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Research Article

Ventricular Dysrhythmias Are Associated With Elevated Cardiac Troponin I Concentrations In Dogs With And Without Underlying Structural Heart Diseaset

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Abstract

This study sought to identify whether circulating cardiac troponin I (cTnI) levels could be used as a screening test to identify dogs with symptomatic cardiac arrhythmias. It further evaluated the association between various arrhythmia characteristics and patient outcome. Forty-seven client-owned dogs presenting with clinical signs suggestive of dysrhythmia underwent evaluation with echocardiography, ambulatory electrocardiography and cTnI levels were drawn concurrently. Twenty-one normal dogs served as controls. Five to eight years after dogs were enrolled in the study, records were reviewed and survival was evaluated by phone interviews with owners. Cardiac TnI was significantly associated with the presence of ventricular ectopy ($P<0.0001$) and several electrocardiographic markers (multiform ventricular premature complexes ($P=0.0471$) and R-on-T phenomenon ($P<0.0001$) as well as outcome. cTnI was significantly correlated with the presence of ventricular arrhythmias in dogs with structural heart disease as well as those dogs without echocardiographically identified structural heart disease. Cardiac TnI elevation is suggestive of ventricular ectopy in dogs with clinical signs consistent with cardiac dysrrhythmias. Although the presence of elevated circulating cTnI does not correlate with increased risk of arrhythmic death in dogs, the presence of multiform ventricular premature complexes and R-on-T on ambulatory electrocardiography are associated with increased risk.

Keywords: Arrhythmic Death; Cardiac Arrhythmia; Ctni; Sudden Cardiac Death

Abbreviations

cTnI - cardiac troponin I;
CHF - congestive heart failure;
DCM - dilated cardiomyopathy;
ECG - electrocardiogram;
VPC - ventricular premature complexes;
ARVC - arrhythmogenic right ventricular cardiomyopathy

Introduction

The presence of ventricular ectopy has long been associated with an increased risk of fatal dysrhythmias and sudden cardiac death. Researchers have explored the relationship between electrocardiographic markers and prognosis in human heart disease. Markers that have been associated with a poor prognosis include ventricular triplets, R-on-T phenomenon, multiform ventricular premature complexes (VPC), sustained or non-sustained ventricular tachycardia, ventricular flutter, and ventricular fibrillation [1-7].In several studies, a complex dysrhythmia was associated with a poorer prognosis in humans with and without symptomatic cardiac disease [8,5,6]. Supporting these findings are studies in congestive heart failure (CHF) patients, which have demonstrated that those individuals with ventricular ectopy have a poorer prognosis than those without ectopy [3,9,10]. While extensive studies have been performed in humans, far fewer studies have investigated how electrocardiographic markers in dogs may be associated with patient outcome. In dogs with dilated cardiomyopathy (DCM), a QRS duration greater than 60 msec was associated with a reduced survival time compared to those dogs with a normal QRS duration (< 60 msec) [11]. In a large retrospective, observational study evaluating 367 dogs with DCM, the presence of ventricular premature complexes negatively correlated with survival [12].

The cardiac troponins, in particular cardiac troponin I (cTnI), are biomarkers of cardiac injury. As part of the contractile myofibrillar apparatus, troponins are released following any insult that damages the sarcolemmal membrane and an elevated circulating cTnI concentration is a well-described biomarker for ischemic myocardial injury [13]. However, in humans certain dysrhythmias also appear to directly cause myocardial cTnI release. cTnI elevations in patients presenting to the hospital with supraventricular tachycardia or atrial fibrillation is a well recognized phenomenon [14,15,16,2], however elevated cTnI concentrations have also been associated with the presence of ventricular arrhythmias in a population with congestive heart failure [17]. An association between circulating cTnI concentrations and cardiac arrhythmias in dogs has not been fully investigated. In dogs with bradyarrhythmias, cTnI was increased prior to pacemaker implantation and remained elevated post pacemaker implantation, suggesting that underlying myocardial injury and/or myocarditis may lead to certain bradyarrhythmias [18]. Serum cTnI concentrations and 24 hour Holter data compared between Boxer dogs with arrhythmgenic right ventricular cardiomyopathy (ARVC), normal Boxers and non-Boxer dogs found that cTnI concentrations correlated with the number of VPCs/24 hours and the grade of dysrhythmia [19]. However, there was overlap between the control and affected groups of Boxers and both Boxer groups had higher cTnI concentrations than the non-Boxer control group [19].

The primary purpose of the study reported here was to determine if cTnI levels could be used as a marker to identify dogs with symptomatic cardiac arrhythmias. In addition, specific rhythm characteristics (such as multiform ventricular ectopic complexes) were evaluated to determine if they were associated with outcome or cTnI level.

Materials and Methods

Study population

Forty-seven dogs that were presented to the cardiology service at the University of Pennsylvania veterinary school for evaluation of signs suggestive of a cardiac dysrhythmia (i.e. history of syncope or acute weakness during exercise) or a dysrhythmia identified on physical examination or on a screening electrocardiogram (ECG) between December 2001 and December 2004 were enrolled. Dogs were excluded if there was evidence of an extracardiac disease process that has been associated with dysrhythmia genesis, such as gastric dilatation-volvulus. A second population of 21 healthy mature dogs (over 1 year of age) representing both sexes was recruited from within the hospital community as a control group. These animals were considered to be free of cardiac disease on the basis of historical and physical examination findings and echocardiography. This study was approved by the University of Pennsylvania Institutional Animal Care and Use Committee and written consent authorizing study participation was obtained from each owner.

Echocardiography

Standard 2-dimensional, M-mode, and Doppler echocardiographic evaluations as has previously been described were performed in all dogs to assess whether structural heart disease was present (Boon, 2011). Echocardiograms were performed by either MS or KB using a Sonos 5500 ultrasound machine and a 5mHz probe (Phillips Healthcare; Andover MA)

Ambulatory ECG

An ambulatory ECG was obtained from each patient and control dog with a 3-channel Holter monitoring recorder (LabCorp, Burlington, NC). The monitors were placed at the veterinary hospital and dogs were sent home for the remainder of the 24-hour period. Owners were encouraged to maintain the dog's normal activity level. The Holter monitor was removed after 24 hours. The entire ECG recording was visually analyzed by two board-certified veterinary cardiologists who remained blind to patient identification and diagnostic test results. The total number of ventricular ectopic beats and supraventricular ectopic beats over the 24-hour period were summed. Holter recordings were also evaluated for the presence of ventricular triplets, the presence of R on T, and the presence of multiform ventricular ectopics. Those individuals with less than 20 hours of readable Holter data were excluded from statistical analysis involving the number of ectopic beats present.

cTnI analysis

Blood for cTnI assessment was drawn at the time of

Holter placement. 1-3mL of whole blood was collected via venipuncture and promptly placed in tubes containing lithium heparin. Samples were centrifuged and plasma was extracted and stored at -80°C if the samples were not run immediately (those animals presenting after hours). These samples remained frozen until analysis with a 2-site sandwich assay using the Stratus II stat fluorometric enzyme immunoassay system (Dade Behring) with a lower detection level of 0.03 ng/mL. This test has been previously validated in the dog[20,21].

Survival Information

Phone interviews were conducted in 2009 with clients to determine survival information including survival time and cause of death. Cause of death was identified as likely arrhythmic or unlikely arrhythmic. Arrhythmic death was suspected when owners reported that otherwise healthy pets died suddenly, typically after a collapse episode. In contrast, unlikely arrhythmic death was suspected when owners elected euthanasia due to congestive heart failure or extracardiac disease.

Therapy

Patients that were treated with any anti-arrhythmic therapy (i.e. sotalol, mexilitine) were noted; however, no distinction between the specific dosages was made.

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro-Wilks test and since the majority were not normally distributed, they are described using median and minimum/maximum. The Mann-Whitney test was used to compare these variables between groups or Spearman's rank correlation was used to assess association between continuous variables or continuous and ordinal variables. Receiver operating curve (ROC) analysis was performed to determine the optimal sensitivity and specificity cutoff points for cTnI and number of aberrant beats and for their prediction of arrhythmia associated death. The trapezoid rule was used to calculate the area under the curve for these analyses. Categorical variables are expressed as proportions and percents and the Fischer's exact test (if the expected count was <5 in any cell) or chi-square test was used for comparison of these variables between groups. The exact method was used to calculate odds ratios and the associated 95% confidence intervals. For all comparisons, a p-value <0.05 was considered significant. All statistical analyses were performed using a statistical software package (Stata 12.0 for Mac, Stata Corporation, College Station, TX).

Results

Study population

Forty-seven dogs with clinical signs suggestive of arrhythmias were included encompassing 14 breeds: Boxer (26), Mixed breed (3), German Shepherd (3), Golden Retriever (3), Doberman Pinscher (2), Great Dane (2), Rottweiler (1), Portuguese Water Dog (1), Labrador Retriever (1), Cocker Spaniel (1), Dalmatian (1), Belgian Tervuren (1), American Pit Bull Terrier (1), and Bull Dog (1). There were 30 males (8 sexually intact and 22 neutered) and 17 females (2 sexually intact and 15 spayed). The age of study dogs ranged from 1 year to 12 years (median = 6 years). The study also included 21 control dogs: Boxer (14), Golden Retriever (2), Mixed breed (2), Airedale (1), German Shepherd (1), and Bull Dog (1). Nine males (5 sexually intact and 4 neutered) and 13 females (4 sexually intact and 9 spayed) were in the control population. Age ranged from 1 year to 8 years (median = 4 years).

Echocardiography

Of the 47 study dogs, echocardiography diagnosed patients with DCM (7), chronic valvular disease (6), myocarditis (1), subaortic stenosis (1), and pericardial effusion secondary to a heart base tumor (1). The remaining 31 study patients had structurally normal hearts. Of these patients with normal cardiac structure, 15/31 were diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC). All control dogs had structurally normal hearts on echocardiography.

Ambulatory ECG

Thirteen patients had more than 40 supraventricular premature complexes during the 24 hour Holter evaluation, 32 had more than 40 ventricular ectopics and 10 had greater than 40 supraventricular and 40 ventricular ectopic complexes. None of the control dogs had more than 40 supraventricular or ventricular premature complexes during the 24 hour evaluation. The total number of supraventricular ectopic beats was not significantly (p=0.06) higher in animals with arrhythmic death (n=7, median 191, range 0-20442) compared to animals that did not suffer arrhythmic death (n=55, median 0, range 0-16772).

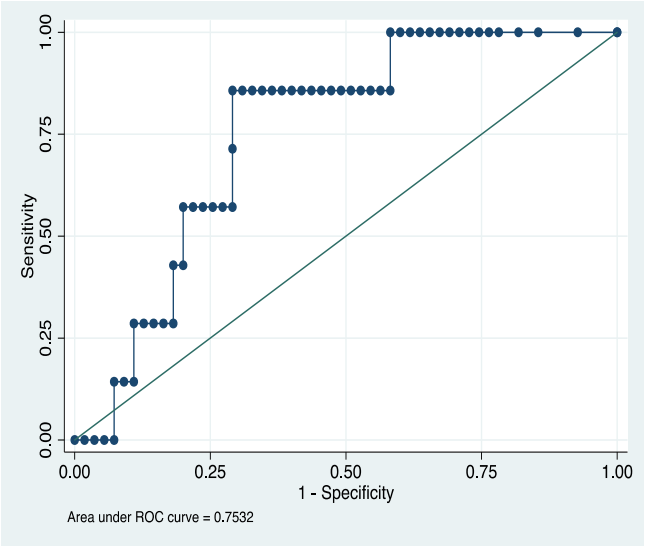

Figure 1. ROC curve for ventricular ectopy

In contrast, the total number of ventricular ectopic beats was significantly (p=0.0301) greater in animals with arrhythmic death (n=7, median 2727, range 27-19365 vs. n=55, median 112, range = 0-120971). The area under the ROC curve assessing the total number of ventricular ectopics was 0.7532 (see Figure 1) whereas the area under the curve assessing the number of supraventricular ectopics was 0.7039 (see Figure 2), however the curves were not significantly different (p=0.6595). Multiform ventricular ectopy (6/6, 100% versus 24/61, 39%) was significantly (P=0.006) associated with arrhythmic death, however neither the presence of ventricular triplets (P=0.106), nor the presence of R on T (P=0.386) was associated with arrhythmic death. Four of the cases enrolled had no abnormalities detected on echocardiography, 24 hour Holter or echocardiography.

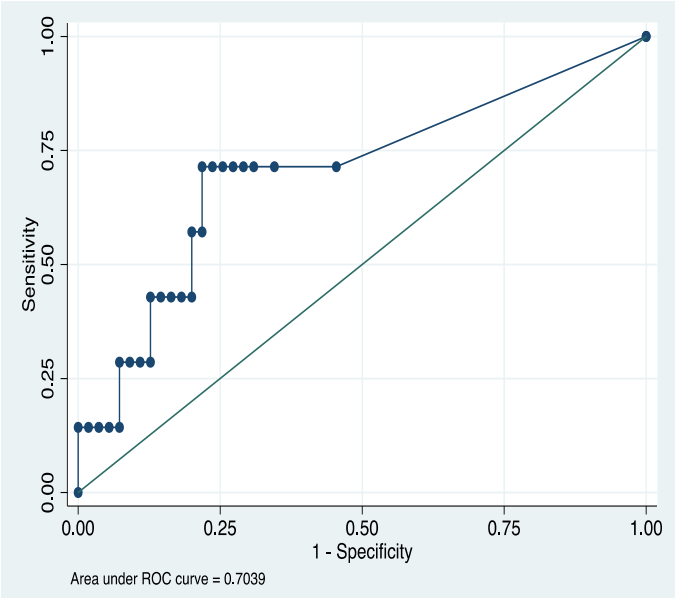

Figure 2. ROC curve for supraventricular ectopy

was normal. The cTnI concentration was not significantly correlated (rho=0.1328, p=0.3246) with the number of supraventricular ectopics on ambulatory ECG (P= 0.3246), however the cTnI concentration increased with increasing frequency of ventricular ectopics (rho=0.5683, P<0.0001), the presence of ventricular triplets (P=0.0001), the presence of multiform ventricular ectopics (P=0.0471) and the presence of R on T (P<0.0001). The cTnI level was associated with the presence of structural heart disease (P=0.0005), but there was no association with arrhythmic death (P=0.2405). Moreover, there was a statistically significant correlation between cTnI and ventricular arrhythmias for animals without structural heart disease as well as animals with structural heart disease (rho= 0.4232, P=0.0073 and rho=0.6440, P=0.0096 respectively). See Table 1.

Variable	n	Median	Range	P-value
Triplets Present	26	0.34	0.02 – 19.97	<0.0001
Triplets Absent	42	0.05	0 – 13.53	
Multiform VPCs Present	29	0.135	0.01 – 19.97	0.0411
Multiform VPCs not present	39	0.06	0 – 16.84	
R on T present	22	0.38	0.07 – 19.97	<0.0001
R on T not present	46	0.06	0 – 16.84	
Structural Heart Disease Present	16	0.345	0.08 – 15.53	0.0005
Structural Heart Disease Absent	52	0.06	0.0 – 19.97	

Table 1. cTnI concentration (pg/ml) by specific cardiac findings.

The presence of R on T, multiform ectopy and triplets were also associated with the presence of underlying structural heart disease (see Table 2).

Variable	OR	95% CI	P value
R on T	4.1	1.1 , 15.6	0.0142
Multiform	2.7	0.7 , 9.7	0.0865
Triplets	5.2	1.3 , 22.7	0.0061

Table 2. Association of selected parameters with structural heart disease.

Holter findings	N	Age (average years)	Sex Male, castrated, female, spayed	Echo Normal vs Abnormal	Aberrant beats (Median)	cTni		
						Min	Max	Med
Normal	25	6.8	4M; 6C; 4F; 11S	24N;1Ab	4	0.03	0.50	0.03
No R on T or multiform	24	7.7	5M;9C; 1F; 9S	20N; 4Ab	604	0.03	16.84	0.19
R on T +/- multiform	19	7.5	4M; 11C; 1F; 3S	8N; 11Ab	5208	0.11	19.87	0.295

Table 3. Summary of dog demographics, cardiac findings and cardiac troponin I.

cTnI analysis

Study patients had a range of cardiac troponin I levels from 0.03 to 19.97 ng/mL (median = 0.16 ng/mL). Control patients had a range of cardiac troponin levels from 0.03 to 0.50 ng/mL (median = 0.055 ng/mL), which was significantly lower than the study dogs (P=0.0008). Based on these data, an animal with an abnormal cTnI concentration (>0.07 ng/mL) was 29 (95% CI:7, 145) times more likely to have an abnormal Holter compared to if the cTnI measurement

There was no difference in cTnI levels between Boxer (range 0.01-15.9, median 0.11 ng/mL) and non-Boxer study dogs (range 0-19.97; median 0.09, P = 0.7861) However, cTnI values were higher in Boxer control dogs compared to non-Boxer control dogs (P=0.002). See Table 3 for cTnI results compared to Holter findings and population demographics.

Survival outcome

Overall outcome between Boxers and other breeds was not

significantly different in the patient group (P=0.60). When specifically comparing arrhythmic deaths between Boxers and the rest of the patient population, the difference did not reach significance but there was a trend for Boxers to be more likely to succumb to arrhythmic deaths than the other breeds (P= 0.054). In 2009, outcome was available for 28 patients (26 study patients and 2 control patients). 4/28 patients were alive (3 study patients and 1 control patient). No significant differences were observed between age (P=0.3518) or sex (P=1.000) when comparing those that had died or were euthanized to those that survived. The deceased control dog died because of lymphosarcoma.

When logistic regression was performed, the only variable that remained significant was structural heart disease (P=0.0043), however calculations could not be performed on the presence of multiform complexes because all of these animals died. With use of a logistic regression model, cTnI is still not significant, but it affects the odds ratio for structural heart disease (10% change). Moreover, the confidence interval for structural heart disease is very wide, likely due to the small number of animals that died. See Table 2. The small number of arrhythmic associated deaths (8) limited any meaningful multiple regression analysis for the outcome of arrhythmia associated death and was not performed.

Seven patients for which long-term follow up was available received anti-arrhythmic therapy: sotalol (n = 3), mexilitine (n = 2), procaineamide (n = 2). All patients (100%) receiving anti-arrhythmic therapy died compared to those that did not receive anti-arrhythmics (71%); however, this finding was not statistically significant (P = 0.255).

Discussion

Elevated cardiac troponin I levels were associated with multiple ECG markers including the presence of ventricular ectopy, multiform ventricular ectopy, ventricular triplets and R on T. The fact that elevated blood cTnI was also associated with structural heart disease is concerning as a potential confounder, however cTnI elevation correlated with the presence of ventricular ectopy in dogs without underlying structural heart disease as well as in those with structural heart disease. Our results are similar to a previous study, which showed that serum cTnI concentrations correlated with the number of VPCs/24 hours and the grade of dysrhythmia in Boxer dogs [19]. This previous study also demonstrated that Boxers, whether affected with ARVC or normal) had higher cTnI concentrations than non-Boxer dogs [19]. In this study there were similar blood cTnI levels in dogs with clinical signs suggestive of cardiac arrhythmias whether they were Boxers or non-Boxers. However, cTnI levels in Boxer control dogs were higher than in non-Boxer control dogs. It is impossible to know the underlying cause of cTnI elevation based on our results, however, our findings suggest that in dogs with a history of symptoms such as syncope or weakness, an elevated cTnI may indicate the presence of cardiac arrhythmias. Based on our results, however, increased cTnI levels cannot be used to determine if a patient is at risk of arrhythmic death.

The results of this study demonstrate that the number of ventricular ectopic beats on a 24-hour Holter monitor is associated with the risk of arrhythmic death. The presence of multiform VPC was also associated with arrhythmic death and suggests this abnormality (either on a resting or Holter ECG) may be a marker associated with an increased risk of death. Interestingly, the presence of R on T was not associated with an increased risk of arrhythmic death in this study. As far as the authors know, only two previous studies evaluated ventricular ectopy and survival in dogs, and both studies were limited to Boxer dogs (Motskla et al., 2013; Meurs et al., 2014). Neither of these studies specifically evaluated R-on-T as a risk factor [22,23], however, similar to our findings, the presence of ventricular triplets did not predict a worse outcome in one of them [22]. Although it did not reach significance, these results suggest a trend for symptomatic Boxers to be more likely to die an arrhythmic death than symptomatic non-Boxers patients (P=0.054)

Spier & Meur's study showed an 80% day-to-day variability in dysrhythmia frequency making interpretation of Holter results from one time point problematic (2004). This variation was corroborated with a more recent study in Boxers that showed a dramatic yearly variation in the number of VPCs in 24 hours [23]. However, this study was designed to evaluate the natural history of ARVC in Boxer dogs and many dogs were asymptomatic, which makes comparison with the results presented here difficult. Moreover, despite the variation in daily ectopy frequency, specific markers of dysrhythmia severity (i.e. presence of R-on-T) and the grade of the dysrhythmia did not change significantly [24], suggesting that the markers identified in the present study as conveying a worse prognosis, would likely be identified irrespective of daily variation.

Results from our study suggest that the administration of anti-arrhythmic therapy may not reduce the risk of cardiac death and/or fatal dysrhythmias. This finding is not surprising given the numerous human studies, which have demonstrated similar results, or even an increased risk of arrhythmogenesis with certain anti-arrhythmics [25-29]. One veterinary study has also shown an increased risk of arrhythmogenesis with anti-arrhythmic therapy [30]. In that study, sotalol and a combination of mexilitine and atenolol were shown to be well tolerated and effective in reducing the number of VPC. However, there was no change in the occurrence of syncope with therapy and survival was not evaluated [30]. Our study was not designed to answer this question and a study specifically designed to evaluate the effect of anti-arrhythmic therapy on survival is indicated.

Conclusions

Cardiac TnI elevation is suggestive of ventricular ectopy in dogs with clinical signs consistent with cardiac dysrrhythmias. Although the presence of elevated circulating cTnI does not correlate with increased risk of arrhythmic death in dogs, the presence of multiform ventricular premature complexes and R-on-T are associated with increased risk based on our results. However, several limitations of our study should be

mentioned. First, a large portion of our animals (both control animals and cases) were Boxer dogs, a breed predisposed to ARVC. Dogs with ARVC may have myocardial damage that could affect cTnI values without echocardiographic changes. The prevalence of this disease in our patient population may have biased our results. A similar issue is the inclusion of dogs with various cardiac diseases. While cTnI is not generally elevated in dogs with DCM or degenerative valve disease unless congestive heart failure is present, diseases such as myocarditis can present with significant elevations in cTnI. One of the cases included in our study was ultimately diagnosed with myocarditis and could have biased our results. Another potential problem is that many of the cases were lost to follow up, which limited our ability to evaluate outcomes and the potential biases associated with them. Additionally, the cTnI testing used was not sensitive enough to detect cTnI serum levels below 0.03 ng/mL (the lower detection limit). It is possible more sensitive cTnI tests that are currently available would yield different results.

Conflict of Interest

The authors have no conflicts of interest to report.

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