Comparison of the effects of four antiarrhythmic treatments for familial ventricular arrhythmias in Boxers

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Objective—To evaluate the effect of 4 antiarrhythmic treatment protocols on number of ventricular premature complexes (VPC), severity of arrhythmia, heart rate (HR), and number of syncopal episodes in Boxers with ventricular tachyarrhythmias.

Design—Randomized controlled clinical trial.

Animals—49 Boxers.

Procedure—Dogs with > 500 VPC/24 h via 24-hour ambulatory ECG (AECG) were treated with atenolol (n = 11), procainamide (11), sotalol (16), or mexiletine and atenolol (11) for 21 to 28 days. Results of pre- and posttreatment AECG were compared with regard to number of VPC/24 h; maximum, mean, and minimum HR; severity of arrhythmia; and occurrence of syncope.

Results—Significant differences between pre- and posttreatment number of VPC, severity of arrhythmia, HR variables, or occurrence of syncope were not observed in dogs treated with atenolol or procainamide. Significant reductions in number of VPC, severity of arrythmia, and maximum and mean HR were observed in dogs treated with mexiletine-atenolol or sotalol; occurrence of syncope was not significantly different between these 2 treatment groups.

Conclusions and Clinical Relevance—Treatment with sotalol or mexiletine-atenolol was well tolerated and efficacious. Treatment with procainamide or atenolol was not effective. (*J Am Vet Med Assoc* 2002;221:522–527)

Ventricular tachyarrhythmias are frequently observed in Boxers with familial arrhythmias and may lead to the development of syncope or sudden death.[1,2] Antiarrhythmic drugs may be prescribed by veterinarians in an attempt to decrease the number of **ventricular premature complexes (VPC)**, severity (grade) of arrhythmia, clinical signs, and the risk of sudden death.

The antiarrhythmic drugs most commonly chosen are quinidine, procainamide, mexelitine, atenolol, propranolol, sotalol, and amiodarone.[3,4] This list of prescribed drugs is based in part on current recommendations in the human medical literature. The drug chosen for an individual animal is typically selected on the basis of a combination of factors, including the clinical experience of the veterinarian, cost of drug, adverse effects, and ease of administration. Some authors have suggested that Boxers with ventricular arrhythmias may have the greatest antiarrhythmic response to quinidine, a combination of procainamide and propranolol, or a combination of mexiletine and atenolol.[1,5] However, there are no comprehensive studies that evaluate the efficacy of any of these medications in Boxers with frequent ventricular arrhythmias.

The objective of the study reported here was to evaluate the effect of 4 commonly used antiarrhythmic treatment protocols on the number of VPC, severity of arrhythmia, **heart rate (HR)** variables, and syncope in Boxers with ventricular tachyarrhythmias.

Materials and Methods

Adult Boxers were selected for participation in a prospective multiphase study of familial ventricular arrhythmias. Dogs were enrolled in the study after approval by the Ohio State University Animal Care and Use Committee and after receiving a signed owner consent form. All dogs were evaluated by obtaining a history detailing the presence of clinical signs (syncope, exercise level), physical examination, 2-dimensional and Doppler echocardiogram, and 24-hour **ambulatory ECG (AECG)**. An echocardiogram was performed from the right parasternal view and left and right atrial, and ventricular dimensions were determined. Systolic function was assessed by use of fractional shortening, ejection fraction, or both.[6] Doppler echocardiography was performed from the subcostal position to evaluate aortic flow velocity.[6] A 3-channel transthoracic AECG system was placed, and the dog was released from the hospital to monitor the dog's ECG in a normal environment.[a] The monitor was removed after 25 hours. Analysis of AECG recordings was performed by a technician under the guidance of a veterinary cardiologist with an analysis system.[a] Any recordings that did not have at least 20 hours of readable data were excluded from analysis. Analysis of AECG included tabulation of the number of VPC/24 h; determination of maximum, mean, and minimum sinus HR;

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and grading of severity of the arrhythmia as 1 (single uniform VPC), 2 (bigeminy, trigeminy, or both), 3 (ventricular couplets, triplets, or both), or 4 (R on T [VPC appears on the downslope of the preceding T wave], ventricular tachycardia [4 or more consecutive VPC], or both).

Dogs were selected for participation in the treatment study if they had an echocardiogram that revealed normal cardiac chamber sizes and function in the absence of any other concurrent cardiac or systemic disease, and a 24-hour AECG that revealed at least 500 VPC/24-h period.

Each dog was assigned to 1 of the following 4 antiarrhythmic treatment groups in consecutive order: atenolol (0.3 to 0.6 mg/kg [0.14 to 0.27mg/lb], PO, q 12 h); procainamide (20 to 26 mg/kg [9 to 11.8 mg/lb], PO, q 8 h); sotalol (1.5 to 3.5 mg/kg [0.68 to 1.6 mg/lb], q 12 h); or a combination of mexiletine (5 to 8 mg/kg [2.3 to 3.6 mg/lb], q 8 h) and atenolol (0.3 to 0.6 mg/kg, q 12 h).[4,7,8] All dogs received the medication for 21 to 28 days, at which time a posttreatment AECG was performed. Dogs that developed adverse effects to the drugs (development of syncope, increase in syncopal episodes, signs of depression, or gastrointestinal upset) that were believed to be intolerable were removed from the study prior to 21 days, and results from the censored animals were not used in subsequent analyses.

The posttreatment AECG was evaluated by the same technician and cardiologist, unaware of treatment groups, who had interpreted the pretreatment AECG. The number of VPC/24 h; maximum, mean, and minimum sinus HR; and grade of arrhythmia were determined. The occurrence of syncope during treatment, defined as 1 or more syncopal episodes after the first 7 days of treatment, was recorded. Treatment efficacy was defined as > 85% reduction in number of VPC. A proarrhythmic effect was attributed to treatment if the number of VPC increased > 85%.

Statistical analyses—Each treatment group was evaluated for differences in age, pretreatment number of VPC/24 h, grade of arrhythmia, sinus HR, and presence of syncope prior to initiation of treatment, because these factors could bias response to treatment. The pretreatment values for age, number of VPC/24 h, and sinus HR were compared by use of a 1-way ANOVA on ranks. A Kruskal-Wallis ANOVA on ranks was used to compare grade of arrhythmia among groups. A χ^2 analysis was used to compare presence of syncope among groups.[b]

The effects of the treatment with regard to maximum, mean, and minimum sinus HR and number of VPC/24 h were evaluated by use of a paired *t* test. Grade of arrhythmia before and after treatment was compared by use of a Wilcoxon signed rank test. The effect of treatment on syncopal episodes was evaluated with a Fischer exact test.[b] For all comparisons, a value of $P < 0.05$ was considered significant.

Results

Sixty-one dogs with at least 500 VPC/24 h were enrolled in the study, including 20 that had at least 1 episode of syncope. Twelve dogs were removed from the study before completing 21 days of treatment for reasons that included development of syncope (n = 6), an increase in syncope (3), or signs of depression and anorexia (3). Forty-nine dogs completed at least 21 days of treatment, including 17 that had syncope.

Significant differences were not observed for age ($P = 0.277$), number of VPC/24 h ($P = 0.873$), maximum sinus HR ($P = 0.185$), mean sinus HR ($P = 0.123$), minimum sinus HR ($P = 0.754$), grade of arrhythmia ($P = 0.869$), or presence of syncope ($P = 0.498$) among the 4 groups prior to treatment.

Atenolol—Sixteen dogs received atenolol. Five dogs were removed from the study because of development of syncope (n = 3) or an increase in syncopal events (2). The 11 dogs that completed the study included 7 females (2 sexually intact and 5 spayed) and 4 males (all castrated). Ages ranged from 5 to 11 years (median, 10 years).

Before treatment, the number of VPC ranged from 1,004 to 35,717/24 h (median, 3,234/24 h), and arrhythmia grade ranged from 1 to 4. Maximum, mean, and minimum HR ranged from 101 to 220 **beats/min** (**bpm**; median, 163 bpm), 58 to 94 bpm (median, 79 bpm), and 37 to 63 bpm (median, 53 bpm), respectively. Two of the 11 dogs had syncope before treatment.

After treatment with atenolol, number of VPC ranged from 17 to 36,163/24 h (median, 935/24 h), and arrhythmia grade ranged from 1 to 4. Four of 11 dogs had > 85% reduction in VPC, and 2 dogs had > 85% increase in VPC. Four dogs had a reduction in arrhythmia grade, 1 dog had an increase in arrhythmia grade, and in 6 dogs arrhythmia grade did not change. Maximum, mean, and minimum HR ranged from 110 to 188 bpm (median, 143 bpm), 56 to 106 bpm (median, 76 bpm), and 36 to 60 bpm (median, 53 bpm), respectively. One of the 2 dogs still had syncope.

No significant differences between pre- and posttreatment VPC ($P = 0.871$), grade of arrhythmia ($P = 0.188$), maximum HR ($P = 0.094$), mean HR ($P = 0.445$), minimum HR ($P = 0.812$), or presence of syncope ($P = 1.0$) were observed.

Procainamide—Fourteen dogs received procainamide. Three dogs were prematurely removed from the study because of signs of depression (n = 1) and gastrointestinal upset (2) that were believed to be associated with the drug and intolerable. Eleven dogs completed the study, including 6 females (2 sexually intact, 4 spayed) and 5 males (all castrated). Ages ranged from 2 to 11 years (median, 7 years).

Before treatment, number of VPC ranged from 895 to 34,620/24 h (median, 6,761/24 h), and arrhythmia grade ranged from 3 to 4. Maximum, mean, and minimum HR ranged from 157 to 230 bpm (median, 187 bpm), 62 to 94 bpm (median, 81 bpm), and 42 to 58 bpm (median, 47 bpm), respectively. Three dogs had syncope before treatment.

After treatment, number of VPC ranged from 0 to 66,312/24 h (median, 3,388/24 h), and arrhythmia grade ranged from 0 to 4. Five dogs had > 85% reduction in VPC, and 5 dogs had > 85% increase in VPC. Four dogs had a reduction in grade of arrythmia, 1 dog had an increase in arrhythmia grade, and in 6 dogs arrhythmia grade did not change. Maximum, mean, and minimum HR ranged from 139 to 201 bpm (median, 176 bpm), 72 to 103 bpm (median, 87 bpm), and 37 to 63 bpm (median, 53 bpm), respectively. No dogs had syncope.

Pre- and posttreatment VPC ($P = 0.226$), grade of arrhythmia (P= 0.188), maximum HR ($P = 0.259$), mean HR ($P = 0.135$), minimum HR ($P = 0.721$), and syncope ($P = 0.214$) were not significantly different.

Sotalol—Eighteen dogs received sotalol. Two were prematurely removed because of development of syn-

cope (n = 1) or an increase in syncopal episodes (1). Sixteen dogs completed the study, including 11 females (3 sexually intact, 8 spayed) and 5 males (2 sexually intact, 3 castrated). Ages ranged from 3 to 13 years (median, 9 years).

Before treatment, number of VPC ranged from 703 to 62,622/24 h (median, 5,907/24 h), and arrhythmia grade ranged from 3 to 4. Maximum, mean, and minimum HR ranged from 144 to 241 bpm (median, 175 bpm), 68 to 128 bpm (median, 83 bpm), and 36 to 66 bpm (median, 45 bpm), respectively. Seven dogs had syncope.

After treatment, number of VPC ranged from 5 to 37,180/24 h (median, 998/24 h), and arrhythmia grade ranged from 1 to 4. Nine dogs had > 85% reduction in VPC, and 1 dog had > 85% increase in VPC number. Seven dogs had a reduction in arrhythmia grade, 1 dog had an increase in arrhythmia grade, and in 8 dogs arrhythmia grade did not change. Maximum, mean, and minimum HR ranged from 117 to 177 bpm (median, 143 bpm), 54 to 92 bpm (median, 68 bpm), and 24 to 54 bpm (median, 43 bpm), respectively. Two dogs still had syncope after treatment.

Significant reductions in VPC ($P = 0.024$), arrhythmia grade ($P = 0.023$), maximum HR ($P < 0.001$), mean HR ($P = 0.014$), and minimum HR ($P = 0.002$) were observed. Presence of syncope was not significantly ($P = 0.113$) different.

Mexiletine-atenolol—Thirteen dogs received mexiletine and atenolol. Two dogs were prematurely removed from the study because of development of syncope. The 11 dogs that completed the study included 5 females (3 sexually intact, 2 spayed) and 6 males (5 sexually intact, 1 castrated). Ages ranged from 2 to 12 years (median, 6 years).

Before treatment, number of VPC ranged from 810 to 23,699/24 h (median, 5,814/24 h), and arrhythmia grade ranged from 2 to 4. Maximum, mean, and minimum HR ranged from 120 to 218 bpm (median, 177 bpm), 63 to 104 bpm (median, 91 bpm), and 36 to 74 bpm (median, 51 bpm), respectively. Five of 11 dogs had syncope before treatment.

After treatment, number of VPC ranged from 2 to 7,996/24 h (median, 801/24 h), and arrhythmia grade ranged from 1 to 4. Eight of 11 dogs had > 85% reduction in VPC, and 2 of 11 dogs had > 85% increase in VPC. Seven dogs had a reduction in arrhythmia grade, 0 dogs had an increase in arrhythmia grade, and in 4 dogs arrhythmia grade did not change. Maximum, mean, and minimum HR ranged from 131 to 203 bpm (median, 152 bpm), 59 to 92 bpm (median, 70 bpm), and 37 to 68 bpm (median, 44 bpm), respectively. One dog still had syncope after treatment.

A significant reduction was observed between pre- and posttreatment VPC ($P = 0.022$), arrhythmia grade ($P = 0.01$), maximum HR ($P = 0.015$), and mean HR ($P = 0.003$) but not for minimum HR ($P = 0.07$) or syncope ($P = 0.149$).

Syncope—The overall impact of treatment on the population of dogs with syncope was a significant ($P = 0.003$) reduction, although no individual treatment was found to have a significant effect. Four dogs still had syncope at the end of the 21 days of treatment. These dogs did not have significant differences with regard to posttreatment VPC ($P = 0.791$), arrhythmia grade ($P = 0.163$), minimum HR ($P = 0.313$), or mean HR ($P = 0.343$), compared with dogs in which syncope resolved with treatment. Maximum HR was significantly ($P = 0.004$) lower in dogs that still had syncope.

Discussion

Sotalol and the combination of mexiletine and atenolol were well tolerated and induced significantly reduced VPC and arrhythmia grade, whereas administration of procainamide or atenolol alone did not significantly reduce either of these variables. None of the individual treatments significantly reduced the incidence of syncope, although for all treatments combined, overall incidence of syncope was significantly reduced. This suggests that treatment can have an effect on syncope and implies that if a larger number of dogs had been studied in each group, an effect may have been observed for individual treatments.

The decision to treat dogs with at least 500 VPC/24 h in this study was somewhat arbitrary. The criteria for initiating treatment for ventricular arrhythmias, particularly in a dog without clinical signs, are uncertain and ill-defined. There is little information linking the number of VPC or their arrhythmia grade with development of clinical signs or risk of sudden death in dogs. In humans, neither the hemodynamic impact of the arrhythmia nor the arrhythmia grade is necessarily a predictor of eventual outcome.[9] Importantly, because a proarrhythmic effect is associated with most antiarrhythmic drugs, the possible risks of proarrythmia must be weighed against the risks of untreated ventricular arrhythmia.[10] In dogs, it has been suggested that pharmacologic control be attempted when there are > 30 VPC/min, multiple complex QRS forms, VPC with short coupling intervals, or indications of decreased cardiac output (syncope, signs of depression).[5,6] Although an adult large-breed dog should probably not have > 50 VPC/24 h,[11] many veterinarians would probably not treat a dog that did not have clinical signs until it had more than several hundred VPC/24 h. We believed that it was clinically relevant to evaluate dogs with at least 500 VPC/24 h.

The number of VPC/24 h was compared between pretreatment and posttreatment recordings; however, there is a substantial amount of day-to-day variability in frequency of VPC in dogs and humans with ventricular tachyarrhythmias.[4,12,13,c] Therefore, evaluation for reduction of the number of VPC alone is believed to be an inaccurate method to assess drug efficacy. Results of studies in both species indicate that an individual may have as much as an 85% day-to-day variation in VPC number.[4,12,13] It has, therefore, been suggested that to differentiate drug effect from day-to-day variability, a reduction of > 85% should be observed.[4,12] For similar reasons, we chose a > 85% increase in VPC to indicate a proarrhythmic effect.

The treatment drugs and protocols chosen were designed to include drugs suggested for treating Boxers with ventricular arrhythmias and to select drugs from different classes of the Vaughan-Williams classification

scheme.[4,7,8] Procainamide was chosen as a representative of class I, atenolol for class II, and sotalol for class III. A fourth treatment protocol included a class I (mexiletine) and class II (atenolol) drug. The Vaughan-Williams scheme is based on a drug's predominant electrophysiologic action and the phase of the action potential at which the drug induces its predominant effect. Historically, it was believed that the antiarrhythmic efficacy of drug might be related to its effect on a specific phase of the action potential. However, a more recent study[14] of arrhythmias and antiarrhythmics has found this classification scheme to be somewhat limited.

Justification for the selection of a β-adrenergic receptor blocker (class II) as a ventricular antiarrhythmic is partially based on the belief that activation of the autonomic nervous system is involved in the development of ventricular tachyarrhythmias.[15,16] Modulation of the autonomic nervous system with β-adrenergic receptor blockers (β blockers) decreases the number of VPC and the mortality rate associated with malignant ventricular arrhythmias in humans.[17] In some situations, the decrease in VPC is mild, but a decrease in mortality rate is still observed.[15,17] β-Blockers have been advocated for treating ventricular tachycardia in patients without identifiable structural heart disease and for ventricular tachycardia, which seems to have an excitement or exercise trigger.[12] The use of β-blockers for treatment of Boxers with familial ventricular arrhythmias has been suggested because these dogs typically do not have substantial structural cardiac changes (although microscopic changes may be apparent). Additionally, they appear to have increased risk of syncopal episodes associated with excitement or stress.[7] Atenolol was chosen as the representative drug because of its β-1 receptor specificity and its convenient dosing interval (every 12 hours).[4] In our study, atenolol did not have a significant effect on VPC number, grade of arrhythmia, HR, or syncope. It is possible that the dose of atenolol used in this study was too low, because the maximum sinus HR was not significantly reduced. However, because the dose was chosen from published canine doses, it was likely similar to the typical clinically prescribed dose.[4,8] Although the number of VPC/24 h during atenolol administration was not reduced, we can not necessarily conclude that the drug was not beneficial. In humans, a reduction in mortality rate is observed even when reduction in VPC is minimal.[15,18,19]

Procainamide, a class I antiarrhythmic, has historically been recommended for use in Boxers with ventricular tachyarrhythmias and is still used frequently.[1] Procainamide did not induce a significant reduction in VPC number, arrhythmia grade, HR, or syncope. The degree of proarrhythmia induced by procainamide in dogs is unknown, but it is of interest that 5 of the 11 dogs that received procainamide had > 85% increase in VPC. However, none of the dogs had an increase in syncope. In a study[20] that evaluated ventricular antiarrhythmics in humans, it was found that procainamide caused a high incidence of adverse effects, including proarrhythmias and gastrointestinal upset. Procainamide was the only drug that caused dogs to be removed from the study for noncardiac causes (eg, gastrointestinal upset, signs of depression).

Sotalol, a class III antiarrhythmic, has both nonselective β-blockade and potassium channel blockade effects.[4] In some human studies,[21-24] sotalol significantly reduced recurrent ventricular tachycardia and risk of sudden death and was more effective at reducing VPC than either the class I or class II (β blocker) antiarrhythmics. In our study, sotalol induced significant reduction in VPC number and grade, but atenolol when given alone did not. It was impossible to determine whether the greater efficacy of sotalol was attributable to greater ability to induce β blockade, the potassium channel blocking effects, or both. Maximum HR was significantly reduced after treatment, which suggested that the drug had at least some β-blocking effect. Potassium channel blockade can sometimes be detected via increased QT interval,[24] but this was not evaluated in our study. Sotalol appeared to have minimal proarrhythmic effects, because only 1 dog had > 85% increase in VPC. This parallels what has been observed in humans. In 1 study[20] that compared 7 ventricular antiarrhythmics, sotalol had the fewest proarrhythmic effects.

Mexiletine, a class I antiarrhythmic, has been administered IV to treat ventricular tachyarrhythmias in dogs, but there is little information regarding its use as an orally administered antiarrhythmic.[25] In humans, the effective therapeutic concentration of mexiletine exceeds the concentration at which it induces intolerable adverse effects.[26] Therefore, although mexiletine is effective against ventricular arrhythmias, it has a high incidence of adverse effects. It has been suggested that combination treatment with this drug and a second antiarrhythmic may permit use of slightly lower dosages and still provide some antiarrhythmic efficacy.[4,27] Because different classes of antiarrhythmics have different effects on membrane responsiveness, duration of action potentials, the repolarization phase, and other electrophysiologic parameters, a combination of drugs may be more effective than 1 drug.[28] In humans, a combination of mexiletine and propranolol is efficacious, particularly in humans who were refractory to monotherapy with a class I or class II agent.[26,28-29] In our study, the combination of mexiletine and atenolol induced significant reduction in VPC number and arrhythmia grade as well as HR and had minimal proarrhythmic effects.

Nine dogs were removed prematurely from the study because of either the development of syncope or an increase in syncopal events. Five dogs were receiving atenolol, 2 were receiving sotalol, and 2 were receiving the mexiletine-atenolol combination; 3, 1, and 2 of these dogs, respectively, had no history of syncopal episodes. Two dogs in the atenolol group and 1 in the sotalol group were censored because of increased rate of syncope after initiation of treatment. It is possible that the development of or increase in syncopal events in these dogs was attributable to a proarrhythmic effect and that either the arrhythmia grade or number of VPC increased after administration of the medication. Unfortunately, in none of the dogs was an AECG evaluated at the time they were removed from

the study. However, censoring these withdrawals from further analysis may have biased the results in a favorable way. It is possible that some of the censored dogs had increased VPC number or arrhythmia grade and, thus, would have been included with dogs that had worsening of the measured variables with treatment. In the group of dogs that completed the 21 days of treatment, 2 dogs that received atenolol, 2 that received mexiletine-atenolol, and 1 that received sotalol had > 85% increase in VPC number. The arrhythmia grade increased in 1 dog that received atenolol and 1 that received mexiletine-atenolol. Therefore, it would appear that the proarrhythmic effect of these medications was small. In comparison, 5 dogs that received procainamide had > 85% increase in VPC number, but none of these dogs had an increase in syncope. This might suggest that a direct relationship between VPC number and syncopal events is less likely. A second theory is that Boxers may have a frequency-dependent arrhythmia that is initiated by bradycardic events and that slowing of the HR increased the likelihood of a syncopal event.[7] It is of interest that the only significant difference between dogs with and without syncope after treatment was reduction in maximum sinus HR. However, this theory is not supported by the historical observation that, in Boxers, in many instances the syncopal episode is preceded by a period of excitement.[7] It is possible that syncope could be associated with development of neurocardiogenic bradycardia as a response to high sympathetic tone. Unfortunately, the electrical activity associated with these events was not recorded, and this could not be proven.

A limitation of this study was the failure to obtain plasma drug concentrations at the time of the AECG obtained after treatment. Drug concentrations can be helpful in guiding the use of antiarrhythmics and would have proven absorption of the drug. It is unlikely that drug concentrations would have added a substantial amount of information to our study, because plasma concentrations of a specific drug do not account for active metabolites or tissue drug concentrations, and antiarrhythmic effects can span wide drug concentrations.[4] In fact, mexiletine concentrations are not usually of value because of an overlap between therapeutic and toxic plasma concentrations.[26]

Finally, it should be emphasized that our study did not attempt to provide information on the effect of antiarrhythmics on risk of sudden death and long-term survival. A direct relationship between the number and complexity of VPC and the risk of sudden death in Boxers with familial ventricular arrhythmias has not been detected; therefore, the ability of a treatment protocol to alter the factors described here does not imply an impact on survival.

Our results suggest that sotalol and mexiletine-atenolol were well tolerated and efficacious. Some owners may find the sotalol protocol easier to comply with because the combination of mexiletine and atenolol requires administration 3 times/d with 2 pills given at 2 of the 3 administrations.

[a]Delmar Accuplus 363 Holter analysis system, Delmar Medical Systems, Irvine, Calif.

[b]SigmaStat for Windows, version 2.03, SPSS Science, Chicago, Ill.

[c]Spier AW, Meurs KM, Lehmkuhl LB, et al. Spontaneous variability in the frequency of ventricular premature complexes in Boxers with ventricular arrhythmias (abstr). *J Vet Intern Med* 2000;14:335.

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