Arrhythmogenic Right Ventricular (Boxer Dog) Cardiomyopathy
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Jonathan A. Abbott, DVM, Dipl. ACVIM (Cardiology)
University of Tennessee,
Knoxville, TN

Although congestive heart failure is occasionally observed, heart muscle disease in North American boxer dogs is principally characterized by ventricular tachyarrhythmia (VTA). Often, arrhythmias are incidentally detected during routine examination but the disorder may become clinically apparent when syncope or sudden unexpected death is a consequence of ventricular tachycardia. The cause, clinical presentation as well as the diagnostic and therapeutic approaches to this common disorder will be reviewed during this session.

ETIOPATHOGENESIS
Cardiomyopathy has been defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of other cardiovascular diseases sufficient to cause the observed myocardial abnormality. Boxer dog cardiomyopathy is a breed-associated myocardial disease that is typically characterized by electrical dysfunction. It is generally accepted that the syndrome of inherited VTA observed in Boxer dogs is a form of arrhythmogenic right ventricular cardiomyopathy (ARVC).

ARVC is histologically characterized by fatty or fibrofatty replacement of right and sometimes left ventricular myocardium. The genetic basis of this disease in affected human beings has been extensively investigated. Numerous causative mutations have been identified although most affect genes that encode desmosomal proteins. VTA in boxer dogs is familial; the results of pedigree analysis are compatible with an autosomal dominant mode of inheritance. Meurs et al. recently identified a mutation of the striatin gene that is strongly associated with the ARVC phenotype in boxer dogs. The pathogenesis of ARVC is believed to involve disruption of cell-cell connections that result in cell death and impaired electrical coupling. The right ventricle is predominantly affected but left ventricular involvement is also observed. The phenotypic expression of ARVC mutations is diverse, which may be explained by genotypic heterogeneity, variable expressivity and perhaps environmental influences. Although the disease has a genetic basis, clinical signs associated with ARVC generally have an adult onset.

CLINICAL PRESENTATION
In the 1980's Harpster classified the clinical presentation of Boxer dog cardiomyopathy:

- **Category I** - ventricular arrhythmias occur in the absence of clinical signs; these patients are identified when presented for routine veterinary care or for evaluation of non-cardiac illness
- **Category II** - syncope/collapse is observed
- **Category III** – congestive heart failure resulting from systolic myocardial dysfunction

In some Boxer dogs, there is progression from Class I to Classes II or III but this is not inevitable. Many Boxer dogs with ARVC are presented with VTA in the absence of myocardial dysfunction; that is, the echocardiogram is normal or is subtly abnormal. Dilated cardiomyopathy is observed in boxer dogs but in many geographical regions appears to be

less common than ARVC. However, recently published data demonstrate a strong association between the striatin mutation and echocardiographically evident myocardial dysfunction, suggesting that dilated cardiomyopathy and VTA in boxer dogs may be different phenotypic expressions of the same desmosomal defect.

History/Physical Findings

ARVC is often incidentally identified when cardiac arrhythmias are detected during routine veterinary examination. If the disease becomes clinically evident, episodes of weakness or syncope are the signs most often reported by pet-owners although tachypnea or abdominal distention due to ascites may also be observed. Premature beats and paroxysmal tachycardia are evident on physical examination. Murmurs are occasionally heard but most affected patients have minimally altered cardiac structure. Accordingly, murmurs – directly resulting from ARVC – are uncommon. Many outwardly healthy boxer dogs have soft basilar systolic murmurs that reflect either a narrow aortic root – a breed-associated trait – or mild forms of aortic stenosis. However, these murmurs do not have a known relationship to ARVC.

Electrocardiographic Findings

The electrocardiographic hallmark of boxer dog ARVC is the occurrence of VTA characterized by premature ventricular complexes (VPC) and in many cases, ventricular couplets and ventricular tachycardia. Most, but not all, ventricular ectopic complexes in affected boxer dogs have a left-bundle block configuration; that is, the QRS is wide and upright with a negative T-wave in lead II. Some affected boxers have relatively few VPC that occur singly and infrequently while others have numerous VPC and sustained paroxysms of ventricular tachycardia (VT).

Ambulatory Electrocardiography

In the management of canine ARVC, 24 hour ambulatory electrocardiographic (Holter) monitoring can provide data that: support, or refine a provisional diagnosis, clarify the cause of syncope and guide antiarrhythmic therapy. The use of ambulatory electrocardiographic event recorders also has a role in the assessment of patients with known or suspected ARVC. These devices are digital loop recorders that can be affixed, by adhesive electrode patches, to patients for days or even weeks. A button on the device interrupts the digital loop and can be pressed if a pet-owner observes an episode of weakness or syncope. The preserved electrocardiographic data sheds light on the cause of intermittent clinical signs by providing a clear association between cardiac rhythm and patient behavior. Implantable loop recorders intended for placement within a surgically created subcutaneous pocket are also available and can usefully document electrocardiographic events that are associated with infrequent clinical episodes.

Echocardiographic Findings

In most affected individuals, the echocardiogram is normal or nearly so. Right atrial and right ventricular dilation can be observed but these findings are neither consistent nor essential for the diagnosis. Systolic myocardial dysfunction, with or without left ventricular dilation, is sometimes observed but it is not known if this is the result of histologic left ventricular involvement, the consequence of persistent tachycardia – tachycardia-induced cardiomyopathy – or reflects a distinct disease process.

DIAGNOSTIC APPROACH

The diagnostic and therapeutic approach to the patient suspected to have ARVC is determined by the clinical presentation. When a patient is urgently presented after a recent syncopal episode and a persistent, rapid ventricular tachycardia is evident, a limited diagnostic approach – perhaps electrocardiography alone – might determine the initial therapeutic strategy. More extensive diagnostic evaluation is generally appropriate for patients that are clinically stable when presented. This diagnostic evaluation may include: thoracic radiography, echocardiography, ambulatory electrocardiography, abdominal sonography and assessment of laboratory data.

When encountered in a mature boxer dog, the occurrence of ventricular ectopy of typical QRS configuration suggests the diagnosis of ARVC. However, other cardiac disorders and indeed, non-cardiac disease, can also predispose to VTA. It is important to recognize that there is a subpopulation of boxer dogs with and without ARVC that experience syncopal episodes that are associated with transient, presumably reflex-mediated, bradycardia. Often these events are precipitated by exertion. When syncopal episodes are relatively infrequent, it is not always possible or practical to define the electrocardiographic rhythm during events. It is probably reasonable to assume that ventricular tachycardia is the cause of syncope when frequent, complex VTA characterized by paroxysms of VT are electrocardiographically documented. However, syncope associated with bradycardia may become more frequent if agents such as sotalol are administered. Therefore, caution is appropriate when making suppositions regarding the cause of fainting when resting electrocardiography fails to reveal dramatic arrhythmias.

THERAPY

Arrhythmias are clinically important because they can cause clinical signs - such as syncope - and because they can cause sudden unexpected cardiac death (SCD). SCD is commonly caused by rapid VT that degenerates to ventricular fibrillation (VF) - VF is a pulseless rhythm that is lethal unless promptly terminated.
There are essentially three reasons to treat arrhythmias:
1) clinical signs are associated with the arrhythmia
2) there is reason to believe that the patient is at risk of sudden death and that treatment will prevent this
3) the burden of arrhythmia places the patient at risk for the development of tachycardia induced cardiomyopathy

The subject of antiarrhythmic therapy is complex because risk factors for poor outcome are largely unknown and while accepting that “absence of evidence is not evidence of absence”, there are no data indicate that the commonly chosen antiarrhythmic agents can prevent sudden death. It is therefore important to consider the relative risk: benefit of antiarrhythmic therapy prior to the administration of antiarrhythmic agents. It is reasonable to treat arrhythmias when they are associated with clinical signs or when the arrhythmia is sufficiently severe that the development of clinical signs can be anticipated. The treatment of subclinical (“asymptomatic”) arrhythmias must be considered more carefully.

Emergent therapy of VTA associated with ARVC generally consists of parenteral therapy with agents such as lidocaine or procainamide. The pathology underlying ARVC is irreversible. Therefore, palliative therapy for canine ARVC consists of the chronic administration of oral antiarrhythmic agents. In canine ARVC, sotalol – a potassium channel antagonist with beta-blocking properties - is the most efficacious single agent in terms of arrhythmia suppression. Whether or not this efficacy translates to a reduction in sudden death, is not known. Data from ambulatory electrocardiographic monitoring is often use to evaluate the effectiveness of therapy, though the value of this approach has not been demonstrated and it is relevant that the frequency of ventricular arrhythmia in affected boxers might vary by as much as 75% independent of therapy. Monitoring of clinical signs is a practical method by which effectiveness of therapy can be judged. In clinically stable patients, careful consideration of the relationship between arrhythmia and clinical signs should guide therapy as recently published data suggest that ventricular tachycardia is not the most important cause of collapse in boxer dogs.

It is not possible to make definitive statements with regard to prognosis. Occurrence of syncope and more frequent or complex VTA are associated with poor outcome. However, studies of the natural history of boxer ARVC provide evidence that survival of affected dogs does not differ from that of unaffected boxer dogs.

Selected References - complete references available on request.

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