

# Boxer dog cardiomyopathy: an update

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Dr. Neil Harpster first described myocardial disease in the Boxer dog in the early 1980s. It was characterized as a degenerative myocardial disease with unique right ventricular histologic findings that include myocyte atrophy and fatty infiltration [1,2]. Affected dogs could be asymptomatic or syncopal with ventricular arrhythmias, and they sometimes developed congestive heart failure. The disease seemed to have a greater prevalence in certain families of dogs. In the early 1990s, Dr. Bruce Keene described a family of Boxers with myocardial dysfunction, tachyarrhythmias and congestive heart failure, and decreased myocardial carnitine levels [3].

## **Arrhythmogenic right ventricular cardiomyopathy**

Careful evaluation of the disease by these investigators as well as others has demonstrated that boxer dog cardiomyopathy has striking similarities to a human myocardial disease called arrhythmogenic right ventricular cardiomyopathy (ARVC) [4,5]. ARVC is an inherited disorder that is characterized by fatty or fibrofatty replacement of right and, sometimes, left ventricular myocardium. Ventricular tachycardia, which often exhibits an upright or left bundle branch configuration, is a common clinical manifestation. Affected individuals are at risk for sudden cardiac death. Similarities in clinical presentation, pathologic findings, and presumed etiologic basis have supported interest in reclassification of the disease as boxer arrhythmogenic right ventricular cardiomyopathy.

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This work was generously supported by the American Kennel Club–Canine Health Foundation and the American Boxer Trust.

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## Cause

ARVC in the Boxer dog is a familial disease apparently inherited as an autosomal dominant trait [5]. The presentation of the disease in affected offspring is quite variable, however, suggesting that incomplete penetrance of the disease may be involved. Affected dogs may experience lethal ventricular arrhythmias and sudden cardiac death, may develop systolic dysfunction and congestive heart failure, or may live an asymptomatic life with frequent ventricular ectopy.

## Clinical presentation

Boxer ARVC is an adult-onset myocardial disease and, as originally proposed by Harpster, there seems to be three forms of the disease, now referred to as concealed, overt, and myocardial dysfunction [1]. The concealed form is characterized by an asymptomatic dog with occasional ventricular premature complexes (VPCs). The overt form is characterized by a dog with tachyarrhythmias and syncope or exercise intolerance. The third group, diagnosed least frequently, is characterized by a dog that has developed myocardial systolic dysfunction, sometimes with evidence of congestive heart failure. Although it is likely that these three forms represent a continuum of the disease (particularly the concealed and overt forms), this has not been well documented.

## Diagnosis

The diagnosis of canine ARVC can be challenging. Unfortunately, a single diagnostic test for ARVC does not exist. The diagnosis is best based on the presence of a combination of factors, including a family history of disease, the presence of a ventricular tachyarrhythmia, a history of syncope or exercise intolerance, and the postmortem finding of fibrofatty infiltration into the myocardium.

### *Physical examination*

Many affected dogs have a normal physical examination. In some cases, an occasional ventricular premature beat may be detected. Heart murmurs are infrequently heard, although the presence of a left apical systolic murmur may suggest the myocardial dysfunction form of the disease. Caution when evaluating heart murmurs in the Boxer is suggested, however, because many adult Boxers have a left basilar systolic heart murmur that may be physiologic or, in some cases, may be associated with subvalvular or valvular aortic stenosis [6,7]. These murmurs should not be confused with the left apical systolic murmur associated with the myocardial dysfunction form of ARVC.

### *Electrocardiography*

Affected dogs should have increased ventricular ectopy, but it may be intermittent. The presence of an upright VPC on a lead II (left bundle branch block morphology) electrocardiogram is suggestive of the disease (Fig. 1). Some affected dogs have a different morphology to their VPCs or may not have any VPCs detected on an electrocardiogram, however. A normal electrocardiogram does not exclude a diagnosis of ARVC because of the intermittent nature of the arrhythmia. If suspicion exists because of auscultation of an arrhythmia, suggestive clinical signs (eg, syncope, exercise intolerance), or a family history of disease, a 24-hour Holter monitoring study is strongly suggested.

### *Holter monitoring*

Holter monitoring is an important part of the diagnosis, screening, and management of canine ARVC. Even if the diagnosis is suspected based on the identification of occasional VPCs on an in-house electrocardiogram, a Holter study can provide the best assessment of overall frequency and complexity of the arrhythmia and serve as an important guide for monitoring treatment. It is uncommon for normal healthy adult dogs to have any VPCs. In one study, healthy adult large-breed dogs had a median of 2 VPCs in 24 hours [8]. An evaluation of more than 300 asymptomatic



Fig. 1. Upright ventricular premature complexes (left bundle branch block morphology) observed in electrocardiogram leads I, II, and III.

adult Boxers in a study performed in our practice found that 75% of the population had less than 75 VPCs in 24 hours. Therefore, the identification of frequent ventricular ectopy (> 100 VPCs over 24 hours) in an adult Boxer is strongly suggestive of a diagnosis of ARVC, particularly if there is significant complexity (couplets, triplets, bigeminy, or ventricular tachycardia) to the arrhythmia.

Alternatively, a strong suspicion of ARVC sometimes exists but the Holter monitor reading is not clearly abnormal. This may be because of the significant day-to-day variability of VPC number in affected dogs. Considerable day-to-day variability in VPC number exists, and affected untreated Boxers have been shown to have up to an 83% change in VPC number from one day to the next [9]. Therefore, if a strong suspicion of ARVC exists but the Holter reading was not diagnostic, a second Holter monitoring study should be performed. If the dog is syncopal, an event monitor may be considered. Additional testing may identify other possible causes of syncope.

### *Echocardiography*

Although ARVC is a myocardial disease, most of the myocardial changes are abnormalities noted at histologic examination as opposed to abnormalities obvious on gross examination of the ventricle. Therefore, most affected dogs have normal echocardiograms, particularly with regard to evaluation of the size and function of the left ventricle. In some cases, careful echocardiographic evaluation of the right ventricle may detect right ventricular enlargement and, possibly, right ventricular dysfunction. Thorough evaluation of the right ventricle by echocardiography is difficult, however, because of the complex anatomy of the right ventricle, and subtle changes may be frequently overlooked. A small percentage of adult Boxers with tachyarrhythmias are observed to have left ventricular dilation with systolic dysfunction [10]. Because these cases are observed infrequently, it should be remembered that most affected dogs do not have echocardiographically apparent abnormalities.

### *Pathology*

Postmortem findings can be helpful in the evaluation of sudden cardiac death in the Boxer. Many affected dogs have a grossly normal appearance to their heart at the time of death; however, some cases may show evidence of right ventricular enlargement and, in some cases, left ventricular enlargement. Careful histologic evaluation should identify fatty, and sometimes fibrofatty, segmental or diffuse replacement of the right ventricular free wall from the epicardium toward the endocardium (Fig. 2). Occasionally, the interventricular septum and left ventricular free wall are also involved [1,4].

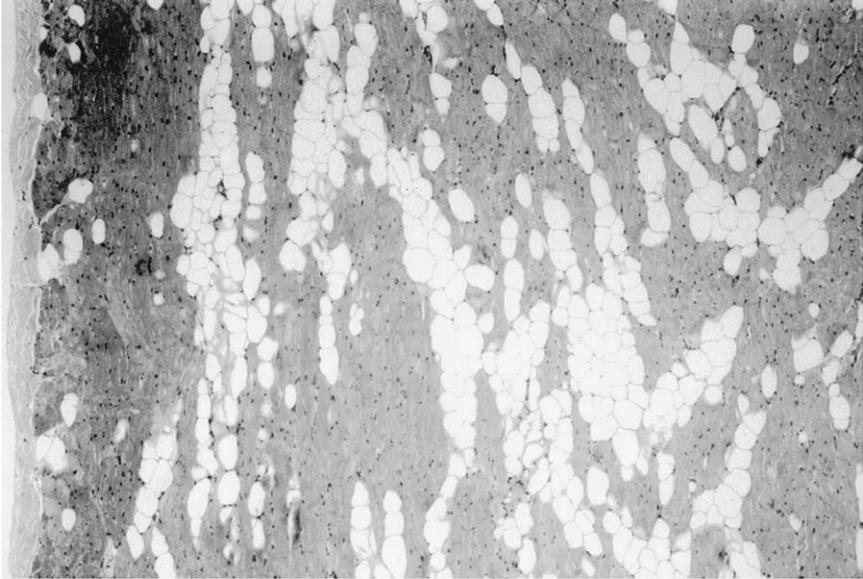


Fig. 2. Right ventricular myocardial sample from a Boxer with arrhythmogenic right ventricular cardiomyopathy. Note the fibrofatty myocardial infiltration observed histologically. The epicardium is located on the left aspect of the image.

## Screening

The familial nature of ARVC has led to increased interest by Boxer breeders in the screening of breeding dogs for the disease. Unfortunately, because of the absence of a perfect diagnostic test for ARVC, screening the asymptomatic dog is challenging, and substantial efforts are being directed toward the development of a genetic test. Careful consideration of multiple criteria should be used to help determine the likelihood that an individual asymptomatic dog is affected. Important factors might include a familial history of ARVC in association with repeatable abnormal Holter monitor readings. Holter monitoring results should be evaluated for the number of VPCs as well as the complexity of arrhythmia (eg, single, couplets, triplets, ventricular tachycardia). As mentioned previously, the identification of frequent ventricular ectopy ( $>100$  VPCs over 24 hours) in an adult Boxer is strongly suggestive of a diagnosis of ARVC, particularly if there is significant complexity (couplets, triplets, bigeminy, or ventricular tachycardia) to the arrhythmia. Long-term studies that evaluate the predictive value of these findings for identifying dogs at risk of dying from ARVC have not been completed, however. Some affected dogs have an abnormal degree of ectopy but never develop clinical signs, whereas some affected dogs with the same degree of ectopy gradually progress and develop more severe arrhythmias as they mature. Finally, some Boxers have thousands of VPCs

over 24 hours and a high grade of complexity and remain asymptomatic [11]. The factors that determine which dogs eventually progress to the clinical form of the disease are not known and increase the frustration of screening for this disease. Although breeders are concerned about passing on this trait, they should be advised about the significant complexities of performing screening and counseled not to remove dogs completely from a breeding program because of a single abnormal Holter reading. Annual Holter monitoring is strongly recommended, and significant emphasis on a single Holter monitor reading is strongly discouraged. ARVC is an adult-onset disease, and the degree of ventricular ectopy seems to increase with age; thus, a single Holter monitoring study performed in a young adult dog may not detect an affected dog that is not yet demonstrating the trait. Additionally, in some cases, systemic disease or other forms of cardiac disease may lead to the development of VPCs on a Holter monitoring study that may not be apparent on subsequent ones. Inadvertently removing a significant number of unaffected dogs from breeding programs may have a detrimental effect on the overall gene pool of a purebred dog.

A possible system for screening asymptomatic dogs might include the following Holter monitoring criteria:

1. None to 20 single VPCs over 24 hours: interpreted as within normal limits
2. Twenty to 100 VPCs over 24 hours: interpreted as indeterminate, suggest repeating in 6 to 12 months
3. One hundred to 300 single VPCs over 24 hours: interpreted as suspicious, consider keeping out of the breeding program for 1 year and repeating the Holter study
4. One hundred to 300 VPCs over 24 hours with increased complexity (frequent couplets, triplets, and ventricular tachycardia) or 300 to 1000 single VPCs over 24 hours: interpreted as likely affected
5. More than 1000 VPCs over 24 hours: interpreted as affected, may consider treatment as discussed below

The criteria listed are based on the appearance of the particular prevalence of the arrhythmias in the asymptomatic population as opposed to long-term outcome studies of dogs with the arrhythmias. They are given as one possible screening method. It is strongly advised to consider all issues for each dog, including family history, evidence of ongoing systemic disease, and repeated Holter studies, before making strict recommendations.

## **Treatment**

Treatment considerations for affected dogs are generally directed toward the use of ventricular antiarrhythmics, because most affected dogs do not have systolic dysfunction and do not seem to progress to heart failure. When

prescribing antiarrhythmics for the affected dog, several considerations should be taken into account. There are known benefits to the use of certain antiarrhythmics in affected dogs, including the ability to decrease the number of VPCs and the complexity of the arrhythmia. Additionally, syncopal episodes have been shown to decrease with antiarrhythmic therapy [12]. There is no evidence that the use of antiarrhythmics alters the risk of sudden cardiac death in affected dogs, however. Additionally, there is a risk of a proarrhythmic effect associated with the use of many antiarrhythmics, and the arrhythmia could potentially be exacerbated. Finally, antiarrhythmic therapy adds increased expense to the management of the case as well as increased labor for the owner.

Therefore, the risks and benefits of treatment should be carefully considered and discussed with owners before starting therapy. Ideally, therapy should be managed by assessing a pretreatment and posttreatment (2–3 weeks later) Holter monitoring study. Comparing the pretreatment and posttreatment readings should help to detect a proarrhythmic effect as well as help to evaluate the efficacy of treatment. Considerable day-to-day variability in VPC number exists, and affected untreated Boxers have been shown to have up to an 83% change in VPC number from one day to the next [9]. Therefore, a positive treatment response is best attributed to treatment when at least an 80% reduction in VPC number as well as a reduction in the complexity of the arrhythmia on the posttreatment Holter reading is observed. Additionally, an increase in symptoms after starting treatment or a significant increase in the number of VPCs may suggest a proarrhythmic effect. The significant day-to-day variability in VPC number even in untreated affected Boxers underscores the inability to make an accurate assessment of treatment on a brief in-house electrocardiogram.

### *Asymptomatic Boxers*

The best indication to start therapy in an asymptomatic affected Boxer is not well understood, and the risks and benefits of therapy should be carefully evaluated. Certainly, some dogs die from their arrhythmia before ever developing clinical signs; thus, the absence of clinical signs does not mean that there is no risk of sudden death. If an arrhythmia is detected on routine examination in an asymptomatic dog, a Holter monitoring study should be performed to evaluate for the frequency and complexity of the arrhythmia. Although a strict relation between the development of symptoms and the number of VPCs does not exist, the development of syncope is associated with higher numbers of VPCs and a greater degree of complexity [11]. Sustained ventricular tachycardia (ie, ventricular tachycardia run that lasts longer than 30 seconds) might be a risk factor for sudden death in people with ARVC [12]. A VPC that occurs early in diastole, the R on T phenomenon, is believed to be dangerous, because the nadir of the ventricular fibrillation threshold occurs at about the time that

the T wave is inscribed on the electrocardiogram. Based on this, treatment may be reasonable if there are at least 1000 VPCs over 24 hours or if runs of ventricular tachycardia or evidence of the R on T phenomenon exists. Nevertheless, it should be recognized that risk factors for sudden death in Boxer dogs with ARVC have been incompletely described; furthermore, studies that evaluate the impact of antiarrhythmic therapy on long-term survival have not been done.

#### *Boxers with syncope/exercise intolerance*

Boxers with syncope and ventricular arrhythmias are generally started on treatment, ideally after a 24-hour Holter monitoring study. In some cases, if the syncope is frequent or ventricular tachycardia is observed, a Holter study may not be performed so as to start therapy as soon as possible. In some cases, however, the absence of a pretreatment study may make it difficult to assess the response to therapy fully. Therefore, when possible, a Holter monitoring study is performed and the owner is advised to start therapy immediately after removing the Holter monitor (before the results are available) if great concern exists.

#### *Treatment options*

A reduction in VPC number and complexity of the arrhythmia in affected Boxers with frequent ectopy has been demonstrated with two treatment protocols [13]. The first is sotalol (1.5–2.0 mg/kg administered orally every 12 hours), and the second is a combination of mexiletine (5–8 mg/kg administered orally every 8 hours) and atenolol (12.5 mg per dog administered orally every 12 hours). In some cases, a loss of appetite or mild gastrointestinal upset may be observed with mexiletine; however, theoretically, the addition of atenolol allows the low end of the mexiletine dose to be used to help reduce this side effect. Additionally, when mexiletine is given with food, side effects may be less frequently observed. It is likely that variations in drug response exist in individual dogs. Therefore, if a poor response is observed with one drug, a different one may prove to be more effective.

#### *Boxers with left ventricular dilation and systolic dysfunction*

A small percentage of Boxers with tachyarrhythmias present with systolic dysfunction and, in many cases, left or biventricular heart failure [10]. If echocardiography demonstrates systolic dysfunction and ventricular dilation, treatment for canine dilated cardiomyopathy is warranted. Additionally, supplementation with L-carnitine might be considered at a rate of 50 mg/kg administered orally every 8 to 12 hours, because a small number of affected dogs have demonstrated improvement in systolic function and prognosis after supplementation [3,14].

## Prognosis

Dogs with ARVC are always at risk of sudden death. Many affected dogs live for years even without treatment, however. Many dogs may be managed, symptom free, for years on antiarrhythmics. A small percentage of these dogs may eventually develop ventricular dilation and systolic dysfunction.

## L-carnitine cardiomyopathy in Boxers

A deficiency in myocardial L-carnitine levels was observed in a family of Boxers with left ventricular dilation and systolic dysfunction. The tachyarrhythmias included atrial fibrillation and VPCs. The dogs had normal to high levels of plasma L-carnitine but low levels of myocardial carnitine. Supplementation with L-carnitine as well as standard heart failure therapy resulted in significant improvement in myocardial function and clinical condition but did not result in total regression of the disease [3]. In general, myocardial carnitine deficiency does not seem to be a common cause of myocardial disease in the Boxer and is not likely to be directly associated with boxer ARVC. Because it is difficult to assess myocardial carnitine levels accurately without an endomyocardial biopsy and because plasma levels are not an accurate assessment of myocardial levels, the true role of carnitine in the boxer with systolic dysfunction and dilation is not known. Supplementation of these cases with L-carnitine, 50 mg/kg every 8 hours, may be considered [14].

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