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Original article

Heart rate turbulence in mild-to-moderate aortic stenosis in boxers

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Abstract

Heart rate turbulence (HRT) is a new electrocardiographic parameter used in human medicine to predict the possibility of death in patients with cardiac diseases. There is no information about HRT in healthy dogs and those with cardiac diseases. The aim of the present study was to compare the HRT in healthy Boxers dogs with Boxers with mild and moderate subaortic stenosis (SAS), to disclose the relationship between HRT and specific echocardiographic parameters and to evaluate if HRT can be used as a prognostic value in dogs with aortic stenosis. The study revealed significantly lower values of turbulence onset (TO) and turbulence slope (TS) HRT dogs with SAS (TO = -0.76 ± 2.6, TS = 7.1 ± 3.21) in compared with healthy dogs (TO = -7.45 ± 9.72, TS = 14.33 ± 8.76). TO values correlated with the left ventricular mass (LVM)/body mass factor (r = 0,32; p = 0.048). Based on the results obtained it can be stated that dogs with SAS have a compromised baroreceptor response, which can influence the mortality of the animals with described cardiac defect.

Key words: aortic stenosis, boxer, heart rate turbulence

Introduction

Heart rate turbulence (HRT) is a physiological index introduced and described by Schmidt et al. (1999). HRT effect represents a short term heart rhythm response to premature ventricular complex (VPC). Shortly after VPC an early rhythm acceleration is observed followed by a late deceleration. HRT lasts for 15-20 following cardiac cycles and is quantified by two parameters: turbulence onset (TO) and turbulence slope (TS). HRT evaluation is successfully used in human medicine to identify patients with higher risk of death related to cardiac diseases (Schmidt et al. 1999, Barthel et al. 2003). Large cohort, randomized studies confirmed that a reduction or lack of HRT in patients after a heart infarct is correlated with a higher risk of death in the follow up observation (Barthel et al. 2003, Sade et al. 2003, Berkowitsch et al. 2004). HRT is a very good risk assessment factor also in patients with congestive heart failure (CHF), dilated cardiomyopathy (DCM) and patients with heart hypertrophy related to aortic stenosis (Koyama at al. 2002, Malberg et al. 2003, Arslan et al. 2008).

The literature in the field contains no information on HRT in healthy dogs and its usability as a risk assessment factor of the mortality rate in the animals with cardiac diseases.

The aim of the present study was to compare the heart rate turbulence in healthy dogs (Boxers) with

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Boxers with mild and moderate aortic stenosis, the relationship between HRT and specific echocardiographic parameters and the evaluation of HRT as a prognostic value in Boxers with subaortic stenosis (SAS).

Materials and Methods

Methods

The study was carried out on 15 healthy dogs – Boxers (group I) with single premature ventricular beats (below 100/24h) and 15 adult Boxers with mild to moderate aortic stenosis (group II). Dogs with SAS were not under treatment. The animals were qualified based on the medical history, preliminary clinical examination and morphological and biochemical blood tests (AST, ALT, urea, creatinine, Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-). No anomalies were found. The echocardiography was performed in all of the dogs. Standard transthoracic views were used to obtain left ventricular ejection fraction (EF), left ventricular end-diastolic diameter (LVEDD), left ventricular systolic diameter (LVEDS), intraventricular septal diameter (IVSD) and left ventricular posteriori wall diameter (PWD) in diastole and intraventricular septal diameter (IVSS) and left ventricular posteriori wall diameter (PWS) in systole. Left ventricular mass (LVM) was calculated according to the formula: 1.04 x $[(LVEDD + IVSD + PWD)^3 - LVEDD^3] - 13.6$. The LVM/body mass ratio was calculated. With continuous Doppler, mean and peak gradients between the left ventricle and aorta were assessed. All the dogs had the NT-pro-BNP index assessed as an indicator of the left ventricle overloading. The ECG and 24-hour Holter monitoring was done. The echocardiography examination was performed on the echocardiograph ALOKA 4000+. The probe used for echocardiography was sector type 5MHz. The ECG recording was performed on BTL SD08 unit. The dogs had a right side recumbent position. Morphological blood tests were performed on Animal Blood Center abc VET analyzer. Biochemistry tests were performed on Max-Mat Pl analyzer. The plasma concentration of NT-proBNP was measured at a commercial laboratory center IDEXX. 24-hour Holter monitoring was performed on Aspel 702 and analyzed by computer software HolCard. Before analyzing the data was manually preprocessing. HRT parameters were calculated using an algorithm from software HolCard. TO which is a measure of the expected normal early sinus acceleration after a ventricular premature beat and TS which is a measure of late sinus deceleration after ventricular premature beat constitute a two components of HRT. TO is the percentage difference between the heart rate immediately following VPC and the heart rate immediately preceding VPC. It is calculated using the equation: TO = ((RR1 + RR2) – (RR-2 + RR-1)) / (RR-2 + RR-1) *100%; with RR-2 and RR-1 being the first two normal intervals preceding the VPC and RR1 and RR2 the first two normal intervals following the VPC. TS corresponds to the steepest slope of the linear regression line for each sequence of five consecutive normal intervals in the local tachogram.

Reference population

The control group enrolled 15 dogs (9 males and 6 females), aged from 2 to 11 years, weighing between 25 and 41 kg. All the dogs did not show abnormalities in the clinical and blood examination, ECG and echocardiography. The NT-proBNP concentration was from 152 to 902 pmol/l. In the Holter monitoring less than 100 VPC during 24 hours were recorded. During the observation period (24-month follow up) 1 dog died due to abdominal torsion.

The SAS group enrolled 12 males and 3 females, aged from 1 to 9 years, weighing between 26 and 31 kg. All the dogs in this group had heart murmurs in the clinical examination (level of 1 to 3) and clinical sings of heart failure (Ib, II and IIIa, ISACHC score) (Freeman et al. 2005). All the dogs did not show abnormalities in the morphological and biochemical blood examination. The level of NT-proBNP in all the dogs was above 500 pmol/l. Among 15 dogs 9 showed VPC in the electrocardiography. In the 24-hour Holter monitoring, 140- 1240 VPC were recorded and 5 dogs had non-persistent (nsVT) and persistent ventricular tachycardia (sVT). Eleven dogs during echocardiography showed peak gradients from 20 to 49 mmHg corresponding to a velocity of 2.25-3.5 m/sec (mild aortic stenosis), 4 dogs had peak gradient from 50 to 80 mmHg corresponding to a velocity of 3.5-4.5 m/sec (moderate aortic stenosis). During the observation period (24 month follow-up) 3 dogs with mild aortic stenosis died and 1 dog with moderate aortic stenosis was euthanized due to severe heart failure.

Statistical analysis

The differences between groups based on parametric data with standard distribution were analyzed using t-Student test. In case of non-parametric data or lack of standard distribution, U Mann-Whitney test was used. The correlation was analyzed by using

Table 1. Clinical characteristics of the control and SAS group.

Parameters	Control group (n=15)	SAS group (n=15)	p-value
Age (year)	6.11 ± 3,43	4.63 ± 2,45	n.s.
Body mass (kg)	34.6 ± 4.49	28.8 ± 2.34	p<0.01
Male sex	9 (60%)	12 (80%)	
NT-proBNP (pmol/l)	581.4 ± 207.35	1740.13 ± 1306.21	p<0.01
Ejection fraction (%)	60.98 ± 13.21	54.22 ± 9.8	n.s.
Shortening fraction (%)	33.16 ± 13.21	28.18 ± 6.95	n.s.
LA/Ao	1.48 ± 0.45	1.82 ± 0.4	n.s.
LVEDD (cm)	4.45 ± 0.62	3.82 ± 0.34	p<0.01
LVEDS (cm)	3.1 ± 0.36	2.8 ± 0.26	n.s.
IVSD (cm)	1.08 ± 0.14	1.29 ± 0.17	p<0.01
IVSS (cm)	1.33 ± 0.26	1.49 ± 0.21	p<0.05
PWD (cm)	1.06 ± 0.09	1.34 ± 0.28	p<0.01
PWS (cm)	1.47 ± 0.29	1.66 ± 0.43	n.s.
LVM (g)	196.67 ± 52.87	210.25 ± 42.72	n.s.
LVM/ Body mass	5.66 ± 1.36	7.36 ± 1.67	p<0.01
Turbulence onset (%)	-7.45 ± 9.72	-0.76 ± 2.6	p<0.01
Turbulence slope (ms/RR)	14.33 ± 8.76	7.1 ± 3.21	p<0.01
P time (s)	0.04 ± 0.003	0.05 ± 0.007	p<0.01
P amp (mV)	0.17 ± 0.07	0.16 ± 0.04	n.s.
PQ (ms)	0.1 ± 0.01	0.1 ± 0.01	n.s.
R amp (mV)	1.22 ± 0.23	1.89 ± 0.84	p<0.01
QRS (s)	0.05 ± 0.008	0.06 ± 0.01	n.s.
QT (s)	0.19 ± 0.03	0.2 ± 0.01	n.s.
HR	121.23 ± 20.43	128.26 ± 23.04	n.s.

R Spearman test. The testing was done based on the significance level p<0.05.

The study was approved by the Ethics Committee of the Wroclaw University of Environmental and Life Sciences (No. 06/2008).

Results

The clinical findings of both groups are presented in Table 1. All of the dogs examined had a sufficient number of VPC during 24 hours, qualifying them for HRT analysis. The group of healthy dogs and those with SAS had significantly different TO and TS values. In the group of dogs with SAS, the TO values were close to zero which indicates lack of heart rhythm acceleration after VPC. The TS values in dogs with SAS were considerably lower than in healthy dogs which can mean lack of or a slower sinus rhythm after VPC. Additionally dogs with SAS had lower HRT parameters compared to healthy dogs corresponding to lack of typical physiological changes in the heart rate after VPC. No correlations between TO, TS and LVM were observed, however due to the statistically significant variation of the dogs' body mass the ratio between the left ventricle weight and the body mass was calculated and its correlation with HRT parameters. A correlation between TO and the LVM/body mass ratio was found (r = 0.32; p = 0.048). There was no correlation between TS and LVM/body mass ratio. TO was not higher than 1% and TS was lower than 5 ms/RR in all the dogs with SAS that died. The dog which was euthanized due to congestive heart failure had TO = 1.6% and TS = 9.6 mm/RR which was a higher value compared to the dogs that suddenly died, but lower compared to the healthy dogs.

Discussion

Subaortic stenosis is one of the most common congenital heart diseases in dogs with Boxers being predominantly affected (Tidholm et al. 1997, Chetboul et al. 2006, Bussadori et al. 2009). Sex predisposition was observed in males (Bussadori et al. 2009); 80% of the examined group of Boxers with SAS were males. SAS is a congenital disease diagnosed in adult animals. In 75% of cases in dogs the aortic stenosis is asymptomatic, especially when the aortic stenosis is mild-to-moderate (Tidholm et al. 1997). Narrowing the flow from the left ventricle results in cardiac hypertrophy and myocardial ischemia what was observed in examined dogs with SAS. These lesions result in fibrosis and necrotic foci, and lead to sudden cardiac death due to ventricular heart rhythm disturbances (Davainis et al. 2004). In 5 dogs from the group of dogs with SAS Holter monitoring revealed incidents of nsVT and sVT. During 24-month observa-

tion, 3 dogs with mild aortic stenosis died. Two dogs out of 3 that died had incidences of ventricular tachycardia in Holter monitoring. During the same time, one dog from the control group died due to stomach torsion. Additionally, in the group of dogs with SAS longer duration of P wave was observed due to the enlargement of the left atrium which could be seen in the echocardiography. Pressure overloading and centripetal cardiac hypertrophy result in a significant increase of the concentration of NT-proBNP. In the research performed by Hori et al. (2008) serum NT-proBNP concentrations were significantly higher 3 and 6 months after aortic constriction. Serum NT-proBNP concentration was significantly correlated with LVEDD and IVSD whereas serum NT-proBNP assay may be used as an additional screening method to stratify early-stage ventricular remodeling because of aortic constriction.

Heart rate turbulence is a physiological issue which can be observed at single VPC (Schmidt et al. 1999). It is important to correctly classify premature beats as the heart rate turbulence does not occur after supraventricular premature beat, intercalated acceleration or surrogate ventricular beat. HRT is a parameter which was under observation in healthy people and those with cardiac diseases (Koyama at al. 2002, Barthel et al. 2003, Malberg et al. 2003, Sade et al. 2003, Berkowitsch et al. 2004, Arslan et al. 2008). Based on these data the suitability of this parameter as an death risk indicator in patients after heart infarct was confirmed. Already in 2002 the European Society of Cardiology recommended to use the HRT indicator (Priori et al. 2001). Many studies have revealed that there are HRT disorders in patients with dilated cardiomyopathy, chronic heart failure and aortic stenosis (Koyama at al. 2002, Malberg et al. 2003, Arslan et al. 2008,). No HRT analysis were performed in healthy dogs or those with cardiac diseases. The present results, although obtained from a small population of dogs, are the first available data concerning HRT in healthy dogs and dogs with SAS. The study was found that there is a significant decrease in HRT parameters in dogs with SAS, compared to healthy dogs. In the dogs which died, TO was close to zero which indicates lack of premature acceleration after VPC. In the same group of dogs, TS value did not overcome 5 mm/RR which indicates lack of late reduction after VPC. HRT is not dependent on the level of stenosis (Arslan et al., 2008) what was confirmed in the preformed observations. All of the dogs that had abnormal values of TO and TS and did die had mild aortic stenosis. HRT depression was observed also in people with aortic stenosis independently from its etiology (Arslan et al. 2008). HRT parameters are different in the group of healthy dogs. In this group the average value of TO was – 7.45%, SD = 9.72, which indicates a premature acceleration after VPC. The average value of TS was 14.33 ± 8.76. The higher is the value of TS, the bigger is the average reduction of sinus rhythm (bradycardia) after VPC. It is also very typical for healthy people and those with low risk of death after heart infarct (Schmidt et al. 1999). The HRT mechanism is not known very well but there are theories that it is related to baroreceptor reflex. Barorecetors found in the aorta arch and carotid bulb are responsible for one of the most basic mechanism controlling the arterial pressure and heart rhythm. Baroreceptors react fast at sudden drops of arterial pressure so they are constantly stimulated by changes of the arterial pressure. Premature ventricular beats evoke rapid, transient drop of arterial pressure. This evokes the baroreceptor reaction leading to parasympathetic system activity reduction and a consecutive domination of the sympathetic system leading to an increase in the heart rhythm. An increase in the arterial pressure due to an premature ventricular beat and an increase in the contractility lead to an opposite reaction – activation of the parasympathetic system and reduction of the heart rate (Bauer and Schmidt 2003).

Autonomic dysfunction characterized by sympathovagal imbalance may lead to arrhythmic complications like ventricular tachycardia, ventricular fibrillation and sudden death due to mild-to-moderate aortic stenosis. Further studies suggest that HRT generally depends on the parasympathetic system as both HRT parameters worsen after the administration of atropine (lower values of TS and higher of TO) (Marine et al. 2002). There is the opinion that abnormal HRT parameters may mirror loss of the protective anti-arrhythmic performance of the vagus nerve. The ISAR-HRT study revealed that the risk of death in patients after the heart infarct is the highest when the TO and TS values are abnormal. The probability of death is lower when only one HRT parameter is abnormal (Barthel et al. 2003). The dogs with SAS which died had significantly different values of TO and TS compared to the healthy animals. Based on the comparison of the results from both groups of dogs, and the comparison of HRT results in humans, the findings obtained were classified as abnormal. The dog which was euthanized due to the development of an advanced congestive heart failure had a low TO value but TS was comparable to the values that healthy dogs had even if it was one of the lowest value in this group. Bonnemeier et al. (2003) study suggests that HRT in some way is dependent on a normal heart blood supply. Heart blood supply is disturbed during the hypertrophy of the myocardium (Davainis et al. 2004). The correlation between the hypertrophy,

heart blood supply and HRT values seems to be confirmed looking at the correlation between TO and LVM/body mass ratio in the group of dogs with SAS.

In summary, the present results of HRT analysis are the first ones available for healthy dogs and those with SAS. There were significant differences in the HRT parameters in both groups of the animals. Based on the results it can be assumed that the baroreceptor response in dogs with SAS is compromised. It seems that HRT is a good prognostic factor, but its usefulness to evaluate the risk of death reguires further research.

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