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Original Article

Holter monitoring demonstrates that ventricular arrhythmias are common in cats with decompensated and compensated hypertrophic cardiomyopathy

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Highlights

- Ventricular arrhythmias occurred at similar frequencies in cats with compensated and decompensated hypertrophic cardiomyopathy (HCM)
- Plasma serum cardiac troponin I (cTnI) concentration did not correlate with the number of ventricular arrhythmias
- Neither the presence or complexity of ventricular arrhythmias was linked to prognosis in cats with HCM

Abstract

Arrhythmias can complicate cardiac disease in cats and are a potential cause of sudden death. The aim of this study was to evaluate the presence and nature of cardiac arrhythmias, and the potential correlation between plasma serum troponin I (cTnI) concentrations and the presence or severity of arrhythmias in cats with decompensated (dHCM) and compensated hypertrophic cardiomyopathy (cHCM). Forty one client-owned cats were studied: 16 with cHCM, 15 with dHCM and 10 healthy control cats. Physical examination, echocardiography, cTnI and 24-h Holter recordings were obtained in all cats and thoracic radiographs in cats with dHCM. Cats in both HCM groups were followed for 1 year after their initial Holter examination.

The median (range) number of ventricular premature complexes (VPCs) over 24 h was 867 (1-35,160) in cats with dHCM, 431 (0-18,919) in cats with cHCM and 2 (0-13) in healthy control cats. The median number of episodes of ventricular tachycardia (VTach) was 0 (0-1,497) in dHCM and 0.5 (0-91) in cats with cHCM. The number of VPCs, VTach episodes and heart rate was not different between the HCM groups. Plasma serum troponin I was highest in the cats with dHCM, but there was no correlation between cTnI concentration and the number of arrhythmias. Thirteen of 31 cats with HCM died, but an association with the presence and complexity of ventricular arrhythmias was not observed. Compared to healthy cats, ventricular arrhythmias were common in cats with cHCM and dHCM, but neither presence nor complexity of arrhythmias could be linked to prognosis.

Keywords: Arrhythmias; Cardiac troponin I; Holter

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in cats. It is characterized by primary concentric hypertrophy of the left ventricle (LV), myofiber disarray, myocardial replacement or interstitial fibrosis, and intramural coronary artery narrowing (Schober et al., 2003; Biasato et al., 2015; Khor et al., 2015). The pathophysiology of HCM is complex, with morphological and functional myocardial changes that can include LV diastolic dysfunction, LV outflow tract obstruction, left atrial enlargement and dysfunction (Christiaans et al., 2010; Schober and Todd, 2010; Schober et al., 2013). The clinical presentation and natural history of HCM reflect the morphologic and functional variability that characterize the disease, with some affected cats remaining compensated for many years, while others experience episodes of congestive heart failure (CHF), aortic thromboembolism (ATE), syncope and sudden cardiac death (SCD; Payne et al., 2013).

In young people with HCM, tachyarrhythmia is a known cause of SCD (Maron and Maron, 2013). A Holter monitoring study in human patients with HCM (both symptomatic and asymptomatic) reported a high prevalence of ventricular premature complexes (VPCs), and a moderate prevalence of ventricular (VTach) and supraventricular tachycardia (SVT; Adabag et al., 2005).

Sudden cardiac death also occurs in cats with HCM (Payne et al., 2013; Granstrom et al., 2015; Maron and Fox, 2015), although the pathogenesis of SCD in cats is not well defined. Recent studies suggest that cats with compensated HCM (cHCM) have more frequent ventricular and supraventricular arrhythmias than healthy cats (Jackson et al., 2014; Hanas et al., 2017)

The primary aim of this study was to evaluate heart rate and the number and complexity of arrhythmias in cats with HCM using 24 h Holter monitoring, and to compare

the results among cats with decompensated HCM (dHCM), compensated HCM (cHCM) and healthy control cats. We hypothesized that cats with dHCM would have a higher frequency and complexity of arrhythmias compared to cats with cHCM and to healthy cats

Material and methods

Animals and echocardiographic examinations

Client-owned cats presented to the Cardiology Division of the Veterinary Teaching Hospital of the University of Zurich were enrolled if they met the entry criteria described below. The study was approved by the State Veterinary Office of Zurich (Application number ZH 154/16; approved 21 July, 2016).

Decompensated cats were presented to the hospital for dyspnea caused by cardiogenic pulmonary edema or pleural effusion, confirmed by thoracic radiography or echocardiography; compensated cats were presented for evaluation of heart murmurs, abnormal transient heart sounds, or suspicion of arrhythmia. Cats considered too clinically unstable to permit all of the required examinations, including placing a Holter monitor within 24 h of admission, were excluded from the study. Cats with systolic blood pressure ≥160 mmHg (obtained by Doppler; Ultrasonic Doppler flow detector, Parks Medical Electronics) or a total serum thyroxin concentration (T_4) > 3.5 ug/dL were also excluded, as were cats whose owners declined informed consent for the study.

Transthoracic echocardiographic examinations were performed (GE Vivid 7 Dimension, General Electric Medical Systems, or Philips Epiq 7, Philips Health Care) with phased-array transducers at frequencies of 7-12 MHz. Two-dimensional and motion mode images were acquired in standard imaging planes. For measurements of cardiac dimensions,

the leading edge to leading edge method was used (Payne et al., 2013). Left ventricular (LV) hypertrophy was defined as segmental or generalized end-diastolic LV posterior wall (LVPWd) or interventricular septum (IVSd) thickness > 5.5 mm, measured in 2-dimensional or motion mode from the right parasternal short or long-axis views. The maximum left atrial diameter (LAD) and the left atrial fractional shortening (LA-FS%) were measured in the cranial to caudal direction from a right parasternal short-axis view (Payne et al., 2015). For each parameter, the average of three measurements was calculated. A control group of 10 cats was recruited from clinically healthy cats owned by hospital employees, students and local cat breeders. The following criteria were set for control cats: (1) be older than 1 year; (2) no abnormalities detected on a physical exam; (3) systolic blood pressure <160 mmHg; (4) euthyroid (total T_4 < 3.5 mg/dL if >7 years old); (5) normal echocardiogram (maximal LVPWd and IVSd <5.0 mm on 2-D and M- mode images and LAD <16 mm in the 2-D right parasternal long-axis 4 chamber view). All echocardiographic measurements were reviewed by one observer (UB).

Cardiac troponin I

Serum concentration of cardiac troponin I (cTnI) was measured with a dedicated point-of-care analyser (Abbott iStat Portable Clinical Analyzer) within the first 24 h after admission. Normal serum cTnI concentration measured with this device is <0.16ng/mL (Sleeper et al., 2001).

Holter monitoring

All Holter (Sentinel, Analyze and Pathfinder Software) recordings were performed at the clinic. All dyspneic cats received routine treatment for heart failure (furosemide), and a narcotic sedative (butorphanol, 0.2mg/kg IV) before the Holter monitor was placed. In

addition, some cats received a standard (18.75mg) oral dose of clopidogrel while hospitalized. Holter recordings were placed after stabilization, but not later than 24 h after admission. Compensated cats did not receive any drugs during hospitalization, but one cat had been treated with atenolol at the time of presentation. Holter monitoring was accomplished by attaching three electrodes to the thoracic skin at the level of the heart, two on the left and one on the right hemithorax. A light wrap was placed over the electrodes, and the recording device was located next to the cat. Because the automated Holter monitoring software did not properly determine the heart rate and did not recognize all abnormal complexes, all recordings were reviewed manually by one author (UB) to avoid incorrect interpretation, as described previously (Jackson et al., 2014; Hanas et al., 2017). Mean heart rates were determined manually by counting heart rate every hour, using the first 10 s of every hour. All arrhythmias were assessed. Tachyarrhythmias were evaluated and categorized semi-quantitatively as follows:

- Four or more consecutive VPCs at of an instantaneous heart rate during ventricular ectopy >180 bpm were classified as VTach;
- If the duration of VTach was < 30 seconds, it was classified as non-sustained VTach (Santilli and Perego, 2009).
- Four or more consecutive supraventricular premature complexes (SPCs) were classified as SVT.

Additionally, the complexity of ventricular arrhythmia was categorized using the following scale:

- no arrhythmias
- single VPCs
- complex ventricular ectopy: couplets, triplets or VTach

Survival analysis

Cats were followed for 12 months following the Holter examination, or until their death. Date of death, whether the cat died naturally or was euthanased, and whether death was related to cardiac disease (CHF, ATE, SCD) or a non-cardiac cause was recorded. Death from congestive heart failure was defined as dying with dyspnea, crackles, cyanosis, with fluid pouring out of the mouth, or euthanasia because of intractable clinical signs despite medication for CHF. Death from ATE was defined as death or euthanasia following a clinical episode of ATE. Sudden cardiac death was defined as being found dead without an obvious cause at home, or as a witnessed event described by the owner in which a cat that had been apparently well in the preceding 24 h died suddenly (Payne et al., 2015). No attempt was made to standardize the treatment of cats once they left the hospital; all of the clinically sick cats continued to receive furosemide and clopidogrel; 10/15 also received benazepril (0.5 mg/kg q24h). In the cHCM group, 4/16 received clopidogrel; no other cardiac medications were administered in this group. Cats in the control group did not receive any type of medication.

Statistical analysis

Statistical analyses were performed by standard computer statistical software (SPSS IBM). Data distribution was tested for normality by the Shapiro- Wilk test, and for comparisons of parameters that were non-normally distributed, non-parametric tests were used. Groups (cHCM, dHCM and normal) were compared using the Kruskal Wallis one-way analysis of variance, and if significant, by pairwise comparison using Mann–Whitney *U* tests in cases of non-normal data distribution. For normally distributed data, a one-way analysis of variance was performed and, if significant, groups were compared by by *t*-tests. All echo data were normally distributed and thus calculated parametrically; all other data non-

parametrically. Nominal scale variables were analyzed with Chi-Square tests. Spearman's rank correlation coefficient was calculated to evaluate an association between the number of VPCs and cTnI. For the survival analysis, Kaplan-Meier curves were generated using a composite end-point of all cardiac-related deaths (CHF, ATE, SCD); cats that were alive at the end of 1 year and those that died of non-cardiac causes were censored at the date of their last known status. Differences between groups were analyzed by the log-rank test. Data are presented as median and range, and a P value <0.05 was considered significant for between group comparisons.

Results

Forty-one privately owned cats were included in the study. Of these, 16 cats had cHCM, 15 had dHCM, and 10 were healthy control cats. Seven breeds were represented, of which the most common were European Shorthair (n= 26), Maine Coon (n= 5), and British Shorthair (n = 5). There were also two Bengals, and one each European Longhair, Birma, and Sphinx. All cats were spayed or castrated. Age, weight and sex of the cats are listed in Table 1.

Left ventricular diastolic wall thickness (P = 0.228), and interventricular diastolic thickness (P = 0.132) were not different between cats with cHCM and those with dHCM, and differences in LAD (P = 0.055) and LA-FS% (P = 0.054) did not quite achieve statistical significance. All of these echo parameters were different between cats with HCM and control cats (Table 1).

Heart rate was higher in all three groups during the first hour after Holter device placement (P <0.001 in both HCM groups; P = 0.02 in the control group), independent of the

time of the day that the monitor was placed, decreasing thereafter in all groups. Mean 24 h heart rate in cats with dHCM compared to cats with cHCM was not statistically different (P = 0.053), but was higher in each HCM group than in the control group (dHCM and cHCM vs. control, P = 0.003 and 0.013, respectively).

Thirty-eight of 41 cats studied had at least one VPC on Holter monitoring, including all cats in the dHCM group, 15/16 in the cHCM group and 8/10 control cats. The number of VPCs (P = 0.217) and of VTach episodes (P = 0.332) was not different between cats with dHCM and cats with cHCM, but was higher in both HCM groups compared to control cats (P <0.01; Table 2).

The complexity grade of the ventricular arrhythmias in cats with dHCM was categorized as complex ventricular ectopy in 11/15, and as single VPCs in 4/15 cases. Cats with cHCM were classified based on the complexity grade of ventricular arrhythmias as complex ventricular ectopy in 12/16 cats, single VPCs in 3/16 cats, and no VPCs in one case. None of the cats had sustained VTach and none had R-on-T. There was no difference between cats with cHCM and cats with dHCM regarding the complexity of their ventricular arrhythmias (P = 0.291). Control cats had either no arrhythmias (n=2) or only single VPCs (n=8); thus, none had complex arrhythmias.

Only a few cats with dHCM and cHCM had SPCs and SVTs (Table 2). In addition, two cats with dHCM had atrial fibrillation, and one cat with cHCM had a complete atrioventricular block without any VPCs or SPCs.

Within 1 year of their entry into the study, 16/31 cats (51%) with HCM had died; this was comprised of 10/15 (67%) cats with dHCM and 6/16 (38%) cats with cHCM. Nine of the 10 cats with dHCM died or were euthanased because of their heart disease (CHF, *n*=5; ATE, *n*=2; SCD, *n*=2), and 4/6 cats with cHCM died or were euthanased because of heart disease (CHF, *n*=2; SCD, *n*=2). The occurrence of cardiogenic deaths was not different between cats with dHCM and cats with cHCM ($P = 0.088$; Fig. 1). Reasons for non-cardiac death included lymphoma, splenic tumor and chronic kidney disease (*n*=1 each). All control cats were alive at 12 months.

Of the 16 cats with cHCM, eight had VTach; of these one died suddenly and 5/8 were still alive one year later. In the dHCM group, VTach was detected in 6/15 cats; one of these died suddenly, but only 1/6 (17%) was still alive 1 year later. The cat with largest number of VTach episodes and the longest episode had dHCM was euthanased because of CHF during the course of the study.

Both cats with dHCM that died suddenly had atrial fibrillation and complex ventricular arrhythmias. The two cats with cHCM that died suddenly did not have any supraventricular arrhythmias on their Holter study, but both of them showed complex ventricular arrhythmias. Neither the number of VPCs (3,087 and 867 VPCs for each cat, respectively) or the number of VTach episodes (0 and 2 VTach episodes for each cat, respectively) of the cats that died suddenly appeared to be different from the surviving cats with HCM; however, the number of cats was too small to test statistically.

The plasma cTnI concentration was higher in cats with dHCM than in those with cHCM ($P = 0.004$; Table 1). In the cats that died of cardiogenic causes at 1 year, cTnI

averaged 0.27 (0.01-1.16) ng/mL, compared to an average of 0.05 (0-1.13) ng/mL in all cats with HCM that were still alive at one year ($P = 0.34$). Of the four cats that died suddenly, cTnI levels were 0.01 and 0.02 ng/mL in those with cHCM, and 0.40 and 0.68 ng/mL in cats with dHCM, respectively. The number of VPCs was not significantly correlated with the plasma cTnI concentration ($r = 0.07$).

Discussion

This study compared 24 h ECGs in cats with dHCM and cHCM, with a year of clinical follow-up to permit meaningful outcome comparisons between HCM subgroups. Surprisingly, cats with cHCM had as many VPCs and VTach episodes as those with dHCM. The observed survival difference between these HCM subgroups was similar to that reported consistently in other studies (Payne et al., 2010; Payne et al., 2013; Payne et al., 2015), suggesting that while ventricular arrhythmias are a common and potentially important complication of HCM, they might not be the primary determinant of survival in most cats.

Examination of our data and methods reveals both potential limitations in interpreting our findings and potential reasons for our findings. Although a power analysis performed before the start of the study suggested that 15 cats in each group would be adequate to identify clinically important differences in the frequency of arrhythmia between groups, variability in the numbers of VPCs within each group was larger than anticipated, reducing the power of the study and calling into question the negative between-group comparisons. Despite the concern that the study had insufficient power to identify potentially important group differences, we believe that the descriptive findings alone make a meaningful contribution to the current body of knowledge regarding cats with HCM.

Non-sustained VTach was common in cats with both cHCM and dHCM. However, we failed to document an association between the number and length of VTach and the occurrence of cardiac-related death, or SCD. Looking specifically at the four cats that died suddenly, the two cats with dHCM had atrial fibrillation in addition to ventricular arrhythmias, but only one had VTach. These two cats had some of the biggest LAD. In people, atrial fibrillation is considered an additional risk factor for SCD (Hecht et al., 1993; Christiaans et al., 2010; Stroumpoulis et al., 2010; Chen, 2013; Chen et al., 2014; Eisen et al., 2016; Weissler-Snir et al., 2016). The two cats with cHCM that died suddenly did not have observed supraventricular arrhythmias, and only one of them had VTach. Thus, this study implies that presence of arrhythmias on a Holter ECG is not a good predictor of death in cats with HCM. However, only a small number of cats died suddenly during the study, and additional work is needed to improve the power of this statement.

All cats had higher heart rates in the first hour after Holter placement, unrelated to the time of the day. This first hour effect has previously been reported in other canine and feline studies (Jackson et al., 2014; Gelzer et al., 2015), and is likely caused by increased sympathetic tone due to stress (manipulation, hair clipping etc.). Additionally, for the entire recording time, the median heart rate in the different groups was relatively high, and we could not document any correlation between heart rate and time of the day. Lower heart rates at night is common in people and dogs, cats and horses (Ware, 1999; Hanas et al., 2009). The relatively high heart rates in our study suggest that the cats could have been stressed by the hospital environment, echoing the findings of previous study (Abbott, 2005). Since elevated sympathetic tone could trigger ventricular arrhythmia, it is possible that the sick cats in our study would have had fewer arrhythmias in a home environment.

In a recent feline study of HCM, elevated cTnI was an important predictor of cardiac death, independent of heart failure or left atrial dilation (Payne et al., 2010; Borgeat et al., 2014). In our study, there was also a marked difference in cTnI between cats that died of cardiogenic causes within 1 year and those that were still alive 1 year after entering the study. Nevertheless, caution should be exercised if a single cTnI value is used as a prognostic tool in cats with an HCM phenotype, in part because an important subgroup might have only transient myocardial thickening, and cTnI may be elevated in some of these cats (Novo Matos et al., 2018).

There are several limitations of our study that could have biased the results. The number of cats per group was small, which does not allow reliable conclusions regarding SCD. Additionally, for ethical reasons, we did not record Holter-ECGs in cats with more than mild respiratory distress; therefore, not all of our feline patients had the Holter examination at the same time point after presentation. However, Holter recording that commenced 24 h after admission was an exclusion criterion. Unstable cats were also excluded and these could have had more severe arrhythmias. The suspicion of an arrhythmia was the reason for referral of one cat with cHCM, which could have biased our study group towards more frequent arrhythmias. Before performing the Holter recordings or echocardiographic examinations all cats with dHCM received mild sedation and furosemide as part of heart failure treatment and one cat with cHCM had been receiving atenolol. These treatments could have influenced heart rhythm, heart rate, quantity and complexity of arrhythmias, and echocardiographic measurements. Finally, control cats were younger than the cats with cHCM, and arrhythmias more likely to occur in older cats; however, arrhythmias are rare also in older cats (Hanas et al., 2009).

In conclusion, in the present study ventricular ectopy was common in cats with both dHCM and cHCM, but the number of ventricular arrhythmias was not different between HCM groups. The study failed to demonstrate quantity and complexity of ventricular arrhythmias as a risk factor for SCD or other causes of cardiac death in cats with HCM, but the number of cats that died suddenly during the study was small.

Conflict of interest statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. None of the authors of this paper have a financial or personal relationship with people or organisations that could inappropriately influence or bias the content of the paper.

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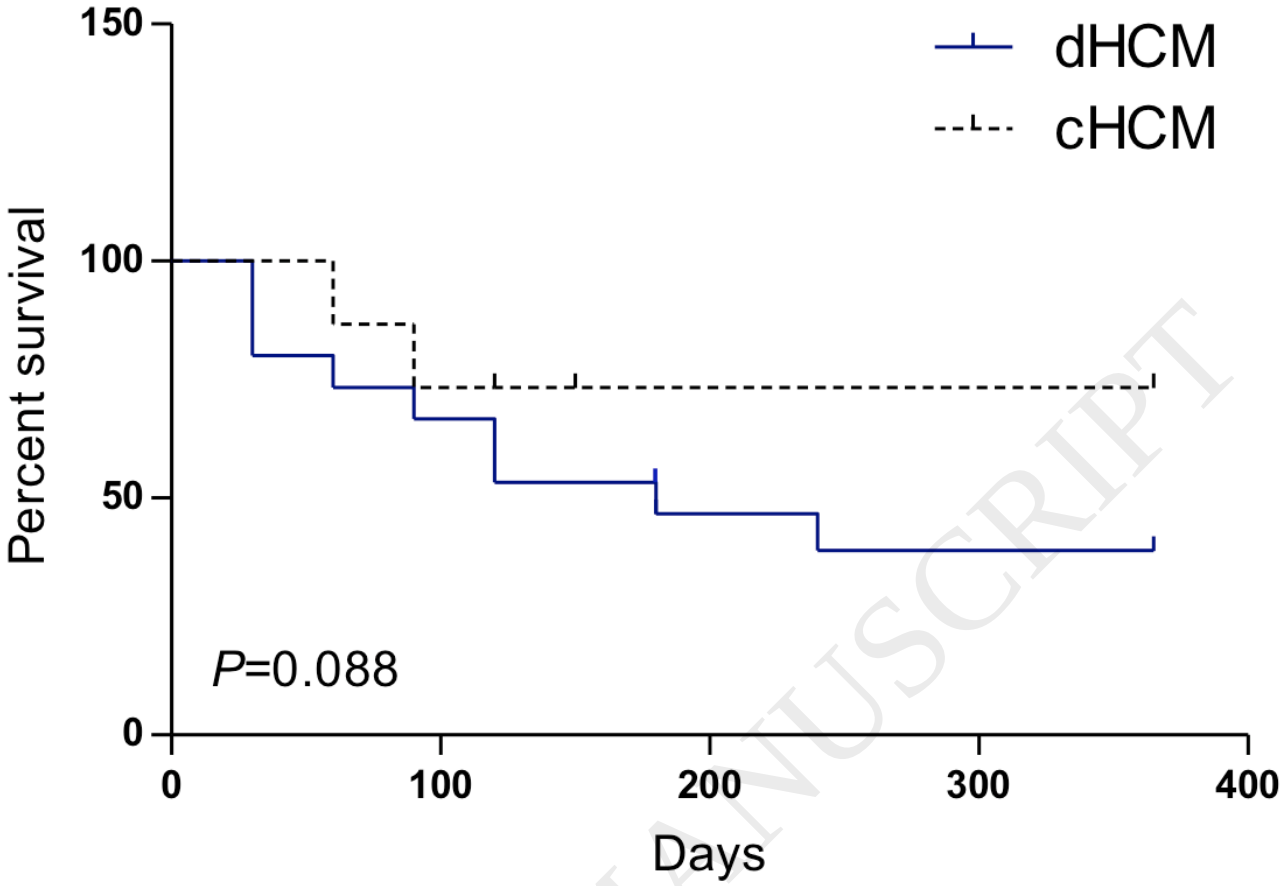

Figure legend

Fig. 1. Kaplan-Meier survival plot in cats with decompensated (dHCM) and compensated HCM (cHCM). The survival difference between the groups was not statistically significant (*P* = 0.088)

Weissler-Snir, A., Adler, A., Williams, L., Gruner, C., Rakowski, H., 2016. Prevention of sudden death in hypertrophic cardiomyopathy: bridging the gaps in knowledge. European Heart Journal, pii:ehw268. Table 1.

Signalment, cardiac Troponin I and selective echocardiography parameters in cats with hypertrophic cardiomyopathy and control cats

	Unit	dHCM *n*=15	cHCM *n*=16	Control cats *n*=10	*P* dHCM vs. cHCM	*P* dHCM vs. Control cats	*P* cHCM vs. Control cats
Sex	F:M	4 : 11	4 : 12	5 : 5	ns	ns	ns
Age	years	6 (1-14.5)	9.5 (1.5-16.5)	4.25 (1-7.5)	0.147	0.115	0.006
Weight	kg	5.2 (3.2-9.5)	4.8 (3.5-7.3)	5.1 (3.7-6.5)	ns	ns	ns
cTnI	ng/mL	0.29 (0.0-1.16)	0.05 (0.0-0.38)	All 0.00	0.004	0.001	0.018
IVSd	mm	6.4 + 1.1	5.8 + 1.0	4.3 + 0.2	0.132	<0.0001	<0.001
LVPWd	mm	6.8 + 1.4	6.3 + 1.4	4.4 + 0.2	0.228	<0.0001	<0.001
LAD	mm	22.1 + 4.8	18.2 + 3.0	14.7 + 0.8	0.055	<0.0001	0.002
LA-FS	%	13.4 + 6.7	18.5 + 7.3	25.5 + 1.6	0.054	<0.0001	0.008

dHCM, cHCM decompensated, compensated HCM; IVSd, LVWd, interventricular septum, left ventricular posterior wall diameter in diastole; LAD, left atrial diameter in the two-dimensional long axis view; LA-FS, left atrial fractional shortening;
F:M, Female:Male ratio; all other numeric data are given as median (range), respectively as mean + SD; ns, not significant.

Table 2.
Holter findings in cats with HCM and control cats

	Unit	dHCM *n*=15	cHCM *n*=16	Control cats *n*=10	*P* dHCM vs cHCM	*P* dHCM vs Control cats	*P* cHCM vs Control cats
HR	bpm	201 (136-253)[a]	183 (131-203) [a]	158 (114-190) [a]	0.053	0.003	0.013
HR first hour	bpm	255 (174-324) [a]	222 (150-270) [a]	216 (170-228) [a]	0.015	0.001	0.033
VPC	number	867 (1-35‘160) [a]	431 (0-18‘919) [a]	2 (0-13) [a]	0.217	0.0069	0.0035
VTach	episodes	0 (0-1497) [a]	0.5 (0-91) [a]	0	0.332	na	na
VTach	episodes	(*n*=6) 2 (1-1,497) [b]	(*n*=8) 11.5 (1-91) [b]	0	0.291	na	na
Longest VTach	VPCs	11 (4-74)	8 (4-41)	na	na	na	na
SPC	number	(*n*=2) 12,498; 28,568 [c]	(*n*=2) 357; 1603 [c]	0	na	na	na
SVT	episodes	(*n*=2) 135, 1075 [c]	(*n*=2) 1, 1 [c]	0	na	na	na
Duration SVT	SPCs	505, 1409	16, 1602	na	na	na	na
Additional events		AFib (*n*=2)	Complete AVB (*n*=1)	0	na	na	na

dHCM, cHCM, decompensated, compensated HCM; HR, heart rate; bpm, beats per minute; VPC, SPC, ventricular, supraventricular premature complex; VTach, ventricular tachycardia; SVT, supraventricular tachycardia; AFib, atrial fibrillation; AVB, atrioventricular block; na, not applicable.

[a] Data are shown as median (range) of all cats in the group

[b] Number of cats in which the abnormality was identified

[c] Number of events in the individual cats with the abnormality