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Original article

Short-term heart rate variability in dogs with sick sinus syndrome or chronic mitral valve disease as compared to healthy controls

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Abstract

Heart rate variability is an established risk factor for mortality in both healthy dogs and animals with heart failure. The aim of this study was to compare short-term heart rate variability (ST-HRV) parameters from 60-min electrocardiograms in dogs with sick sinus syndrome (SSS, n=20) or chronic mitral valve disease (CMVD, n=20) and healthy controls (n=50), and to verify the clinical application of ST-HRV analysis. The study groups differed significantly in terms of both time – and frequency-domain ST-HRV parameters. In the case of dogs with SSS and healthy controls, particularly evident differences pertained to HRV parameters linked directly to the variability of R-R intervals. Lower values of standard deviation of all R-R intervals (SDNN), standard deviation of the averaged R-R intervals for all 5-min segments (SDANN), mean of the standard deviations of all R-R intervals for all 5-min segments (SDNNI) and percentage of successive R-R intervals >50 ms (pNN50) corresponded to a decrease in parasympathetic regulation of heart rate in dogs with CMVD. These findings imply that ST-HRV may be useful for the identification of dogs with SSS and for detection of dysautonomia in animals with CMVD.

Key words: conduction disorders, dysautonomia, electrocardiography, heart rate variability, Holter electrocardiography

Introduction

The phenomenon of heart rate variability has been known for a long time. Already in 1847, Ludwig demonstrated that heart rate variability of healthy humans changes during inspiration and expiration, and in 1978, an association was documented between a decrease in circadian heart rate variability (HRV) and mortality risk after myocardial infarct (Wolf et al. 1978). Since implementation of computer-aided HRV analysis, it became a relatively simple and non-invasive test to examine autonomic function of the heart. Canine HRV, obtained during 24-h Holter electrocardiography, has been analyzed in both clinical and

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experimental settings, inter alia in dogs with mitral valve endocardiosis, tachycardiomyopathy and diabetes mellitus (Piccirillo et al. 2009, Oliveira et al. 2012, Pirintr et al. 2012, Rasmussen et al. 2012, Chompoosan et al. 2014). However, analysis of HRV from 24-h electrocardiograms is challenging due to the long time of recording, unstable conditions of registration and the large number of artifacts. Therefore, standards for short-term HRV analysis have been developed both in humans and dogs (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996, Bogucki and Noszczyk-Nowak 2015). Many previous studies confirmed the usefulness of short-term HRV (ST-HRV) in humans. According to Voss et al. (2013), the results recorded during the first 30 min of HRV analysis have nearly the same classification power (81% accuracy) as the optimal 24-h parameter set in ischemic heart failure patients. However, neither the diagnostic value of ST-HRV analysis nor its application in veterinary patients with heart diseases have been established to date. The issue is important, since some therapeutic agents used in veterinary cardiology, including medications for chronic mitral valve disease (CMVD), may alter sympathetic tone, which is also reflected by changes in HRV parameters. This implies that HRV may soon become a therapeutic target in canine cardiology (Chompoosan et al. 2014).

The aim of this study was to compare ST-HRV parameters from 60-min electrocardiograms of dogs with sick sinus syndrome (SSS) or CMVD and healthy controls, and to verify clinical application of ST-HRV analysis.

Materials and Methods

The study included 40 dogs of various breeds, age and sex (Table 1), among them 20 animals with SSS and 20 with advanced CMVD (stage Cc according to ACVIM). Their results were compared with previously published data of 50 healthy dogs (Bogucki and Noszczyk-Nowak 2015). The dogs from the study groups did not receive any medication, both prior to the diagnosis of SSS/CMVD and before Holter electrocardiography.

SSS was diagnosed on the basis of clinical examination (presence of bradycardia), complete blood count and biochemical testing of the blood (to exclude hypothyroidism, electrolyte disorders, renal and liver failure, i.e. conditions with a potential effect on heart rate), echocardiography (to exclude other heart diseases), resting electrocardiography and 24-h Holter electrocardiography (presence of bradycardia below 40 bpm, numerous R-R pauses longer than 3.2 seconds and cardiac conduction defects: sinoatrial block, 1st or 2nd degree atrioventricular block) (Noszczyk-Nowak et al. 2009). CMVD was diagnosed based on clinical findings (systolic murmur and signs of heart failure), complete blood count and biochemistry (to exclude hypothyroidism, electrolyte disorders, renal and liver failure), echocardiography (degenerative changes of mitral valve resulting in its significant insufficiency, enlargement of cardiac chambers) and resting electrocardiography.

Complete blood count was determined using as Animal Blood Center abc VET analyzer, and biochemical tests of the blood were conducted using a MaxMat Pl analyzer. Echocardiographic examination was performed with ALOKA 4000+ or HITACH ALOKA 37F ultrasonograph with 5-7.5 MHz sector probes. Ejection fraction (EF), shortening fraction (SF), left ventricular end-diastolic and end-systolic internal diameters (LVIDd and LVIDs), interventricular septal diameters at diastole and systole (IVSd and IVSs) and left ventricular end-diastolic and end-systolic posterior wall diameters (LVPWd and LVPWs) were calculated from standard transthoracic projections. Electrocardiographic recordings were obtained in a right-lateral recumbent position, with BTL SD08 electrocardiograph equipped with filters for power line interference and muscle noise. 3-h Holter electrocardiograms were obtained using an Aspel 702 recorder in a quiet and darkened room, and HRV analysis was the conducted using a HolCard computer module as described previously by Bogucki and Noszczyk-Nowak (2015). HRV parameters of both study groups: mean R-R interval over the analyzed time period, number of QRS complexes (#QRS), standard deviation of all R-R intervals (SDNN), standard deviation of the averaged R-R intervals for all 5-min segments (SDANN), mean of the standard deviations of all R-R intervals for all 5-min segments (SDNNI), percentage of successive R-R intervals >50 ms (pNN50), root-mean-square of successive R-R interval difference (rMSSD), total spectral power of all R-R intervals in 5-min segments (TP), its high frequency (HF), low frequency (LF) and very low frequency (VLF) components and LF/HF ratio, were expressed as mean values and their standard deviations, and compared with previously determined values for healthy dogs.

Statistical analysis of the results was conducted using a Statistica 12.5 package (StatSoft, Poland). The significance of intergroup differences was verified with ANOVA.

Table 1. Clinical characteristics of the study group.

Parameter	Healthy dogs[1]	SSS group	CMVD group
Age (years)	4.86 ± 2.74*	8.91 ± 3.14*	6.65 ± 3.21
Body weight (kg)	12.20 ± 3,88	15.56 ± 6.21	13.21 ± 7.67
Males	15 (30%)	6 (30%)	8 (40%)
Urea (mg/dl)	45.9 ± 14.4***	55.7 ± 18.4	78.6 ± 20.1***
ALT (U/l)	50.1 ± 12.4***	56.22 ± 7.98	87.56 ± 17.98***
Ejection fraction (%)	69.21 ± 7.07	67.11 ± 6.54	73.11 ± 10.21
Shortening fraction (%)	37.84 ± 5.91	35.84 ± 4.67	41.31 ± 9.11
LA/Ao	1.27 ± 0.15***	1.36 ± 0.2**	1.98 ± 0.31**,***
LVIDd (cm)	2.86 ± 0.36**	3.34 ± 0.86	3.76 ± 0.96**
P time (ms)	36.81 ± 2.73***	39.41 ± 2.11	47.34 ± 3.86***
P amp (mV)	0.14 ± 0.03	0.15 ± 0.02	0.14 ± 0.03
PQ (ms)	84.88 ± 12.59*	119.11 ± 10.65*,**	89.78 ± 17.21**
R amp (mV)	1.12 ± 0.34	1.12 ± 0.34	1.12 ± 0.34
QRS (ms)	53.96 ± 3.66	58.36 ± 4.88	61.29 ± 4.31
QT (ms)	229.18 ± 31.27	289.87 ± 51.34	267.68 ± 42.11
HR	122.43 ± 29.61*	59.2 ± 4.3*,**	106.9 ± 24.76**
#QRS	5345.03 ± 1105.11*	3552.09 ± 200.99*,**	6416 ± 1486.81**
mean NN	677.68 ± 126.89*	1004.2 ± 64.95*,**	655.25 ± 85.33**
SDNN (ms)	208.86 ± 77.1*,***	378.16 ± 40.43*,**	138.2 ± 56.23**,***
SDANN (ms)	70.75 ± 30.9*,***	125.5 ± 58,69*,**	54.33 ± 25.7**,***
SDNNI (ms)	190.75 ± 76.12*,***	341.4 ± 56.69*,**	117.32 ± 70.5**,***
rMSSD (ms)	259 ± 120.17*	534.1 ± 87.55*	172.66 ± 116.68
pNN50 (%)	71.84 ± 13.96*,***	85.68 ± 8.12*,**	51.56 ± 32.5**,***
TP (ms^2)	11065.31 ± 3866.87*,***	19072.33 ± 2577.33*,**	7113.11 ± 4210.67**,***
HF (ms^2)	5845.45 ± 2914.20*,***	11106.16 ± 2528.95*,**	2920.32 ± 1986.19**,***
LF (ms^2)	1501.24 ± 736.32*	2769.83 ± 924.36*,**	1024.67 ± 551.07**
VLF (ms^2)	984.96 ± 327.7*	1678.5 ± 482.78*,**	798.24 ± 299.11**
LF/HF	0.28 ± 0.11***	0.25 ± 0.11**	0.4 ± 0.13**,***

LVIDd – left ventricular end-diastolic internal diameter, LVIDs – left ventricular end-systolic internal diameter, IVSd – intraventricular septal diameter in diastole, LVPWd – left ventricular end-diastolic posterior wall diameter, IVSs – intraventricular septal diameter in systole, LVPWs – left ventricular end-systolic posterior wall diameter, HR – heart rate, #QRS – mean number of QRS complexes, SDNN – standard deviation of all R-R intervals, SDNNI (ms) – mean of the standard deviations of all R-R intervals for all 5-min segments, SDANN (ms) – standard deviation of the averaged R-R intervals for all 5-min segments, rMSSD (ms) – root-mean-square of successive R-R interval difference, pNN_{50} (%) -percentage of successive R-R intervals >50 ms, TP – total power, HF – high frequency component, LF – low frequency component, VLF – very low frequency component.

[1] As published by Bogucki and Noszczyk-Nowak (2015).

Asterisks denote statistically significant intergroup differences.

Results

Analyzed groups of dogs did not differ significantly in terms of their body weight and sex distributions. However, statistically significant differences in age were found between healthy controls and dogs with SSS. All parameters of complete blood count, electrolyte concentrations, thyroid hormone, creatinine and AST levels were within their reference ranges and did not differ significantly between the study groups. The only statistically significant differences were found for urea concentration and ALT activity in healthy controls and dogs with CMVD. Furthermore, a number of statistically significant intergroup differences in electrocardiographic and echocardiographic parameters were observed (Table 1).

Moreover, the study groups differed significantly in terms of their ST-HRV parameters (Table 1). Visual observation of normal R-R distribution histograms (time-domain bar graphs) over a 60-min examination period revealed a distinct pattern of intergroup differences (Fig. 1).

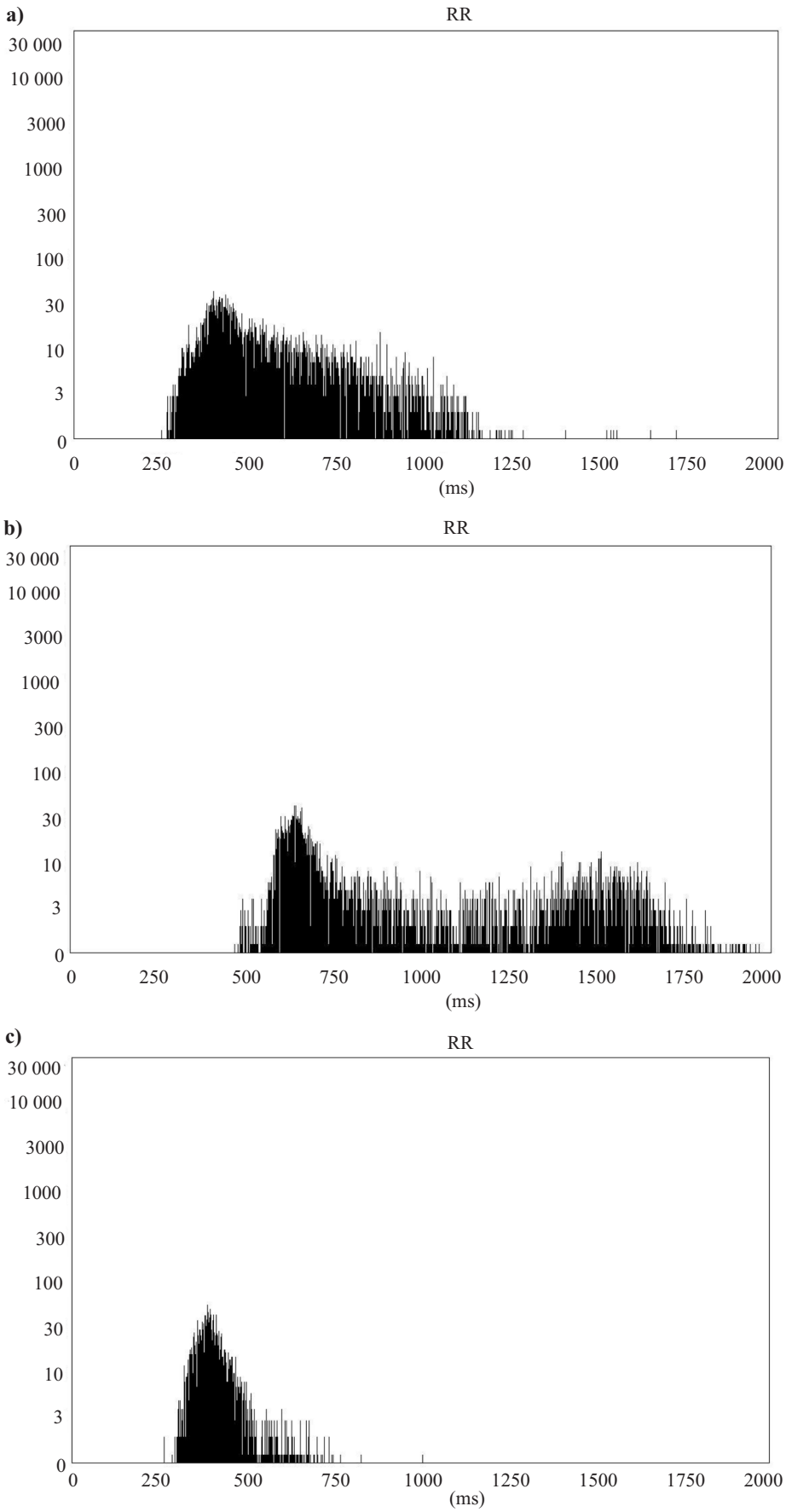

Fig. 1. Normal R-R distribution histograms (time-domain graphs) obtained from short-term Holter electrocardiograms of healthy controls, (a) dogs with sick sinus syndrome (b) and chronic mitral valve disease (c).

Discussion

CMVD is listed among the most common diseases of the canine heart. This condition is diagnosed predominantly in small and miniature dog breeds. The prevalence of SSS is the highest also in the same group of patients (small and miniature dogs older than 8 years) (Ward et al. 2016). The intergroup differences in the results of adjunct tests reflected the type of underlying condition. SSS is usually diagnosed in older dogs (Nakao et al. 2012, Ward et al. 2016). In many cases, dysfunction of the sinus node (bradycardia) co-exists with conduction disorders in the atrioventricular node, which explains lower HR and longer PQ intervals found in this group of patients. CMVD is associated with left atrial enlargement and frequently also with dilation of the left ventricle. Larger dimension of the atrium is reflected by longer P wave.

HRV analysis plays an important role in human cardiology whereby it is used both to assess the severity of heart failure and to establish prognosis in patients with this condition (Smilde et al. 2009, Compostella et al. 2014). Both CMVD and SSS are associated with changes in HRV parameters, which may both facilitate the diagnosis and improve the accuracy of prognosis (Nicolin et al. 1994). In the case of dogs, bradycardia or clinically relevant R-R pauses cannot always be detected in a veterinary practice setting, usually due to examination-related stress and random timing of resting electrocardiography. Also the loss of consciousness resulting from conduction disorders or significant bradycardia cannot always be visualized on 24-h Holter electrocardiograms. Conduction disorders associated with SSS are not necessarily equally severe over time, which may explain false positive results obtained during Holter electrocardiography. This results in uncertainty in the diagnosis and delayed treatment (implantation of a pacemaker, pharmacotherapy). ST-HRV analysis demonstrated that dogs with SSS and healthy controls differed significantly in terms of their time- and frequency-domain ST-HRV parameters. The values of all time-domain parameters in SSS patients significantly exceeded their reference limits proposed by Bogucki and Noszczyk-Nowak (2015). This was particularly evident in the case of parameters directly linked to the variability of R-R intervals (SDNN, SDANN), averaged R-R interval and the number of QRS complexes (#QRS). Such a spectrum of HRV abnormalities should raise a suspicion of SSS, even in dogs without clinically relevant bradycardia or conduction disorders in the form of atrioventricular block. Although the values of frequency-domain parameters were also higher in dogs with SSS than in healthy controls, the analyzed groups did not differ in terms of their LF/HF ratios, which remained within the respective reference limit. This implies that SSS is not associated with a disruption of sympathetic-parasympathetic balance. All dogs with sinus node dysfunction require particular attention due to the potential risk of severe conduction disorders or life-threatening R-R pauses. Once the diagnosis of SSS is established on the basis of ST-HRV findings, treatment with positive ionotropes can be implemented early, preventing loss of consciousness and prolonging survival (Ward et al. 2016). Ward et al. demonstrated a significant contribution of increased vagal tone to SSS etiology. Although we did not identify dogs with impaired sympathetic-parasympathetic regulation in our series, such cases can be detected on the basis of ST-HRV analysis. Dogs with increased vagal tone present with higher HF values, as was the case in our SSS patients, but also with abnormal values of LF/HF ratio, not observed in our series. Under physiological conditions, autonomic regulation the of canine heart is predominantly influenced by parasympathetic tone; as a result, healthy dogs present with greater HRV than heart failure patients and their LF/HF ratio is well below one (Oliveira et al. 2012). Although SSS may co-exist with CMVD, it usually manifests as bradycardia-tachycardia syndrome in such cases (Nakao et al. 2012). We did not observe arrhythmia in our series of dogs with CMVD. The differences in ST-HRV parameters of dogs with CMVD reflected an increase in sympathetic and a decrease in parasympathetic regulation of HR; our findings in this matter are consistent with the results published by Oliveira et al. (2012) and Rasmussen et al. (2012) who analyzed HRV from 24-h Holter electrocardiograms. The similarity between our findings and the results of previous studies, especially in terms of the significant decrease in SDNN, SDANN, SDNNI and pNN50 values, corresponding to a lesser parasympathetic input to HR, implies that ST-HRV can be used for evaluation of dysautonomia in dogs with CMVD. Not only did the values of all the parameters mentioned above turn out to be significantly lower than in healthy dogs, but they were also well below their respective reference limits (Oliveira et al. 2012, Rasmussen et al. 2012, Bogucki and Noszczyk-Nowak 2015). The decrease in HF values and a concomitant change in LF/HF ratio corresponded to a decrease of parasympathetic tone. Both the results of experimental studies in rats and clinical observations in humans and dogs imply that HRV parameters may change during pharmacotherapy of heart failure, irrespective of its etiology (Tacoy et al. 2007, Nolan et al. 2008, Sal'nikov 2009, Henze et al. 2013, Chom-

poosan et al. 2014, Dias da Silva et al. 2015). Consequently, ST-HRV parameters may soon be applied as prognostic and predictive markers in dogs treated due to CMVD.

Conclusions

ST-HRV may be useful for the identification of dogs with SSS. Presence of dysautonomia in dogs with CMVD may be evaluated on ST-HRV analysis. SDNN, SDANN, SDNNI and HF turned out to be the most useful ST-HRV parameters in the assessment of dogs with SSS and CMVD.

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