Review Article

Presumed Neurally-Mediated Bradycardia and Syncope in Boxers with Normal Echocardiograms and Absence of Ventricular Tachycardia

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ABSTRACT

Episodic weakness and syncope are common in Boxers. Reported causes include ventricular tachycardia (VT) and neurally-mediated bradycardia (NMB). The purpose of this study was to describe the features of presumed NMB in Boxers. A total of 27 Boxer dogs were identified. To be included in the study, each dog must have been overtly healthy with a history of syncope or presyncope; had a normal echocardiogram; had absence of ventricular tachycardia (VT) and fewer than 500 ventricular premature complexes on 24 hour Holter recordings; and been alive and clearly healthy for at least six months following the initial evaluation. Heart rhythm were documented at the time of an episode in only eight dogs (30%) and only once on the first Holter recording. Bradycardia was subsequently recorded in five times during 120 hour Holter recordings and during the 5th day of an event recording. Bradycardia was documented during auscultation in two additional dogs. The heart rate was not documented in 19 (70%) dogs in this study. Documentation of the heart rhythm during episodes of collapse was difficult and was carried out in only 30% of dogs and was unlikely to occur during the first Holter recording. In Boxers with suspected NMB, extended ambulatory monitoring, including implantable loop recorders, may be required for heart rate documentation.

Keywords: Neurocardiogenic Bradycardia; Arrhythmogenic Right Ventricular Cardiomyopathy; Holter Monitor; Implantable Loop Recorder.

INTRODUCTION

Episodic weakness and syncope are common problems encountered in Boxer dogs. Reported causes include rapid ventricular tachycardia (VT) and neurally-mediated bradycardia (NMB) (1-3). Rapid VT is often associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) with or without echocardiographic evidence of systolic dysfunction (dilated cardiomyopathy) (1, 2). Neurally-mediated bradycardia and syncope have also been reported in Boxers with comorbid VT (3). Whether neurally-mediated bradycardia is a marker for ARVC in this breed is uncertain.

Neurally-mediated episodic or reflex weakness/syncope comprises of a group of syndromes triggered by either sympathetic or parasympathetic surges (4-6). The term neurally-mediated emphasizes the role of the nervous system. Parasympathetic (vagal) triggers induce the situational syncopes. These include tussive, emesis, micturition and defecation syncope (4). Other neurally-mediated episodic weaknesses are triggered by sympathetic surges (4-6). The term neurocardiogenic bradycardia emphasizes the cardiac origin of the afferent arm of the reflex, but ignores the important vasodilation component of the efferent arm. It is

recommended that this term be used when there is a sympathetic trigger believed to arise in the heart (5). The term vasovagal syncope emphasizes both the vasodilatory and cardioinhibitory efferent arms. In humans, it is recommended that this term be reserved for reflex bradycardia and hypotension which is usually triggered by pain, instrumentation or prolonged standing. The term vasodepressor syncope refers to reflex syncope wherein vasodilation-hypotension develops in the absence of sinus bradycardia (5). The purpose of this retrospective report was to describe the features of NMB in Boxer dogs with normal echocardiograms and absence of ventricular tachycardia.

MATERIALS AND METHODS

Study dogs

The subjects of this report were overtly healthy, client owned Boxer dogs that had experienced at least one prior episode of syncope or presyncope and were then examined at the University of Georgia Veterinary Teaching Hospital (UGVTH).

All echocardiogram (Vingmed Ultrasound, GE Medical, Horten, Norway) and Holter recording (Lifecard CF, Spacelabs Healthcare, Snoqualmie, WA) results performed on Boxers from January 1996 to December 2008 were reviewed. The medical records of each of these patients were then assessed. Data from the medical record, echocardiogram and Holter recordings were extracted from each Boxer that was presented for a history of syncope or presyncope.

To be included in the study, each dog must have been overtly healthy with a history of syncope or presyncope; had a normal echocardiogram; had an absence of VT; had fewer than 500 ventricular premature contractions (VPC) on an initial 24 hour Holter recording and must have been alive and overtly healthy for at least 6 months following the initial evaluation.

RESULTS

A total of 27 Boxers were identified that fulfilled the study criteria. Sixteen were male and 11 were female. Twenty-four dogs (90%) were either less than 4 years old or ≥ 7 years old. Bradycardia was documented at the time of syncope or presyncope in 8 of the 27 (30%) dogs and the heart rate during syncope was not documented in 19 (70%) dogs. Only one Boxer experienced an episode during the first 24 hour Holter recording. All dogs were alive and overtly healthy for longer than 6 months following initial evaluation.

Initial 24 hour Holter recordings in 18 (67%) dogs contained no VPCs. Only one dog had more than 100 (222) VPCs. Eight dogs had less than 50 VPCs; most (six dogs) of these having less than 10 VPCs.

Most (16/27, 59%) Boxers had only one observed episode prior to evaluation. Each dog had one or more subsequent episodes following initial examination. Episodes in each dog occurred soon after a change from less to more activity. Episodes in 24 dogs were triggered by vigorous exertion or excitement. Episodes were triggered by climbing stairs or straining at the leash in 2 dogs. The only episode in one dog was triggered by startle.

The heart rate was documented in a minority of dogs. A presumptive diagnosis of neurally-mediated bradycardia in 19 dogs was based on being overtly healthy survival for longer than 6 months after initial evaluation, the absence of echocardiographic abnormalities, and the absence of VT or many VPC's during initial Holter recordings and extended ambulatory monitoring. Extended ambulatory monitoring was performed in 8 of 19 (42%) dogs wherein the episode related heart rate was never determined. Extended Holter recording periods were 48 hours (1), 120 hours (4) and 168 hours (1). Event monitoring of 5 days (1) and 7 days (1) were performed in two additional dogs.

Bradycardia was documented on the first Holter recording (24 hour recording) in only 1 of 27 (4%) dogs as only one dog experienced an episode during that period. Among the 27 dogs, bradycardia associated episodes were eventually documented in 8 dogs (30%). These episodes were documented by extended ambulatory monitoring (extended Holter and event recordings). Six owners were instructed to attempt to precipitate episodes. Bradycardia related episodes were subsequently recorded in 5 of these 6 dogs: during the 2nd (1 dog), 3rd (2 dogs) or 4th (1 dog) day of 120 hour Holter recordings and during the 5th day of an event recording in 1 dog.

Additional extended ambulatory recordings were not performed after the initial Holter recordings in 13 dogs. Subsequently, collapse and bradycardia were documented during auscultation in 2 of these 13 dogs. Collapse with profound bradycardia occurred in a referring veterinarian's dog during excitement prior to eating. A veterinary intern documented bradycardia by auscultation during the third known episode in her dog.

None of the extended ECG recordings contained rhythms consistent with sick sinus syndrome similar to that seen in Miniature Schnauzers and American Cocker Spaniels (7).

Medical treatment was not recommended for 7 of 8 dogs. Rather the owners were educated as to the cause or likely cause of episodes and encouraged to avoid the instigating activities. Treatment was prescribed for 1 of 8 dogs. This dog occasionally experienced episodes after being indoors all day and then released to run in a park. Hyoscyamine sulfate drops (Levsin drops, Schwarz Pharma Inc., Meguon, WI, USA) (0.125 mg/1 ml) at a dosage of 0.005 mg/kg was prescribed to be administered 15 minutes prior to activity. The episodes of collapse resolved. The remaining 7 dogs were followed for at least 6 months with 19 of 26 dogs (73%) having occasional episodes. Subsequently, most dogs were lost to follow-up.

DISCUSSION

Brief episodes of collapse or syncope in humans and dogs are usually due to transient disturbances of the heart rhythm (1-6, 8). Episodic weakness, collapse or syncope occur in some Boxers (3). Documentation of the heart rate/rhythm during episodes can be problematic. The detection of ventricular tachyarrhythmia as the likely cause of recent episodes in Boxers is much easier to document than when infrequent bradycardia is the cause. In our experience, when VT is the cause of recent syncope in Boxers with ARVC, either static ECG or 24 hour Holter recordings contain many VPCs and often VT.

Documentation of the heart rhythm during episodes among the dogs of this study was difficult, accomplished in only 30% and was unlikely to take place during the first Holter recording. Extended ambulatory recording or, in selected cases, auscultation was usually required for identification of infrequent disturbances of heart rhythm. Although not performed in this study, implantable loop recorders (Implantable Loop Recorder, Medtronic, Minneapolis, MN) may be required for documentation of NMB. Documentation of neurally-mediated syncope in humans is also problematic (4-6).

The diagnosis of neurally-mediated reflex bradycardia was presumptive in most of the dogs reported here. This presumption was based on episodic weakness, normal echocardiograms, absence of severe ventricular tachyarrhythmia, triggering activities that could be reasonably associated with sympathetic surge, infrequent episodes and healthy survival of each Boxer longer than 6 months.

Although the total number of cases reported here were small, there was a bimodal age distribution. Most dogs were either <1 to 4 years of age (14 dogs, 52%) or 7 years of age or older (10 dogs, 37%). There were only 3 dogs (11%) between 4 and 7 years of age. The significance, if any, of this age distribution is unknown.

The differential diagnosis of the fainting Boxer can be challenging. One cause of Boxer collapse is rapid VT associated with ARVC (1, 2). Arrhythmogenic right ventricular cardiomyopathy in this breed may be identified with systolic failure or, more often, prior to any evidence of systolic failure. In our experience, a less common cause of collapse or syncope in Boxers is NMB (3). Some Boxers are affected by both disorders (3). Collapse caused by rapid VT can occur at rest, during normal activity or during exertion or excitement (3). On the other hand, neurally-mediated episodes are overwhelmingly triggered by exertion with excitement or startle (3).

Spontaneous neurally-mediated bradycardias are induced by either a sympathetic trigger or a parasympathetic trigger (4-6). The former can be referred to as neurocardiogenic and the latter as situational (4-6). The initial trigger invokes an afferent limb of a reflex arc that is complex and not fully understood (5). Increased vagal traffic is carried by various afferent nerves to the cardiovascular control center in the brainstem. This invokes the Bezold-Jarisch reflex which is a sudden withdrawal of sympathetic tone accompanied by heightened or unopposed vagal efferent traffic (9). The contribution of bradycardia versus hypotension to syncope varies considerably.

The Bezold-Jarisch reflex is two-fold: increased vagal signals to the sino-atrial node (primary pacemaker) suppressing its discharge and sympathetic withdrawal leading to vasodilation and hypotension (9). Vagal stimulation of the atrio-ventricular node can cause AV block and impaired escape of this subsidiary pacemaker.

It is often difficult to document neurocardiogenic episodes as they tend to be sporadic and pathologic bradycardia occuring only during episodes. Documentation of blood pressure during episodes is even more difficult. Extended ambulatory monitoring is usually required (3-6). Occasionally

episodes can be provoked by vigorous activity or administration of a beta-adrenergic-blocking drug (3).

Documentation of ARVC associated ventricular tachyarrhythmia is facilitated by their high frequency (1). Either standard ECG or 24 hour Holter recordings will usually contain many VPC and often VT in Boxers with ARVC and a recent history of episodic weakness (3). When a static ECG or Holter recording contains VT or many VPC, episodes should be considered the result of rapid VT until proven otherwise. If no or few VPC are identified by Holter recording, then NMB is more likely than VT as the etiology of syncope/collapse (3).

An occasional Boxer may be affected by both ventricular tachyarrhythmia caused by ARVC and NMB (3). These Boxers may or may not have a history of collapse or syncope. In this cohort, treatment of ventricular tachyarrhythmia with sotalol or a beta-adrenergic-blocking drugs tended to either uncover an occult tendency for NMB or increase the frequency of episodes (3, 8).

Whether NMB and syncope in dogs can prove lethal is uncertain (3). We believe that death does not occur or at least is rare in the natural or home environment. Death might be more likely if episodes are triggered by fight, flight or fright scenarios in the hospital setting. Death might also be more likely when episodes are aggravated by the use of drugs known to cause bradycardia. Such drugs include beta-adrenergic blockers, sotalol, opiods, acetylpromazine and other vagatonic drugs. We have observed non-lethal severe bradycardia in Boxers administered sotalol (3). One of the authors (Calvert) witnessed acute, collapse and sudden death in a young adult, overtly healthy, hyperactive Boxer administered a low-dose of acetylpromazine intravenously.

Whether to treat neurocardiogenic syncope in Boxers is problematic. Treatment decisions should be individualized. One approach is to educate the client to avoid instigating activities. In some dogs, episodes are infrequent and treatment is probably not feasible for drug adverse effects. We only treated one dog medically and recommended avoidance behavior in the rest. Most of the dogs continued to have occasional episodes during the next several years after initial evaluation but most were eventually lost to follow-up.

If episodes are frequent and cannot be adequately prevented by avoidance behavior, then conservative management or pacemaker implantation are options. An anticholinergic drug such as hyoscyamine (Levsin drops, Schwarz Pharma Inc., Meguon, WI, USA) can be used (5-6, 8). However, we do not recommend anticholinergic treatment in dogs with ventricular tachyarrhythmia. We have occasionally prescribed sustained release hyoscyamine (Levsinex Timecaps, Schwarz Pharma Inc., Meguon, WI) at a starting dosage of 0.375 mg twice daily for large dogs, including Boxers, with symptomatic bradycardia.

In humans, beta-blocking drugs have been used to prevent neurally-mediated bradycardia (5-6, 8). The negative inotropic action of this class of drug could attenuate the effects of sympathetic surge and prevent the activation of receptors thought to initiate the afferent arc of the reflex. However, most studies do not support their use. In fact, beta-blockers can enhance bradycardia in all cardio-inhibitory forms of neurally-mediated syncope (3, 8-14).

Another treatment option is pacemaker implantation. Pacemakers are effective in preventing the bradycardia. However, pacemakers are not likely to be effective in patients with concurrent vasodilation secondary to sympathetic withdrawal. Whether Boxers experience hypotension during syncope with NMB is unknown. We have placed a pacemaker in a Boxer with ARVC and comorbid syncope secondary to NMB documented with an implantable loop recorder (Implantable Loop Recorder, Medtronic, Minneapolis, MN). Following pacemaker implantation, the syncopal episodes continued. During the syncopal episodes, Holter recordings documented a paced ventricular rhythm. Therefore, this patient likely experienced syncope secondary to vasodilatory hypotension from sympathetic withdrawal. Owners should be cautioned that syncope may persist if pacemakers are placed in Boxers with NMB.

The etiology of the apparent neurally-mediated syncope in Boxers is unknown. Boxers seem to be predisposed by a more sensitive reflex response to sympathetic surges compared to other overtly healthy, large dogs that do not have systolic failure or volume overload. A specific predisposing factor has not been identified in overtly healthy humans that experience neurocardiogenic syncope in the absence of dehydration or comorbid disease.

In conclusion, NMB should be suspected in Boxer dogs with syncope triggered by exertion, excitement, and startle in which a 24 hour Holter recording contains few VPCs and absence of VT. When NMB is suspected, extended ambulatory monitoring and implantable loop recorders may be best for heart rate documentation.

REFERENCES

1. Meurs, K.M., Spier, A.W., Miller, M.W., Lehmkuhl, L. and Towbin, J.A.: Familial ventricular arrhythmias in boxers. J. Vet. Intern. Med. 13:437-439, 1999.
2. Meurs, K.M. Spier, A.W., Wright, N.A., Atkins, C.E., DeFrancesco, T.C., Gordon, S.G., Hamlin, R.L., Keene, B.W., Miller, M.W. and Moise, N.S.: Comparison of the effects of four antiarrhythmic treatments for familial ventricular arrhythmias in boxers. J. Am. Vet. Med. Assoc. 221:522-527, 2002.
3. Thomason, J.D., Kraus, M.S., Surdyk, K.K. Fallaw, T. and Calvert, C.A.: Bradycardia-associated syncope in 7 Boxers with ventricular tachycardia (2002-2005). J. Vet. Intern. Med. 22:931-936, 2008.
4. Grubb, B.P.: Clinical practice: Neurocardiogenic syncope. N. Engl. J. Med. 352:1004-1010, 2005.
5. Brignole, M., Alboni, P., Benditt, D.G., Bergfeldt, L., Blanc, J.J., Thomsen, P.E., van Dijk, G., Fitzpatrick, A., Hohnloser, S., Janousek, J., Kapoor, W., Kenny, R.A., Kulakowski, P., Masotti, G., Moya, A., Raviele, A., Sutton, R., Theodorakis, G., Ungar, A., Wieling, W., Priori, S.G., Garcia, M.A., Budaj, A., Cowie, M., Deckers, J., Burgos, E.F., Lekakis, J., Lindhal, B., Mazzotta, G., Morais, J., Oto, A., Smiseth, O., Menozzi, C., Ector, H. and Vardas, P.: for the Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope—update 2004. Eur. Heart J. 25:2054-2072, 2004.
6. Strano, S., Colosimo, C., Sparagna, A Mazzei, A., Fattouch, J., Giallonardo, A.T., Calcagnini, G. and Bagnato, F.: Multidisciplinary approach for diagnosing syncope: a retrospective study on 521 outpatients. J. Neurol. Neruosurg. Psychiatry. 76:1597-1600, 2005.
7. Tilley, L.P., Smith, F.W.K., Oyama, M.A. and Sleeper, M.M.: Manual of Canine and Feline Cardiology. 4th edition. St. Louis: Saunders Elsevier 138, 2008.
8. Calvert, C.A., Jacobs, G.J. and Pickus, C.W.: Bradycardia-associated episodic weakness, syncope, and aborted sudden death in cardiomyopathic Doberman pinschers. J. Vet. Int. Med. 10:88-93, 1996.
9. Mark, A.L.: The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J. Am. Coll. Cardiol. 1:90-102, 1983.
10. Cadman, C.S.: Medical therapy of neurocardiogenic syncope. Cardiol. Clin. 203-213, 2001.
11. Madrid, A., Ortega, J., Rebollo, G.J. Manzano, J.G., Segovia, J.G., Sánchez, A., Peña, G. and Moro, C.: Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: a prospective double-blind, randomized and placebo-controlled study. J. Am. Coll. Cardiol. 37:554-559, 2001.
12. Ventura, R., Maas, R., Zeidler, D., Schoder, V., Nienaber, C.A., Schuchert, A. and Meinertz, T.: A randomized and controlled pilot trial of beta-blockers for the treatment of recurrent syncope in patients with a positive or negative response to head-up tilt test. Pacing Clin. Electrophysiol. 25:816-821, 2002.
13. Flevari, P., Livanis, E.G., Theodorakis, G.N., Zarvalis, E., Mesiskli, T. and Kremastinos, D.T.: Vasovagal syncope: a prospective randomized, cross-over evaluation of the effects of propranolol, nadolol and placebo on syncope recurrence and patients' well being. J Am. Coll. Cardiol. 40:499-504, 2002.
14. Alegria, J.R., Gersh, B.J., Scott, C.G., Hodge, D.O., Hammill, S.C. and Shen, W.K.: Comparison of frequency of recurrent syncope after beta-blocker therapy versus conservative management of patients with vasovagal syncope. Am. J. Cardiol. 92:82-84, 2003.