Review

Inherited arrhythmias in the dog: potential experimental models of cardiac disease

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Abstract

Centuries of inbreeding the domestic dog has resulted in numerous spontaneous breed-specific and familial diseases of all body systems [1]. Although few animal models of spontaneous arrhythmic death exists [2] veterinary cardiologists have recognized potentially inherited arrhythmias in the dog for years. The purpose of this paper is to describe the proven inherited, and the likely inherited, arrhythmias diagnosed commonly in the dog with the intent to provide information of potential models for investigation of primary arrhythmias. Additionally, examples of common arrhythmias that are secondary to inherited cardiac disease in the dog will be provided. © 1999 Elsevier Science B.V. All rights reserved.


Initial studies of the inheritance of this disease in the German shepherd have revealed that a sex-linked or autosomal dominant trait is unlikely [3].

1.1. Circumstances of arrhythmic death

Death of affected German shepherd dogs usually occurs during sleep in the early morning hours (0400 h–0700 h) or during rest shortly after exercise [4]. A window of vulnerability to death exists between 15 and 76 weeks of age (mean±SE, 37 6.3, median 28) [3,8]. Before death, clinical signs are absent, laboratory data is normal, and echocardiographic parameters do not support obvious structural or functional anomalies [3]. Postmortem examinations have failed to identify, thus far, a cause of death [3].

1.2. The lethal arrhythmia

Death is caused by the degeneration of ventricular tachycardia (VT) into ventricular fibrillation (Fig. 1). The phenotypic spectrum of the ventricular arrhythmias is wide [3,8]. Rhythms of affected dogs range from infrequent premature ventricular complexes (PVCs) to numerous PVCs, pairs, triplets, and frequent runs of VT. The VT is most frequently (85%) rapid (rate >300 beats/min), polymorphic and nonsustained, although occasionally the VT (15%) is slower (rate 200 beats/min), monomorphic and sustained. Death is associated with the former [3]. The rapid polymorphic VT is bradycardia dependent (VT preceded by a longer RR interval) [7,13]. Circumstances that have more sinus pauses (sleep) or perturbations that cause a slowing of heart rate (vagal stimulation) induce this type of VT [4,6]. The slower monomorphic VT is tachycardia dependent (decreasing RR interval before VT) [15]. The amount of the ventricular arrhythmias is age dependent [8]. Before 12 weeks of age PVCs are rare, but gradually increase with a peak frequency of VA, including VT, between the ages of 24 to 28 weeks of age [8]. After

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28 weeks the number of ventricular arrhythmias decreases such that many dogs after 100 weeks of age no longer have arrhythmias. The most severely affected dogs do continue to have occasional ventricular arrhythmias [7,8].

1.3. Mechanism(s) of the arrhythmia

Based on in vitro studies initiation of the bradycardia dependent VT is hypothesized to be triggered activity; specifically EADs [13]. Delayed afterdepolarizations are believed, but not proven to be the cause of the tachycardia dependent VT [15]. Spontaneous EADs and prolongation of the action potential duration have been identified in Purkinje fibers. Prolongation of the action potential of the M-cells and induction of DADs have been documented after isoproterenol in tissues that lacked normal innervation (see below). Also, an increase in Purkinje fiber automaticity occurs after isoproterenol. The mechanism for sustaining either of the VT rhythms is unknown, but may be caused either by continued triggered activity (continued propagation of EADs has been documented in the tissue bath) or reentry (the rapid VT setting up the substrate by causing dispersion of refractoriness). During studies to reflexly slow the heart rate in the intact animal with phenylephrine, it was noted that the VT was exacerbated with this \( \alpha_1 \)-adrenergic stimulation even in dogs with
ablation induced complete heart block [6]. Thus, a direct \( \alpha_1 \)-adrenergic effect was hypothesized and confirmed by the potentiation of the EADs in the Purkinje fibers [13]. It is known that \( \alpha_1 \)-adrenergic stimulation inhibits the calcium-independent component of the transient outward current \( (I_{to}) \). Whole-cell patch clamp studies of isolated myocytes revealed that this current was markedly reduced and inactivation altered in a proportion of epicardial cells from affected dogs [10]. The capacitance of the myocytes was reduced, indicating that the cells were smaller than those from unaffected dogs [12].

1.4. Autonomic influence

The clinical ventricular arrhythmia in these dogs is influenced by perturbations in the autonomic nervous system [3,4,6]. The circumstances of death during sleep suggest this effect and the identification of the greatest frequency of VT during rapid eye movement sleep (REM) further supports this conclusion [4]. During sleep elevated parasympathetic tone is peppered with bursts of sympathetic tone, and such a combination could be the trigger for the ventricular arrhythmias in these dogs. This sensitivity to some autonomic perturbation suggested a possible cardiac innervation abnormality. Scintigraphy, using \( ^{123} \)I-metaiodobenzylguanidine, revealed abnormal distribution of sympathetic innervation in affected dogs [14]. The lack of innervation was further demonstrated by immunocytochemical localization of tryosine hydroxylase showing a paucity of nerve fibers that corresponded to the same regions identified by the scintigraphy [14]. There was a tendency for the denervation to localize to the apical, anterior, septal, and lateral regions of the left venticle, as opposed to the posterior and basal regions. Sympathetic innervation of the developing dog heart can be demonstrated immunohistochemically from midgestation, increasing until about 2 months of age, when the adult pattern of neural tissue is present [16]. Sympathetic innervation in the newborn dog is asymmetric [17]. Whether the regional absence of sympathetic nerves in these animals results from the failure of nerve in-growth to specific regions of the heart (noninnervation) or to subsequent degeneration of previously intact nerves (denervation) has not been determined [14].

1.5. Lack of innervation and arrhythmias

Purkinje fibers harvested from regions that lacked innervation have demonstrated a greater tendency for triggered activity than regions with normal innervation [13,15], especially after \( \alpha_1 \)-adrenergic stimulation with phenylephrine [13]. The heterogeneity in innervation may also be cause for dispersion of refractoriness and the development of reentrant arrhythmias, although this has as yet been proven. Increased response to \( \beta \)-adrenergic stimulation with isoproterenol is reflected by an increase in ectopy in tissues from regions without sympathetic innervation [15]. In regions of reduced sympathetic innervation the \( \beta \)-adrenergic receptor number is greater than that in regions with normal innervation. Thus, an increased responsiveness to \( \alpha_1 \)-adrenergic and \( \beta \)-adrenergic stimulation has been documented in these dogs.

1.6. A developmental arrest?

Several observations (e.g. reduced cell capacitance, reduced \( I_{to} \) current density, regional paucity of sympathetic nerve fibers) suggest an error in the normal development of the heart in the arrhythmic German shepherd. The reduced cell capacitance indicates a small myocyte characteristic of the neonate [12]. Normal sympathetic innervation is known to affect the development of cardiac ion channels [18]. \( I_{to} \) expression is developmentally regulated such that the current density is significantly lower in fetal and neonatal myocytes than in adult myocytes [11]. The lack of innervation in these dogs may have an impact on the normal development of \( I_{to} \). It is unknown whether the regional paucity of sympathetic nerve fibers is the cause of ion channel defect(s) or simply a concurrent anomaly.

1.7. Abnormal T wave reflects repolarization defect

Basic investigations have shown that abnormal ventricular repolarization (VR) occurs in the arrhythmic German shepherd as evidenced by the triggered activity and a reduced current \( I_{to} \) [12,13]. The defective repolarization is detectable by noninvasive means. Because these dogs do not have prolonged QT intervals [3], this test does not allow differentiation and prediction of affected dogs. Using a vector quantization (neural net) and first derivative analysis of the 24-hour ambulatory ECG recording from affected and control dogs different T wave morphologies were identified that allowed differentiation between dogs [9]. Affected dogs had significantly more frequent notching of the T wave compared to unaffected dogs.

1.8. A model for what disease?

Abnormalities in ventricular repolarization underpin the mechanisms of reentry and triggered activity that are responsible for many of the cardiac arrhythmias that lead to death [19–21]. Such fatal arrhythmias can occur because of structural derangements that affect ventricular repolarization or from purely electrophysiological defects. The latter are present in four inherited diseases of humans. These include the long QT syndrome (LQTS), Brugada syndrome, catecholaminergic idiopathic ventricular tachycardias, and the short-coupled torsades de pointes [22]. Additionally, evidence of abnormal ventricular repolarization was discovered in a subpopulation of infants who died of sudden infant death syndrome (SIDS) [23]. In each of these diseases, the autonomic nervous system is believed...
to play a role in the genesis of sudden death [22–24]. Moreover, abnormal sympathetic innervation has been identified in patients with Brugada syndrome which, like these dogs, does not display prolongation of the QT interval [25] and in some patients with the long QT syndrome [26]. Although each of these clinical disorders is unique, the common thread amongst them is an abnormality in ventricular repolarization and an influence by the autonomic nervous system. In spite of fact that the German shepherd model does not template with a specific disease, it too shares these collective features.

2. Boxer model of sudden death

Pedigree analysis of affected Boxers has revealed that their ventricular arrhythmias are inherited as an autosomal dominant trait [27].

2.1. Circumstances of arrhythmic death

Sudden death occurs in affected Boxers commonly in adulthood with a wide age range (2 and 8) years of age. Although the first clinical sign of disease may be sudden death, most Boxers have episodes of syncope. Both death and syncope are often associated with exercise and excitement [28,29]. At this point however, it is difficult to separate exercise from excitement because Boxers are usually emotionally excited when they exercise. Although some dogs have coexisting myocardial failure, most with VT have no clinical signs of congestive heart failure and normal echocardiographic examinations.

2.2. The lethal arrhythmia

Ventricular fibrillation is the fatal rhythm in the Boxer [28]. Before the final rhythm affected dogs have a rapid monomorphic VT. The rate is frequently greater than 200 beats/min, often approaching 300 beats/min. Approximately 90% of the Boxers have a VT that is positive in the inferior leads (II, III, aVF) and negative in aVR (Fig. 2). The left precordial leads (V2–V6) are positive. In lead I and V1 the polarity is not consistent. Although Boxers exhibiting syncope have VT, many affected dogs have only single PVCs without VT. Some animals have bradyarrhythmias in addition to the VT (Fig. 3). Although clinical trials evaluating the efficacy of treatment have not been completed, affected dogs appear to respond most effectively to sotalol or a combination of mexiletine plus atenolol.

2.3. Natural history

The clinical presentation of these dogs usually follows three scenarios [28]. Some Boxers have no clinical signs, but have ventricular arrhythmias detected during routine examination. Signs of left heart failure with eventual death due to myocardial failure afflicts other dogs. While others are presented with syncope or sudden death. Although the percentage is unknown, a proportion of dogs with syncope caused by the rapid VT develop myocardial failure, sometimes years after the initial signs of the arrhythmia.

Fig. 2. Electrocardiographic recordings from a Boxer with a right bundle branch block and ventricular tachycardia (VT). The 12 lead recording (separate recordings for limb leads and precordial leads) illustrates the most common (approximately 80% of affected Boxers) morphology of monomorphic VT. The most consistent morphologic characteristics are positive polarity in the inferior leads II, III, aVF and in precordial leads V2–V6. The polarity in leads I and V1 vary. This dog died suddenly (paper speed 50 mm/s, 5 mm=1 mV).
Fig. 3. Twenty-four hour ambulatory electrocardiographic recordings from a Boxer with syncope during excitement. A. Baseline artifact and the diary of activity recorded by the owner indicated excitement before the run of monomorphic ventricular tachycardia. B. However, throughout the recording period many long sinus pauses were documented that could have also caused syncope. Within each frame the two leads are continuous with each line representing 10 s.

is not known at what age affected Boxers develop the arrhythmias before clinical signs of syncope. Although thorough histopathologic correlations to the severity of the arrhythmia and the presence of coexisting myocardial failure have not been made, the ventricular myocardium is abnormal [28]. All portions of the atria and ventricles are usually involved to some degree, but the changes predominate in the right ventricular free wall. Histologic characteristics include variation in myofiber size, loss of myofibers, fibrosis and fatty infiltration.

2.4. A model for what disease?

The electrocardiographic and histologic features that characterize Boxers with sudden death are similar to arrhythmogenic right ventricular dysplasia [30–32]. Left ventricular involvement is a feature commonly recognized in the Boxer and in some humans [32]. Although there are similarities between the disease seen in the Boxer and arrhythmogenic right ventricular dysplasia, proof of similar disease is lacking.

3. Sick sinus syndrome in Miniature Schnauzers

Sick sinus syndrome of the Miniature Schnauzer has not been studied to determine the mode of inheritance; however, it only afflicts females and familial occurrence has been documented [33]. West Highland White terriers and Dachshunds are two other breeds in which sick sinus syndrome occurs.

Female middle-aged (e.g. 6–12 years) dogs are usually presented with syncope as the most common clinical sign. Prolonged sinus pauses are the cause of the syncope (Fig. 4). Collapse usually occurs after pauses of 8 s or longer because subsidiary pacemakers fail to escape in an adequate amount of time. Junctional escape complexes are frequently replaced by ventricular escape complexes. Some affected dogs do not have marked pauses, but instead have inappropriate sinus bradycardia for the physiological conditions. Others have sinus pauses followed by periods of supraventricular tachycardia. Commonly affected dogs have coexisting mitral valve incompetence due to prolapse of the leaflets and myxomatous degeneration with deposition of acid-staining glycosaminoglycans and fibrous tissue.
in the valve leaflets. Syncope is controlled with implantation of cardiac pacemaker, although over a period of years decompensation with congestive heart failure from the mitral valve disease develops.

3.1. A model for what disease?

Although this disorder is termed sick sinus syndrome, the inability of the junctional tissue to discharge before subsidiary pacemakers in the ventricle and the occurrence of supraventricular tachycardias in many affected dogs marks this as a disorder of more than just the sinus node. Consequently, it is similar to the disease in humans.

4. Atrial standstill in English Springer Spaniels

Although the inheritance of atrial standstill in the English Springer Spaniel is unknown, it has been recognized as a familial disease [34,35].

A bradycardia of junctional escape complexes and no identifiable P waves most commonly identifies atrial standstill in affected dogs (Fig. 5) [35]. The atria are dilated with thin walls of fibrous connective tissue. Affected animals are usually young adults (e.g. 1 to 3 years of age). Clinical signs include syncope, lethargy or congestive heart failure. Facioscapulohumeral atrophy has been identified in some of the dogs with atrial standstill. Although atrial standstill was not identified in one family of young
English Springer Spaniels with slowly progressive temporal muscle atrophy, dyserythropoietic anemia and megaesophagus, dilation of the right atrium and ventricle were documented [35]. It is unknown whether some variation of this constellation of abnormalities is present in the dogs with isolated atrial standstill. Affected dogs frequently die of congestive heart failure although their life is prolonged by pacemaker implantation.

4.1. A model for what disease?

In humans with inherited facioscapulohumeral muscular dystrophy and phenotypically similar Emery-Dreifuss dystrophy, permanent atrial paralysis, atrial arrhythmias and abnormalities of atrioventricular conduction exist [36,37]. The clinical features seen in the English Springer Spaniel with atrial standstill are similar to this human condition.

5. Duchenne’s cardiomyopathy in golden retriever

Golden retrievers are known to inherit muscular dystrophy as an X-linked trait [38,39]. Dystrophin is a protein that is believed to form a network on the cytoplasmic face of the plasma membrane, and may serve to stabilize the membrane. In muscular dystrophy this protein is lacking from skeletal and cardiac muscle cells. In addition to the severe skeletal muscle dysfunction, affected male dogs develop cardiac disease. Although the clinical signs of skeletal muscle disease are apparent only in the affected males, carrier females do have abnormal hearts [40,41]. In skeletal muscle of dogs that carry the Duchenne’s muscular dystrophy gene, dystrophin is initially expressed in a mosaic pattern. However, as carriers mature, this heterogeneity is lost. In contrast, mosaicism for dystrophin apparently persists in the heart for the life of the animal, with approximately 50% of cardiac myocytes lacking dystrophin [41].

Although carrier females can develop myocardial disease, affected males are afflicted to a much greater degree [40]. Echocardiography reveals distinctive hyperechoic lesions that correspond to calcified myocardium and surrounding dense connective tissue. Electrocardiographically deep Q waves (increased Q/R ratio) develop as the dogs age and reflect the changes in the myocardium (Fig. 6). The posterobasal location of myocardial involvement is believed to account for the distinctive pattern [42]. The PR

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**Fig. 6.** Electrocardiograms recorded from two Golden retriever dogs with Duchenne’s cardiomyopathy. Deep Q waves with delayed positive terminal forces are seen in lead II (A) (paper speed 50 mm/s, 10 mm=1 mV). In the other dog polymorphic ventricular tachycardia is identified in the excerpt of a continuous lead II recording (B). The top frame and lower frame of (B) were separated by 2 s. The fourth complex from the right of the top frame is a fusion complex confirming the ventricular origin of the rhythm (paper speed 25 mm/s, 5 mm=1 mV). Calibration marker equals 400 ms and 2 mV.
interval is shorter in affected dogs when compared to control dogs [40]. Polymorphic ventricular arrhythmias occur in approximately a third of the affected dogs (Fig. 6).

5.1. A model for what disease?

The phenotypic expression of the disease in the dog is more similar to that in humans than is the muscular dystrophy in the mouse [43]. The large size of the dog potentially allows more cardiovascular examination of the Duchenne’s cardiomyopathy.

6. Ebstein’s malformation and tricuspid valve dysplasia in Labrador Retrievers

The Labrador Retriever is significantly overrepresented in the population of dogs with Ebstein’s malformation and tricuspid valve dysplasia [44]. Multiple dogs in litters may be affected; however, the inheritance is unknown.

6.1. Electrocardiographic characteristics of the disorder

The ECG reveals a characteristic splintering (R′r′, RR′, rR′ or rr′) of the QRS complexes in approximately half of the affected dogs (Fig. 7) [44]. In the very young dogs the splintering may not be apparent until early adulthood. Enlarged P waves and supraventricular tachyarrhythmias are common (Fig. 7). Some of these tachycardias may be caused by atrioventricular by-pass tracts and this breed is the most commonly represented dog with preexcitation [45,46].

6.2. A model for what disease?

Although the atrioventricular tachycardias are not thought of as common aspect of the structural defect in the Labrador Retriever, it may be a lack of recognition. The familial appearance strongly suggest an inherited congenital defect.

7. Atrial fibrillation and ventricular arrhythmias secondary to dilated cardiomyopathy in the Doberman Pinscher, Great Dane, Irish Wolfhound, and Newfoundland

Dilated cardiomyopathy (DCM) is the second most common cardiac disease of the dog (most common is atrioventricular valve regurgitation secondary to degeneration (myxomatous thickening with deposition of acid-staining glycosaminoglycans and fibrous tissue) of the valve leaflets and chordae tendineae) [47–52]. In the United States and Canada the Doberman pinscher is the most frequently afflicted dog with a breed incidence in some surveys a staggering 50% [48]. This high incidence may be because most of the Doberman pinschers in the United States can be traced to one of seven closely related dogs, three of which died suddenly [53]. Familial occurrence of DCM in the Doberman pinscher is common. Moreover Dobermans have the worst prognosis, with survival after the development of clinical signs of only 2 to 4 months. In a study from Sweden the most commonly affected breed was the Newfoundland and Cocker spaniel [50]. Other breeds have been diagnosed with inherited DCM including the English Cocker spaniel and the Portuguese water spaniel [54–56]. Although the arrhythmias in dogs are secondary to the myocardial failure, the fact that this disease is so common in dogs offers the opportunity for the study of DCM and its sequella.

7.1. Electrocardiographic characteristics of the disorder

Atrial fibrillation is the most common arrhythmia associated with DCM in the dog (Fig. 8). Some dogs, in particular the Irish Wolfhound, can develop atrial fibrillation before evidence of cardiomegaly or myocardial failure. The atrial fibrillation associated with myocardial failure is most frequently present with atrial enlargement. Cardioversion of the atrial fibrillation is rarely effective in these dogs. Polymorphic ventricular arrhythmias are common in Doberman pinschers with DCM, although sudden death may be the result of a bradycardia.

Fig. 7. Lead II electrocardiogram recorded from a 9 month old Labrador Retriever with severe Ebstein’s malformation. Large P waves change in morphology and the QRS complexes are splintered with an r R′ pattern. A premature complex (second from the right) is of supraventricular origin (paper speed 50 mm/s, 10 mm=1 mV).
7.2. A model for what disease?

The etiology of DCM in each of these breeds probably differs, although the likelihood of an inheritable trait is high. Although the method of inheritance has not been determined, the extremely high incidence in the Doberman pinscher offers an opportunity to study DCM and the associate arrhythmias.

8. Summary

A number of inherited cardiac disorders in the dog mimic certain conditions identified in humans. Although detailed studies are lacking, the purpose of this report was to provide an introduction to the cardiac diseases of the dog that might be investigated with regards to the underlying mechanism of the arrhythmia, specific genetic defect(s), influence of the autonomic nervous system in arrhythmias, connection of myocardial failure and arrhythmias, and therapeutic interventions.

References

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