVC [41]. Decreased TAPSE has also been associated with poorer outcomes in Boxers with ventricular ectopy suspected to have ARVC [42]. However, the interindividual variability in measurements of RV systolic function and substantial overlap between

normal and affected Boxers limits the utility of these parameters as stand-alone screening measures for ARVC in the dog. More advanced echocardiographic techniques utilizing four-dimensional echocardiography and speckle tracking-derived longitudinal strain imaging of the RV (Fig. II; available in Supplementary Material online) may allow for a more accurate assessment of RV volumes and systolic function, respectively, than conventional echocardiography. These modalities require substantial operator experience and specialized software and currently have limited clinical use; however, further investigation is needed to define the potential role of these techniques in the evaluation of dogs with ARVC.

Biomarkers

To date, no blood-based biomarker has been identified to reliably diagnose ARVC. Increased serum cardiac troponin-I (cTnI) levels were shown in one study of Boxers with ARVC, and cTnI levels were correlated positively with the frequency and severity of ventricular arrhythmias seen on Holter monitoring [43]. However, there was large inter-individual variability and significant overlap between cTnI levels in control Boxers and Boxers with ARVC, thus limiting the clinical utility of cTnI as a screening test for this disease. Plasma concentrations of C-terminal brain natriuretic peptide (BNP) have also been evaluated in Boxers with ARVC, with no differences identified in BNP levels of affected dogs compared to clinically normal Boxer and non-Boxer dogs [44]. Although there are no published studies of N-terminal (NT)-pro-hormone BNP in dogs with ARVC, in the authors' clinical experience this biomarker is useful in screening for dogs with significant cardiac dilation or systolic dysfunction.

Recent human studies have shown increased levels of antiheart and antidesmosomal proteins in people with ARVC to be correlated with disease severity, suggesting that autoimmunity and inflammation may play a role in the pathogenesis of the disease [45,46]. Circulating antidesmosomal antibodies have also been detected in a small number of Boxer dogs with clinical evidence of ARVC, while dogs without overt evidence of disease were not found to have circulating antibodies [45]. Further studies in dogs and people are needed to determine whether these markers may be able to predict disease development in predisposed individuals with a family history of disease or whether they are present only in the face of active disease. A biomarker for ARVC that could allow for screening of dogs early in life, prior to the phenotypic expression of the disease, could have enormous ramifications for reducing the prevalence of the disease and improving monitoring and treatment recommendations for individual pets. The authors are currently evaluating circulating antidesmosomal antibodies in clinically normal Boxers and Boxers with ARVC.

Treatment and prognosis

The current treatment of ARVC in the dog is palliative, with a focus on controlling ventricular arrhythmias and ameliorating associated clinical signs such as syncope. In dogs with severe cardiac dilation, control of CHF may also be necessary. In people and experimental animals with ARVC, exercise and intense physical activity are known to precipitate arrhythmias and promote disease progression [22]. Exercise may potentiate myocyte damage by accelerating the disruption of altered desmosomes [22], and prolonged or intense physical activity should be discouraged in affected animals.

There is no absolute number of VPCs that automatically warrant medical therapy, and the trigger to begin antiarrhythmic drugs is often dictated by clinician preference. In humans, empiric beta-blocker therapy is recommended for symptomatic individuals in an attempt to reduce arrhythmias and RV wall stress [47]. Although antiarrhythmic medications may reduce the frequency of arrhythmia and ameliorate clinical signs such as syncope [48], all antiarrhythmic agents can have proarrhythmic effects, and there is no data at this time to show that they reduce the risk of sudden arrhythmic death or prolong survival times. In general, antiarrhythmic drugs are warranted in dogs with clinical signs attributed to their arrhythmia, in those with very frequent ventricular ectopy on 24-h Holter monitoring, or in those that exhibit malignant arrhythmias with increased complexity (R-on-T phenomenon, couplets, triplets, frequent bigeminy, ventricular tachycardia).

For dogs without severe LV systolic dysfunction or CHF, the first-line antiarrhythmic drug of choice is sotalol. Sotalol is a class III antiarrhythmic with significant concomitant beta-blocking effects that have been shown to reduce the frequency of ventricular ectopy and ameliorate clinical signs in Boxers with ARVC [48]. The starting dose is typically 1.5—2.0 mg/kg q 12 h, but the dose may be increased up to 2.5—3.0 mg/kg q 12 h if needed. For dogs with mild to moderate LV systolic dysfunction but no CHF, pimobendan (0.2—0.3 mg/kg q 12 h) may be started concurrently with sotalol to

counteract the drug's negative inotropic effects. When sotalol alone is not sufficient to control the arrhythmia, mexiletine may be used in addition to sotalol at a starting dose of 5.0—6.0 mg/kg every 8 h [39,48]. Mexiletine is an oral Class 1b antiarrhythmic with electrophysiologic properties similar to those of lidocaine. It commonly results in gastrointestinal upset, particularly at higher doses (7.0—8.0 mg/kg), and should be given with food to minimize gastrointestinal complications.

If the combination of sotalol and mexiletine is not effective, or if severe LV systolic dysfunction or CHF precludes the use of sotalol, then amiodarone may be considered. Amiodarone is a broad-spectrum class III antiarrhythmic that can have serious long-term side effects, including hepatotoxicity and thyrotoxicity. For this reason, it is not often used as a first-line antiarrhythmic agent in dogs. Amiodarone is typically instituted at a loading dose of 5—7.5 mg/kg q 12 h for one week, at which time the frequency is reduced to 5—7.5 mg/kg once daily [49]. Liver values and thyroid function should be assessed at baseline, and a chemistry profile is recommended two weeks after starting the medication and every two—three months thereafter. Serum levels of amiodarone and its active metabolite desethylamiodarone may be useful for monitoring the adequacy of blood concentrations during chronic amiodarone therapy, particularly if an increase in hepatic transaminases might prompt a dose reduction or discontinuation of the drug.

In dogs with significant cardiac dilation and systolic dysfunction, treatment with pimobendan and an angiotensin-converting enzyme inhibitor are recommended, with furosemide ± spironolactone added if warranted by signs of CHF. A small number of affected Boxers with DCM-phenotype were shown in one study to have an improvement in systolic function with carnitine supplementation, and supplementation with L-carnitine may be considered at a dose of 50 mg/kg every 8—12 h, in addition to standard pharmacologic therapy [50]. Another optional ancillary therapy for ARVC is supplementation with omega-3 fatty acids. Omega-3 fatty acids were shown to reduce the frequency of ventricular arrhythmia in one study of dogs with ARVC [51], and supplementation of fish oil (1000 mg of EPA/DHA per 10 pounds of body weight), or feeding a diet rich in omega-3s may be considered for affected dogs.

In dogs with sustained rapid ventricular tachycardia that is refractory to pharmacologic treatment, synchronized electrical cardioversion utilizing a biphasic defibrillator may be effective in terminating the arrhythmia [52]. Given the risks of the procedure and the need for anesthesia in a hemodynamically unstable patient, this should be a method of last resort if all attempts at pharmacologic cardioversion fail. Although randomized clinical trials of internal cardioverter defibrillators (ICD) in humans with ARVC are not available, observational studies support their efficacy, with life-saving ICD interventions (appropriate shocks) seen in 30—50% of patients during follow-up [15,47]. Implantation of an ICD is recommended in human ARVC patients that have experienced an episode of hemodynamically unstable, sustained ventricular tachycardia or ventricular fibrillation; and in those with severe systolic dysfunction of the LV, RV, or both, independent of the severity of arrhythmia [47]. There is one case report of ICD implantation in a Boxer with ARVC [53]. Implantation of ICDs is not commonplace in veterinary medicine at this time due to cost and the programming difficulties inherent in trying to adapt these devices for use in the dog. Given the arrhythmic nature of this disease and limitations of current medical therapy, further investigation of the use of ICDs and automated external defibrillators in dogs with ARVC is warranted.

Endocardial radiofrequency ablation of ventricular tachycardia in humans with ARVC can produce short-term success in the treatment of sustained monomorphic ventricular tachycardia. However, the recurrence rate is quite high, and the treatment is considered only palliative [47]. The frequent recurrence of ectopy may be explained by the progressive nature of the disease and/or the typical epicardial location of the arrhythmic substrate.

The prognosis of dogs with ARVC is variable and often difficult to predict. Dogs with syncope or ventricular tachycardia are at increased risk of sudden death [35]; however, dogs that respond favorably to antiarrhythmic therapy and do not go on to develop cardiac dilation and CHF can do remarkably well, with some dogs living five to six years or more from the time of diagnosis [34]. The prognosis of dogs with LV dilation, systolic dysfunction, and CHF is guarded to poor, with most dogs living three to nine months from the time of CHF diagnosis [33,35].

Prospective trials focused on novel therapeutic approaches for the treatment of ARVC are lacking in both dogs and humans.

Pharmacologic agents that could directly target the underlying mechanisms of this disease, including immunomodulatory drugs and small molecule inhibitors of glycogen synthase kinase 3β (GSK3β), a major regulator of Wnt/β-catenin signaling, are currently under investigation in experimental models [54,55]. Investigation of additional mechanism-based therapies for ARVC is anticipated in the future as research continues to elucidate the molecular underpinnings of this complex disease.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Supplementary data

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