Assessment of heart rate variability in Boxers with arrhythmogenic right ventricular cardiomyopathy

Alan W. Spier, DVM, PhD, DACVIM, and Kathryn M. Meurs, DVM, PhD, DACVIM

Objective—To assess heart rate variability (HRV) in Boxers with arrhythmogenic right ventricular cardiomyopathy (ARVC), assess the ability of HRV analysis to identify differences in Boxers on the basis of severity of their arrhythmia, and evaluate the use of HRV to determine whether persistently high sympathetic tone is present in these dogs.

Design—Prospective study.

Animals—24 Boxers with ARVC and 10 clinically normal non-Boxer dogs.

Procedure—Boxers were categorized as dogs with congestive heart failure (CHF), dogs with ≤ 2 ventricular premature complexes (VPCs)/24 h (designated unaffected), or dogs with > 1,000 VPCs/24 h (designated affected). Ambulatory electrocardiography (24 hours) was performed in each dog. Recordings were analyzed for HRV variables at a commercial laboratory; differences in HRV variables among groups were compared with 1-way ANOVA.

Results—Compared with control non-Boxer dogs and Boxers without CHF (affected and unaffected Boxers), HRV was reduced in Boxers with CHF. No differences in HRV variables were detected between affected and unaffected Boxers. Inconsistent differences were identified between the control dogs and Boxers without CHF that had various degrees of arrhythmias.

Conclusions and Clinical Relevance—Results suggest that persistently high sympathetic tone is not a consistent feature of ARVC. Differences in some HRV variables between Boxers without CHF and control dogs suggest that Boxers may have different autonomic control of heart rate, compared with that of clinically normal non-Boxer dogs. The usefulness of HRV analysis appears limited to Boxers with ARVC that have systolic dysfunction and CHF. (*J Am Vet Med Assoc* 2004;224:534–537)

The autonomic nervous system plays a major role in the control of the cardiovascular system, particularly in the modulation of heart rate.[1-4] The degree of variation in heart rate (ie, **heart rate variability [HRV]**) can be used as an assessment of the influence of the autonomic system on the heart.[2-5] Electrocardiographically, increased sympathetic innervation induces decreased variability of **R-R intervals (RRs)**, whereas increased parasympathetic tone induces increase in the degree of variation in RRs. Sympathetic and parasympathetic tones not only impact HRV but also affect heart rhythm. Autonomic balance influences the occurrence and severity of ventricular arrhythmias; increased sympathetic tone exacerbates these arrhythmias, and increased parasympathetic tone has a protective effect.[5]

Reduced HRV associated with increased sympathetic tone and withdrawal of parasympathetic tone has been used in humans to predict death resulting from congestive heart failure and identify risk of sudden death in patients with ventricular arrhythmias.[3,6-8] Boxers with **arrhythmogenic right ventricular cardiomyopathy (ARVC)** have a primary heart disease that is characterized by the presence of ventricular arrhythmias and risk of sudden death; a small subset of these Boxers develop systolic dysfunction and congestive heart failure.[9] Because of the influence of the sympathetic nervous system on occurrence of arrhythmias, we hypothesized that Boxers with ARVC would have reduced HRV (even in the absence of congestive heart failure) that would be a factor in the development of ventricular arrhythmias. The purpose of the study reported here was to assess HRV in Boxers with and without ARVC, evaluate the ability of this method to identify differences in Boxers on the basis of severity of their arrhythmia, and examine the use of HRV to determine whether persistently high sympathetic tone is present in affected dogs.

Materials and Methods

Inclusion criteria—Boxers were recruited for a prospective multiphase research study to evaluate arrhythmogenic cardiomyopathy. The dogs were client-owned, and owner consent was obtained prior to data collection. The study included 24 Boxers that were > 2 years old and without evidence of congenital heart disease. All dogs were evaluated by physical examination, standard 6-lead electrocardiography (performed in the hospital), 2-dimensional and Doppler echocardiography, and 24-hour ambulatory electrocardiography (Holter monitoring). Twenty-four hour ambulatory ECGs[a] were obtained with a 7-lead, 3-channel electrode system and acquired with an analog tape recorder. Leads were arranged to approximate the frontal leads I, II, and III. Only those recordings with > 20 hours of data were included. All dogs were sent home with their owners; none of the ambulatory ECGs were obtained from dogs that were in the hospital environment. Recordings were analyzed by use of a prospective software analysis algorithm with continuous user interaction[b] by a trained cardiology research assistant under the guidance of a veterinary cardiologist (AWS or KMM). The control group comprised 10 clinically normal non-Boxer dogs (> 6 months old). These dogs were considered clinical-

From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210. Dr. Spier's present address is Department of Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, MO 65211.

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Address correspondence to Dr. Spier.

ly normal on the basis of results of physical examination and 24-hour ambulatory ECGs (< 10 **ventricular premature complexes [VPCs]**/24 h). As with the Boxers, these dogs were also client owned and owner consent was obtained prior to data collection. These dogs were selected because of similar body size to that of the Boxers.

Study groups—Twenty-four Boxers that were selected for the HRV study were assigned to 1 of 3 groups on the basis of presence or absence of VPCs on Holter recordings or presence of heart failure. These groups included unaffected Boxers that had ≤ 2 VPCs/24 h with normal ventricular size and systolic function (n = 10); affected Boxers that had > 1,000 VPCs/24 h with normal ventricular size and systolic function (10); or Boxers with systolic dysfunction and **congestive heart failure** (**CHF**; 4). Congestive heart failure was diagnosed on the basis of fluid retention (pulmonary, pleural, or abdominal). This latter group served as a reference group that was expected to have reduced HRV and increased sympathetic tone. A fourth group, comprised of clinically normal non-Boxer dogs, served as a control group.

Heart rate variability analyses—Analyses of HRV were performed on 24-hour Holter recordings at a commercial laboratory.[c] Analyses were performed in the time domain. For each group of dogs, 4 variables were assessed. Mean and SD of the normal RRs during the entire recording period were calculated and designated as **mean RR** and **SDNN**. To calculate additional variables, each 24-hour recording was divided into 288 distinct 5-minute periods. The mean and SD of all normal RRs for each 5-minute period were then calculated. From this, the **SD of the mean value of all normal RRs (SDANN)** from these two hundred eighty-eight 5-minute periods was calculated. The **mean value of the SDs (ASDNN)** from these two hundred eighty-eight 5-minute periods was also calculated.

Statistical analyses—Data were analyzed by comparing the mean value for each time domain variable among groups of dogs with a 1-way ANOVA. Differences were evaluated among the 4 groups of dogs (normal non-Boxer dogs, affected Boxers, unaffected Boxers, and Boxers with CHF). Significance was defined as $P \leq 0.05$. If a significant difference was identified, post hoc analysis (Tukey pairwise comparison) was performed.

Results

Thirty-four dogs were included in the study, 24 of which were Boxers. The Boxers were 2 to 12 years old (mean age, 6 years); there were 10 (42%) males and 14 (58%) females. Mean age of Boxers in each group was 8.2 years for affected Boxers, 3.6 years for unaffected Boxers, and 5.8 years for Boxers with CHF. The age of the non-Boxer dogs ranged from 6 months to 8 years (mean age, 4 years); there were 7 males and 3 females. These dogs had similar body size as that of the Boxers (weight, 20 to 40 kg [44 to 88 lb]).

From Holter recordings of dogs in each group, the range of VPCs per 24 hours was determined: affected Boxers, 1,131 to 14,778 VPCs/24 h; unaffected Boxers, 0 to 2 VPCs/24 h; Boxers with CHF, 1,226 to 3,460 VPCs/24 h; and control non-Boxer dogs, 0 to 3 VPCs/24 h. Values of mean RR, SDNN, SDANN, and ASDNN were calculated (**Table 1**). Results of 1-way ANOVA identified differences between the Boxers with CHF and all other groups for all 4 variables. However, no differences were identified between affected and unaffected Boxers for any variable evaluated.

Table 1— Assessment of heart rate variability (values ± SD) in clinically normal non-Boxer dogs (n = 10) and Boxers with ≤ 2 VPCs/24 h (unaffected; 10), with > 1,000 VPCs/24 h (affected; 10), or congestive heart failure (CHF; 4)

Variable	Normal non-Boxer dogs	Boxers		
		Unaffected	Affected	CHF
Mean RR	913 ± 112[a]	734 ± 99[b]	734 ± 93[b]	530 ± 65[c]
SDNN	412 ± 66[a]	293 ± 122[b]	328 ± 73[a,b]	152 ± 46[c]
ASDNN	35 ± 71[a]	280 ± 68[a]	283 ± 79[a]	122 ± 46[b]
SDANN	244 ± 36[a]	172 ± 46[b]	176 ± 35[b]	82 ± 21[c]

Mean RR = Mean value (milliseconds) of normal R-R intervals during 24-hour Holter recording. SDNN = Standard deviation (milliseconds) of the R-R intervals during 24-hour Holter recording. ASDNN = Mean value (milliseconds) of SDs of 288 individual 5-minute periods within a 24-hour recording. SDANN = SD (milliseconds) of the mean values of 288 individual 5-minute periods within a 24-hour recording.

[a-c]Results of 1-way ANOVA calculation for each variable relative to category of dog. Categories with same superscript letters do not differ significantly with respect to variable; categories with different superscript letters are significantly ($P < 0.05$) different.

Differences in some variables were identified between Boxers without CHF (ie, affected and unaffected groups) and control non-Boxer dogs. Values of each HRV variable were always greater for control non-Boxer dogs than those for affected and unaffected Boxers, although these differences were not always significant. Similarly, for each HRV variable, values for affected Boxers were greater than those for unaffected Boxers, but none of these differences was significant.

Discussion

The purpose of the study reported here was to evaluate HRV in Boxers with ARVC. The results of our study indicated less HRV in Boxers with CHF, compared with that of all other dog groups (including Boxers with high numbers of VPCs per 24 hours, Boxers with low numbers of VPCs per 24 hours, and clinically normal non-Boxer dogs). However, the analyses of HRV did not reveal any differences between affected and unaffected Boxers. Furthermore, differences in some (but not all) HRV variables were detected between control non-Boxer dogs and the 2 groups of Boxers without CHF (ie, affected and unaffected Boxers).

From our data, it appears that findings of HRV analysis in Boxers with CHF are similar to those of studies[10-17] performed in humans in which patients with CHF had high sympathetic tone associated with low HRV. In fact, the reduction of HRV in humans with CHF is predictive for death, especially in patients with dilated cardiomyopathy.[6,8,18] In veterinary medicine, analysis of HRV has been used in the evaluation of Doberman Pinschers with dilated cardiomyopathy.[19-21] In contrast to Boxers with arrhythmogenic disease, dilated cardiomyopathy in Doberman Pinschers is characterized primarily by the development of CHF, with a small subset of dogs that die suddenly from cardiac arrhythmias.[22,23] Our data regarding HRV evaluation in Boxers with ARVC are similar to the HRV findings in Doberman Pinschers with dilated cardiomyopathy; in these Doberman Pinschers, there is a reduction in HRV in dogs with CHF, compared with that in affected dogs with less severe disease.[20,21] Although the car-

diomyopathy in Boxers is commonly more arrhythmogenic than that of Doberman Pinschers, the group of Boxers with CHF was included in the study reported here to validate the HRV evaluation technique. On the basis of results of studies in humans and dogs, HRV in Boxers with CHF was expected to be low, and these dogs would serve as a positive control group with which to assess increased sympathetic tone.

In Boxers with ARVC, the assessment of HRV in dogs with ventricular arrhythmias in the absence of myocardial failure is more intriguing. The majority of Boxers with ventricular arrhythmias have preserved systolic function, and the nature of the arrhythmia is not well understood. The formation of ventricular arrhythmias is complex and is multifactorial in nature. The underlying anatomic or functional abnormalities that allow for altered impulse formation and conduction (ie, the arrhythmic substrate) can be modified by several factors.[24] Boxers with ARVC have an abnormal substrate in the right ventricle characterized by fatty infiltration and fibrous replacement.[d] However, the arrhythmia may fail to develop despite the presence of an arrhythmogenic substrate if the necessary triggers are absent. An important trigger for many arrhythmias is autonomic modulation, particularly sympathetic tone.[1] In Boxers with arrhythmias, syncope or sudden death may occur in association with increased activity or excitement, which is suggestive of an increased adrenergic state in these dogs.[25] The finding that Boxers with frequent arrhythmias do not necessarily have a reduction in HRV may simply reflect a lack of persistently high sympathetic tone, despite the potential importance of transient increases in sympathetic tone on development of arrhythmias in these dogs.

Differences observed in some HRV variables between Boxers without CHF (ie, affected and unaffected Boxers) and control non-Boxer dogs suggested that Boxers may have different autonomic patterns, compared with those of other breeds of dog. For those variables in which a significant difference between Boxers without CHF and clinically normal non-Boxer dogs was not identified, values of those HRV variables were greater for the clinically normal non-Boxer dogs, compared with values for the Boxers without CHF. Whether or not this apparent distinction between Boxers and other breeds of dogs is factual remains to be elucidated.

One limitation of the study reported here was the small number of dogs. Power calculations were performed with 1-way ANOVA for each HRV variable, and the result for each variable was > 0.9. However, a significant difference was identified for each HRV variable when compared among all groups. Power calculations were not performed on post hoc analyses (Tukey pairwise comparison) that failed to identify significant differences among all groups. This is a potential explanation for why no differences were identified between affected and unaffected Boxers. However, in many instances, the values for HRV variables were nearly identical in these groups. It is unlikely that the addition of more dogs to each group would have identified a significant difference between these groups.

Another potential confounding factor was age. The age of the affected Boxers was significantly greater than that of the unaffected Boxers. As Boxers get older, the number of VPCs increases; therefore, it may have been expected that affected dogs would be older than unaffected dogs.[e] It is possible that the inability to identify a difference between these 2 groups of dogs was because of the effect of age. However, the influence of age on HRV analysis in dogs is unknown, and thus the importance of the age difference between the affected and unaffected Boxers is not clear.

Our analysis of HRV in Boxers with ventricular arrhythmias identified that there was a significant reduction in HRV in dogs with concomitant CHF, compared with that in those dogs without CHF. This was an expected finding because persistently increased sympathetic tone is associated with CHF. The inability to identify a difference in HRV between Boxers with and without severe arrhythmias may be a result of a lack of persistently high sympathetic innervation associated with arrhythmias or may reflect the insensitivity of HRV analysis in this group of dogs. It is likely that sympathetic modulation is important in the development of ventricular arrhythmias, but may occur in a phasic or intermittent fashion. Other techniques to evaluate sympathetic innervation may be necessary in the evaluation of Boxers with ventricular arrhythmias.

[a]Cardiocorder cassette recorder, Del Mar, Irvine, Calif.
[b]Accuplus Holter analysis system, Del Mar, Irvine, Calif.
[c]Biomedical Systems, St Louis, Mo.
[d]Basso C, Fox PR, Meurs KM, et al. Arrhythmogenic right ventricular cardiomyopathy causing sudden death in Boxer dogs: new animal model of human disease (abstr). *Circulation* 2002;106(suppl 2):199.
[e]Spier AW, Meurs KM, Lehmkuhl LB, et al. Evaluation of ambulatory ECG monitoring in asymptomatic boxer dogs (abstr). *J Vet Intern Med* 1999;13:248.

References

1. Schwartz PJ. The autonomic nervous system and sudden death. *Eur Heart J* 1998;19:F72–F80.
2. Malik M. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;17:354–381.
3. Stein PK, Kleiger RE. Insights from the study of heart rate variability. *Annu Rev Med* 1999;50:249–261.
4. Stein PK, Bosner MS, Kleiger RE, et al. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J* 1994;127:1376–1381.
5. Hohnloser SH, Klingenheben T, Zabel M, et al. Heart rate variability used as an arrhythmia risk stratifier after myocardial infarction. *Pacing Clin Electrophysiol* 1997;20(Pt II):2594–2601.
6. Fauchier L, Babuty D, Cosnay P, et al. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1998;33:1203–1207.
7. Bikkina M, Alpert MA, Mukerji R, et al. Diminished short-term heart rate variability predicts inducible ventricular tachycardia. *Chest* 1998;113:312–316.
8. Fauchier L, Babuty D, Cosnay P, et al. Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *J Am Coll Cardiol* 1997;30:1009–1014.
9. Harpster NK. Boxer cardiomyopathy. In: Kirk RW, ed. *Current veterinary therapy: small animal practice*. Philadelphia: WB Saunders Co, 1983;329–337.
10. Tygesen H, Rundqvist B, Waagstein F, et al. Heart rate variability measurement correlates with cardiac norepinephrine spillover in congestive heart failure. *Am J Cardiol* 2001;87:1308–1311.
11. Jiang W, Hathaway WR, McNulty S, et al. Ability of heart rate variability to predict prognosis in patients with advanced congestive heart failure. *Am J Cardiol* 1997;80:808–811.

12. Ferrari R, Ceconi C, Curello S, et al. The neuroendocrine and sympathetic nervous system in congestive heart failure. *Eur Heart J* 1998;19(suppl F):F45–F51.

13. Galinier M, Pathak A, Fourcade J, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. *Eur Heart J* 2000;21:475–482.

14. Bonaduce D, Petretta M, Marciano F, et al. Independent and incremental prognostic value of heart rate variability in patients with chronic heart failure. *Am Heart J* 1999;138:273–284.

15. Boveda S, Galinier M, Pathak A, et al. Prognostic value of heart rate variability in time domain analysis in congestive heart failure. *J Interv Card Electrophysiol* 2001;5:181–187.

16. Yoshikawa T, Baba A, Akaishi M, et al. Neurohormonal activations in congestive heart failure: correlations with cardiac function, heart rate variability, and baroreceptor sensitivity. *Am Heart J* 1999;137:666–671.

17. Wijbenga JA, Balk AH, Meij SH, et al. Heart rate variability index in congestive heart failure: relation to clinical variables and prognosis. *Eur Heart J* 1998;19:1719–1724.

18. Yi G, Goldman JH, Keeling PJ, et al. Heart rate variability in dilated cardiomyopathy: relation to disease severity and prognosis. *Heart* 1997;77:108–114.

19. Calvert CA, Wall TM. Correlations among time and frequency measures of heart rate variability recorded by use of a Holter monitor in overtly healthy Doberman Pinschers with and without echocardiographic evidence of dilated cardiomyopathy. *Am J Vet Res* 2001;62:1787–1792.

20. Calvert CA, Jacobs GJ. Heart rate variability in Doberman Pinschers with and without echocardiographic evidence of dilated cardiomyopathy. *Am J Vet Res* 2000;61:506–511.

21. Minors SL, O'Grady MR. Heart rate variability in the dog: is it too variable? *Can J Vet Res* 1997;61:134–144.

22. Calvert CA, Chapman WL Jr, Toal RL. Congestive cardiomyopathy in Doberman Pinscher dogs. *J Am Vet Med Assoc* 1982; 181:598–602.

23. Calvert CA, Hall G, Jacobs G, et al. Clinical and pathologic findings in Doberman Pinschers with occult cardiomyopathy that died suddenly or developed congestive heart failure: 54 cases (1984–1991). *J Am Vet Med Assoc* 1997;210:505–511.

24. Calvert CA. Heart rate variability. *Vet Clin North Am Small Anim Pract* 1998;28:1409–1427.

25. Goodwin JK, Cattiny G. Further characterization of Boxer cardiomyopathy, in *Proceedings*. 13th Am Coll Vet Intern Med Forum 1995;300–302.