Evaluation of spontaneous variability in the frequency of ventricular arrhythmias in Boxers with arrhythmogenic right ventricular cardiomyopathy

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Objective—To evaluate spontaneous variability in the frequency of ventricular arrhythmias and assess the influence of day of ECG recording and day of week on arrhythmia frequency in Boxers affected with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Design—Prospective study.

Animals—10 Boxers with ARVC with prior ambulatory ECG recordings that included ≥ 500 ventricular premature complexes/24 h.

Procedure—Consecutive 24-hour ambulatory ECG recordings were obtained during a 7-day period in each dog. The number of ventricular premature complexes and grade of the arrhythmia were obtained from each recording. For each dog, the number of ventricular premature complexes for each recording was evaluated to identify any differences relative to the day of recording (recording 1 to 7) and day of the week (Monday through Sunday).

Results—Spontaneous variability accounted for as much as 80% of the change in frequency of ventricular premature complexes in dogs with frequent arrhythmias; this value was almost 100% in dogs with less frequent arrhythmias. Grade of arrhythmia was less variable but was also inversely related to frequency of arrhythmia. No significant differences in frequency values were identified among days of recording or among days of the week.

Conclusions and Clinical Relevance—Changes of ≤ 80% in the frequency of ventricular arrhythmias may be within the limit of spontaneous variability in dogs with ARVC. This degree of variability should be considered in evaluations of ambulatory ECG recordings, particularly in the assessment of the efficacy of antiarrhythmic drugs. (*J Am Vet Med Assoc* 2004;224: 538–541)

Boxers with **arrhythmogenic right ventricular cardiomyopathy (ARVC)** are predisposed to the development of **ventricular premature complexes (VPCs)** that are believed to arise from an ectopic focus in the right ventricle; these VPCs are readily identified as wide and bizarre QRS complexes on ECGs.[1,a] The presence of these ventricular arrhythmias predisposes affected animals to sudden death.[1,a] In the diagnosis of ARVC in Boxers, echocardiography is of limited use because myocardial function is typically preserved; consequently, the disease in this breed is frequently diagnosed by ECG monitoring. In dogs, 24-hour ambulatory ECG evaluation (Holter monitoring) has greater sensitivity for detection of intermittent arrhythmias than traditional brief in-hospital recordings.[2] In veterinary medicine, Holter monitoring is used in the diagnosis of disease, assessment of disease severity, and evaluation of the response to antiarrhythmic treatment and progression of disease.[3-8] On the basis of these recordings, many dogs in which a diagnosis of ARVC is made receive long-term treatment with antiarrhythmic drugs; efficacy of that treatment is often assessed by performing follow-up Holter monitor evaluations. Although many variables are measured on a Holter monitor, the number and complexity of VPCs are most widely used. In veterinary medicine, usually only a single ambulatory ECG recording is obtained, and from its analysis, clinical decisions are made. Therefore, day-to-day variability in the number of VPCs is an important variable to consider in the interpretation of such recordings.

In humans with VPCs, the frequency of the arrhythmia can vary considerably. Evaluation of 72-hour ECG recordings suggests that reduction in VPC frequency of as much as 83% can occur spontaneously, independent of therapeutic intervention.[9] Findings of studies[10,11] investigating antiarrhythmic agents suggest that a reduction in VPC frequency of 80% to 90% may be necessary to document drug response. Because of the concern that variability in VPC frequency could mimic the effects of antiarrhythmic treatment, another study[12] was conducted in a manner similar to that of the antiarrhythmic drug trials, except that no medication was administered. At the time of these studies, a response to antiarrhythmic treatment was defined standardly as detection of a 50% reduction in the number of VPCs after treatment. Without antiarrhythmic medication, 65% of humans in the study had a reduction in VPCs of ≥ 50%.[12] If these individuals had been included in an antiarrhythmic drug trial, they would have been classified as drug responders, despite the absence of treatment.

It is unknown, however, to what extent the frequency of ventricular arrhythmias varies on a day-to-day basis in dogs. The assumption that the spontaneous variability in ventricular arrhythmias in dogs is similar to that found in humans may not be valid

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because the frequency of VPCs in dogs and humans differs. As many as 50% of clinically normal humans have ectopic ventricular activity with several thousand VPCs per 24 hours.[13-15] Decades ago, it was suggested that the occurrence of arrhythmias in clinically normal dogs is rare.[16] Results of a more recent assessment[17] of the electrical activity in clinically normal dogs suggest that clinically normal dogs do not have the same frequency of ectopic ventricular activity that is seen in clinically normal humans. That study[17] included 228 clinically normal Beagles, of which only 49 (21.5%) had any VPCs; of those 49 dogs, only 4 (1.8%) had > 9 VPCs in 24 hours. Evaluation of a group of 49 dogs of various breeds revealed that none of the dogs had > 24 VPCs/24 h, and the median value was 0.[18] Another study[19] involving a group of 16 healthy dogs found that only 2 dogs had > 24 VPCs/recording, and both these dogs were Boxers.

Compared with data accumulated from studies in humans, little information is available regarding the biologic variability of electrical activity in dogs. Biologic variability may influence disease diagnosis, assessment of disease severity, and decisions regarding treatment options. We hypothesized that there is substantial spontaneous variability in the frequency of ventricular arrhythmias in dogs (similar to that detected in humans) and the degree of variability detected depends on when the ECG recordings are obtained. Because dogs might become accustomed to wearing the Holter monitor and interactions between dogs and owners might differ day to day, we also hypothesized that the day of recording (accustomedness) and day of the week (dog-owner interaction) would influence the degree of day-to-day variability detected. The purpose of the study reported here was to evaluate the degree of spontaneous variability in the frequency of ventricular arrhythmias and assess the influence of day of recording and day of week on arrhythmia frequency in Boxers affected with ARVC.

Materials and Methods

Inclusion criteria—Boxers were prospectively recruited for a multiphase study to evaluate ARVC. For inclusion in the study, dogs had to be ≥ 2 years old, have no evidence of structural heart disease detectable via 2-dimensional and Doppler echocardiography, and have ≥ 500 VPCs/24 h detected previously via Holter monitoring (median days elapsed since previous Holter monitoring, 25; range, 1 to 139). The Holter recording used to assess suitability for inclusion in the study was not included in data analyses. Eleven dogs met the inclusion criteria for further examination.

Ambulatory (24-hour) electrocardiography—Holter recordings were obtained over 7 consecutive days by means of a 7-lead, 3-channel electrode system and acquired by use of an analog tape recorder.[b] Electrodes were arranged to approximate the frontal leads I, II, and III. By use of a prospective software analysis algorithm with continuous user interaction,[c] recordings were analyzed by a trained cardiology research assistant under the guidance of a veterinary cardiologist (AWS or KMM). Data obtained for each 24-hour Holter recording included duration of recording, number of VPCs per recording, day of recording (1 to 7), day of week (Monday through Sunday), and grade of arrhythmia. If VPCs were identified, the arrhythmia was graded on the basis of a modification of the Lown grading scheme[20] as follows: grade 1 = single, uniform VPC only; grade 2 = bigeminy, trigeminy, or multiform VPCs; grade 3 = presence of VPC couplets or triplets; and grade 4 = R-on-T phenomenon or ventricular tachycardia (≥ 4 consecutive VPCs). Dogs in which no VPCs were identified were classified as grade 0. Only Holter recordings with durations ≥ 20 hours were included in the analysis.

Statistical analyses—Variability in the frequency of VPCs (number of VPCs/24 h) was evaluated, including variability associated with days of recording and day of the week, by use of a repeated-measures 1-way ANOVA. The nonparametric repeated-measures ANOVA on ranks was used because the data were not normally distributed, despite multiple transformations to normalize the data. Significance was defined as $P \leq 0.05$. For some variables, data were examined collectively for dogs with ≥ 500 and < 500 VPCs/24 h, but data for these 2 groups of dogs were not compared statistically. Overall variability during the 7 days of recording was determined via assessment of the differences between maximum and minimum arrhythmia grade scores and analysis of the percentage difference between the maximum daily frequency of VPCs and the minimum daily frequency of VPCs obtained, via the equation:

$$\text{Percentage difference} = \frac{\text{Maximum daily value} - \text{Minimum daily value}}{\text{Maximum daily value}} \times 100$$

Results

Eleven dogs were initially evaluated for the study. In 6 dogs, Holter monitoring recordings were obtained during 7 consecutive days. Because of client compli-

Table 1—Frequency of ventricular premature complexes (VPCs) per 24 hours and grade of arrhythmia recorded during 7 consecutive days via Holter monitoring in 10 Boxers with arrhythmogenic right ventricular cardiomyopathy

	No. of VPCs/24 h				Grade		
Dog No.	Minimum	Maximum	Median	Variability (%)*	Minimum	Maximum	Median
1	62	144	90	57	2	3	2
2	20	228	44	91	2	3	2
3	0	27	2	100	0	2	1
4	1,257	2,325	1,608	46	3	3	3
6	623	1,609	817	61	2	3	2
7	4,447	20,679	4,989	78	2	3	3
8	3	32	9	91	1	3	2
9	2,644	11,215	7,808	76	3	3	3
10	1,384	6,194	3,795	78	3	3	3
11	1,316	5,507	2,243	76	2	3	3

*Variability (%) = $\frac{\text{Maximum daily value} - \text{Minimum daily value}}{\text{Maximum daily value}} \times 100$

ance issues, 7 recordings were obtained over an 8-day period in 2 dogs. Because of technical difficulties, in 2 of the 11 dogs, only 6 of the 7 recordings contained ≥ 20 hours of usable data; therefore, 6 recordings were obtained over 7 days in these 2 dogs. Data from 1 dog (dog 5) were excluded entirely because > 1 recording failed to provide more than 20 hours of usable data. Therefore, data from 10 dogs were included in the analyses: 6 dogs with 7 recordings over 7 days, 2 dogs with 7 recordings over 8 days, and another 2 dogs with 6 recordings over 7 days.

Of the 10 dogs, 4 were female and 6 were male. Mean age of the dogs was 7.5 years (range, 5 to 11 years). The median interval between acquisition of the initial Holter recording (for determination of suitability for inclusion in the study) and the 7-day study evaluation was 25 days (range, 1 to 139 days). For dogs with frequent arrhythmias (≥ 500 VPCs/24 h; n = 6), the percentage change between maximum and minimum values of the number of VPCs was as much as 80% and grade of arrhythmia did not differ by more than 1 category. In those dogs that had < 500 VPCs/24 h (n = 4), the percentage change in number of VPCs was > 80% and was 100% in 1 dog; the differences between maximum and minimum arrhythmia grade scores in these dogs were ≤ 2 categories. Data for these 2 groups of dogs were not compared statistically. However, for each variable in each dog, no significant difference in values was identified among days of recording or among days of the week.

Discussion

The results of the study reported here indicated that variability in the frequency of ventricular arrhythmias in dogs with > 500 VPCs/24 h during the study period did not exceed 80%. Therefore, changes in VPC frequency of ≤ 80% may be within the limits of spontaneous variability. These findings are consistent with results of similar studies[9-11] in which variability of ventricular arrhythmias in humans was investigated.

In contrast, the grade of arrhythmia did not vary to the same extent. In 5 of the 10 dogs, the maximum and minimum grades of arrhythmia only differed by 1 category. In 3 dogs, the grade of arrhythmia did not differ at all during the week of study; each day, the arrhythmia was grade 3 in these dogs, which was the highest grade observed in the study. Furthermore, all the dogs that did not have any variability in grade of arrhythmia had very frequent VPCs. Over the 7-day period, a difference between maximum and minimum grades of arrhythmia that was > 1 category was noted in only 2 dogs. These 2 dogs had the least frequent arrhythmias; during any of the 7 days, 1 dog had ≤ 32 VPCs and the other had the lowest number (including 0) of VPCs recorded of all dogs. Therefore, the grade of arrhythmia (as defined for the purposes of this study) appeared less variable than the frequency of VPCs but appeared to also vary inversely with VPC frequency.

Statistical evaluation of the differences in variables measured with regard to the day of recording and day of the week revealed no association of either factor with the data obtained. It was hypothesized that during the initial days of Holter monitoring, dogs would be agitated by the monitor units, and as a consequence, the frequency of arrhythmia might increase; later, the dogs would become more adapted to wearing the monitors, and the VPC frequency might decrease. However, no such consistent relationship between VPC frequency and day of recording was observed. It was also postulated that the day of the week may have influence on arrhythmia frequency; for example, owners might have different levels of activity during the weekend, compared with that of a weekday, which could indirectly affect the dogs' activity and subsequently affect the number of VPCs detected. However, no relationship between day of the week and number of VPCs was observed.

In recent years, Holter monitoring has been used in the assessment of ventricular arrhythmias in dogs with cardiovascular disease. In many reports,[4,5,7,21] the usefulness of detection of ventricular arrhythmias as a diagnostic and prognostic tool in Doberman Pinschers with dilated cardiomyopathy is described. Other reports include descriptions of the findings of Holter monitoring in German Shepherd Dogs[22] and Boxers[3] with inherited ventricular arrhythmias. Holter monitoring has also been performed to assess ventricular arrhythmias associated with noncardiac disease, such as traumatic myocarditis and splenectomy.[23,24] The importance of spontaneous variability in ventricular arrhythmias with regard to disease diagnosis is not clear. However, spontaneous variation in the frequency of ventricular arrhythmias is particularly important as it applies to response to treatment. Studies that attempt to evaluate the efficacy of an antiarrhythmic drug must take these variations into account. In the past, studies[25,26] of antiarrhythmic drugs have been performed in dogs but the response to therapy was not assessed via the use of Holter monitors. In more recent studies,[8,27] Holter monitoring has been used to evaluate the effect of antiarrhythmic treatments. In both of these later studies, criteria used for an antiarrhythmic response were consistent with the guidelines discussed in this report (eg, an 80% reduction in VPC number), as well as those described in the human literature (spontaneous variability of 83%).

The study reported here had limitations. The dogs included in this investigation were all Boxers, and all were believed to have the same cardiovascular disease (ARVC). Therefore, the results of this study may only apply to this population of dogs. However, as described, the degree of variation in this study closely resembled the values obtained in the human literature. It may therefore be reasonable to apply these same guidelines to disease processes associated with ventricular arrhythmias in other breeds with other disease processes.

Another problematic finding in our study was the disparity between the Holter data obtained during the study in some of the dogs and the data obtained from the recording used to confirm their eligibility for inclusion in the study. The inclusion criterion for this particular study was that previous Holter monitoring (not analyzed as part of the 7-day evaluation) identified ≥ 500 VPCs/24 h in each dog. In 4 of the dogs that met this inclusion criterion, the number of VPCs was much

< 500 during the study; in 1 of these dogs, the number of VPCs was 0. Additionally, the variability in frequency of VPCs in these dogs was into the 90% range (and as high as 100% in a dog with no VPCs). These findings were unexpected and are difficult to explain. However, a study[28] performed in humans revealed that in addition to short-term variations in VPC frequency, spontaneous variability also occurs over time. To determine short-term and long-term variability in frequency of VPCs in humans, 2 recordings were obtained at 2- to 14-day intervals, which were repeated 6 to 12 months later.[28] Statistical analysis of recordings separated by a short interval (2 to 14 days) revealed variations in VPC frequency of 69% between the first pair of values and 73% for the pair obtained months later. However, comparison of 2 recordings that were obtained after a long interval (6 to 12 months) revealed variability in VPC frequency of as much as 98% to 100%. In the study reported here, the 2 dogs with the least number of VPCs and highest variability in VPC frequency had the longest interval between completion of the Holter monitoring for assessment of suitability for inclusion in the study and the 7-day Holter monitoring evaluation (74 and 139 days). Longer-term variability may provide some explanation for the difference between frequency of VPCs detected at the inclusion assessment (ie, > 500 VPCs/24 h) and the values obtained during the 7-day recording period of the study. Therefore, great care must be taken in assessing Holter recordings obtained many months apart.

Ambulatory (24-hour) ECG monitoring is a highly reliable method available for obtaining ECG data in humans and dogs. However, notable spontaneous variability in frequency of VPCs makes repeatable sequential analyses of cardiac electrical activity difficult. The impact of this variability appears to be most important in assessments of the efficacy of antiarrhythmic treatments or progression of disease. The influence of this variability in VPC frequency in the application of Holter monitoring for the purpose of disease diagnosis is less clear and remains to be elucidated.

[a]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.
[b]Cardiocorder cassette recorder, Del Mar, Irvine, Calif.
[c]Accuplus Holter analysis system, Del Mar, Irvine, Calif.

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