Original Article

Relationship between RR and QT Intervals in Normal and Pacing-induced Heart Failure Dogs

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Abstract

This study was conducted to determine the effects of rapid ventricular pacing on cardiac function and hemodynamics, and to determine the most suitable QTc formula for the effects of alterations in the RR interval on the QT interval of conscious dog with heart failure (HF). Electrocardiograms were acquired from dogs (n=18) at baseline and after rapid ventricular pacing (6, 9, 12 weeks). RR and QT intervals were measured and QTc intervals were calculated using 3 common formulae (Bazett, Fridericia and Van de Water). HF was confirmed by reduced left ventricular fractional shortening ($p<0.05$), significantly faster heart rate ($p<0.001$) and significantly changed QT and QTc intervals ($p<0.001$) when compared to the baseline. This model also demonstrated decreased systolic arterial pressure ($p<0.01$) and increased BNP ($p<0.05$). The appropriate regression equations were QT = 152.4+0.08RR for normal dogs and QT = 32.3 (RR) 0.29 for HF dogs. In normal dogs, the Van de Water formula reveals the least dependency of QTc on RR interval. In HF dogs, the Fridericia formula appears to be the best equation to remove the influence of heart rate.

Keywords: BNP, cardiac performance, dog, heart failure, pacing, QT interval

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Introduction

It seems to be reasonable to search for potential toxicity in animal models known to sensitize humans to toxicity since several drugs have adverse reactions in people with naturally-occurring diseases (Hamlin and Kijtawornrat, 2008). It has been known that heart failure is one of the independent risk factors for ventricular arrhythmia and sudden cardiac death (Piccirilloet al., 2009). Congestive heart failure (CHF) is characterized, ultimately, by the inability of the left ventricle to maintain a forward stroke volume sufficient to meet metabolic demands (Yarbrough and Spinale, 2003). CHF is a leading cause of morbidity and mortality in the United States, with over 600,000 new cases diagnosed each year (Kochanek et al., 2011).The challenge to preclinical safety pharmacologists is to develop reliable and reproducible models of heart failure that can be used to evaluate innovative pharmacological strategies.

Several animal models with heart failure (HF) have become increasingly popular to explore potential toxicity of drugs on delaying ventricular repolarization (Dixon and Spinale, 2009). Issues of small and large animal models of heart failure are composed of methods of creation (*i.e.*, rapid pacing (Roche et al., 2002), microembolization (Sabbah et al., 1991), ligation (Lowe et al., 1978), and intracoronary doxorubicin (Toyoda et al., 1998)), methods of evaluation and how the animal model responds to new chemical entities. Additionally, the model must be reproduced in an animal species whose physiology more closely mimics human physiology and anatomy (Yarbrough and Spinale, 2003). Heart failure in animal models can be evaluated by invasive methods (*e.g.* cardiac catheterization and alterations in calcium kinetics); however, these methods are expensive and non-reproducible. Therefore, the non-invasive methods (*e.g.* echocardiography and serum biomarkers) may be preferable in clinical practice.

An early study by Whipple et al. (1961) on rapid ventricular pacing in dogs resulted in the development of left ventricular failure and the model has been developed and become a method to induce CHF in animals. Rapid ventricular pacing is relatively uncomplicated and requires simple instrumentation. This model provides neurohormonal alterations similar to HF in humans and generates progressive and predictable degrees of left ventricular dilation and pump dysfunction (Yarbrough and Spinale, 2003).

Assessment of electrocardiographic parameters especially QT interval is crucial in Safety Pharmacology studies. Beagles are commonly used for drug safety evaluation (Greaves et al., 2004). It has been suggested that evaluation of QT interval in dogs is very difficult especially in HF dogs since the heart rate (HR) is increased in various degrees (Koyama et al., 2004). Therefore, an effective correction formula to correct QT for heart rate in heart failure dogs is needed. Bazett and Fridericia formulae are widely used for preclinical studies in normal beagles with a caution of some limitations (Hammond et al., 2001). However, data on QT-RR interval relationship and adequate QTc formula in pacing-induced heart failure are limited.

The purposes of this paper were (1) to describe the production of HF in dogs using a rapid ventricular pacing model, (2) to evaluate the severity of HF using non-invasive methods (*e.g.* echocardiography, brain natriuretic peptide (BNP) and indirect sphygmomanometry), and (3) to validate the most suitable QTc formula for the effects of alterations in the RR interval on the QT interval of conscious normal dog and dog with HF.

Materials and Methods

This study was performed at QTest Labs, LLC and approved by the Institutional Animal Care and Use Committee (IACUC) of QTest Labs, LLC. The facility is in compliance with USDA regulations. All animal procedures were conducted in accordance with the guideline published in the Guide for the Care and Use of Laboratory Animals (NRC, 2011). A total of 18 male beagles aged 1.2-2.0 years and weighing 10-12.3 kg were used in this study. All animals were trained to stand comfortably in slings in a quiet room up to 1 h and at least 7 days before the beginning of the study. During sling training, they were monitored to ensure behavioral irregularities or cardiac arrhythmias by electrocardiographic examination.

Surgical and experimental procedure: All animals were pre-anesthetized intravenously with acepromazine/diazepam (0.1 mg/kg and 0.5 mg/kg, respectively) and anesthetized with isofluorane. Anesthesia was maintained with 1.5 to 3% isofluorane and 98.5% oxygen until completion of the surgery. All animals were chronically instrumented with Kappa KSR903 pacemakers (Medtronic, Minneapolis, MN) with the pacing lead (Medtronic Model 5054) placed in the right ventricular (RV) apex (Fig 1). Cephalexin (20-25 mg/kg) was administered intravenously before surgery. Buprenorphine (0.02 mg/kg, IM) was administered post-surgery for pain relief. Oral cephalexin was given for 3 days after surgery (25 mg/kg, bid). Baseline data including electrocardiograms, 2-dimensional M-mode echocardiograms, and plasma samples were collected after 14 days of recovery from surgery while they were conscious. After baseline measurement, pacing was performed at: 180 beats/min for 2 weeks, 200 beats/min for 6 weeks, 220 beats/min for 2 weeks, and 160-180 beats/min for 2 weeks to achieve and maintain stable LV dysfunction. The duration of activation of program generator was set at 0.35-0.5 msec. After 6, 9 and 12 weeks of RV tachypacing, plasma samples, blood pressure, electrocardiography, and echocardiography were done when the pacemaker was briefly deactivated (15 min before measurement) for data acquisition during normal sinus rhythm. Plasma samples were obtained to evaluate the level of N-final part of pro-BNP (NTproBNP).

Electrocardiography and Echocardiography: After clipping hair from the ventral region of the thorax, the dogs were placed in a ventrally recumbent position in

a comfortable sling. Bipolar, transthoracic ECGs between points rV2 (right, 5th intercostal space at the costochondral junction) and V2 (left, 6th intercostal space at the costochondral junction) were obtained from 18 conscious dogs at baseline (pre-pacing), and weeks 6, 9, and 12 during pacing. ECG data were acquired on the EMKA IOX 1.8.5 system (EMKA Technologies, Falls Church, VA, USA). Signals were sampled at 1 kHz. All studies were performed at the same time of the day to minimize circadian rhythm effects.

Echocardiographic examination was performed while they were fully conscious at baseline (pre-pacing), and weeks 6, 9, and 12 of pacing. Each dog was placed in right lateral recumbency, with an area of the right hemithorax shaved to allow echocardiographic images to be obtained. Images were obtained using the Biosound Esaote Megas ES 7038 Echocardiographic System (Biosound Esaote, Inc, IN, USA) with a 5-MHz transducer. Echocardiographic recordings included a simultaneously recorded ECG, and all raw data were captured digitally for offline measurement. Left ventricular function was assessed by an evaluation of standard two-dimensional and M-mode imaging planes (Schiller et al., 1989). Measurement of left ventricular wall thickness and internal ventricular dimensions during systole and diastole were made from M-mode images obtained from the right parasternal short-axis view at a level just beneath the mitral valve, with the M-mode cursor directed between the papillary muscles (Fig 2). These measurements were subsequently used to calculate fractional shortening (FS). All images were acquired and analyzed by a single experienced operator.

Blood pressure: Blood pressure was measured while the dogs were sling restrained at baseline (pre-pacing), and weeks 6, 9, and 12 of pacing. A tail cuff sphygmomanometer was placed for the collection of systemic blood pressure (BP) including systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and pulse pressure (PP). An average of BP was calculated from 3 blood pressure measurements for each time-point.

Brain Natriuretic Peptide (BNP): Blood samples were collected while the dogs were sling restrained. Two milliliter of blood samples were collected in EDTA glass tubes at baseline (pre-pacing), weeks 6, 9, and 12 of pacing. The samples were gently inverted and placed on ice until centrifugation. Blood samples were centrifuged within 30 min after collection at 2500 rpm for 15 min, at 5°C. The plasma sample (~1 ml) was pipetted into 2.5 ml polypropylene cryogenic tubes labeled with date, time of collection, and animal identification. The plasma samples were immediately placed on dry ice and frozen in a -80°C freezer pending analysis by sending to IDEXX Laboratories, Ohio, USA.

Data Analysis: RR, PQ, QRS, and QT intervals of beats originating from the sinus node were measured automatically using ECG Auto software v2.5.1.31 (EMKA Technologies, VA), taking the mean of at least 60 consecutive cardiac cycles. All data represent mean±standard error of mean (SEM). Values obtained before and 6, 9, 12 weeks after pacing were compared utilizing one-way ANOVA with repeated measures followed by Dunnett's test. Differences were considered significant for P values less than 0.05. Plots of QT versus RR intervals were constructed using commercial software. QT intervals were corrected for the preceding RR intervals using common exponential (Bazett [QTcB], $QTcB = QT/RR^{1/2}$; Fridericia [QTcF], $QTcF = QT/RR^{1/3}$) (Bazett, 1920; Fridericia, 1920) and linear (Van de Water [QTcVW], QTcVW = QT-0.087x(RR-1000)) equations (Van de Water et al., 1989). Plots were made of QTc versus RR interval, and regression lines with correlation (r^2) were calculated for the baseline (pre-pacing) and heart failure dogs (12 weeks after pacing). These plots were made to determine which method(s) for the conscious, normal beagles and beagles with HF produced the least dependence of QTc on RR.

Results

After 12 weeks of pacing, all dogs survived. The status of heart failure was confirmed by reduced FS, increased plasma NTproBNP level, faster HR, and longer QTc intervals when compared to the baseline. One of the 18 dogs was unable to tolerate the rapid ventricular pacing (200 bpm) and ascites was developed after 6 weeks of pacing, therefore, the pacing rate was reduced to 180 bpm throughout the experiment.

High quality electrocardiograms were obtained from all of the conscious dogs at baseline (pre-pacing) and at HF states (6, 9, 12 weeks after pacing) (Fig 3). There were no changes in the PQ interval or QRS duration in any week of the pacing measured (Table 1). After 6, 9, and 12 weeks of pacing, the RR (inverse of HR) and QT intervals were decreased significantly whereas the QTcF and QTcB intervals were significantly lengthened when compared to the baseline ($p<0.001$). There was no change in the QTcVW interval in any week of the pacing measured. FS decreased significantly after 6 weeks of pacing (13±0.93%) when compared to the baseline (34±1.11%, $p<0.05$) (Table 1) and it continued to decrease until 12 weeks of pacing.

SAP decreased significantly after 6 weeks of pacing (-19.33%) when compared to the baseline (Table 1). SAP slowly increased after 9 weeks of pacing and more so after 12 weeks but those values were still significantly lower than the baseline's values ($p<0.01$). DAP and PP appeared to decrease slightly after 6 weeks of pacing before returning to near baseline values after 12 weeks of pacing. MAP significantly decreased only after 6 weeks of pacing ($p<0.05$), after which the values increased slightly back towards the baseline values.

BNP increased significantly after 6 weeks of pacing (7.57 times) when compared to the baseline ($p<0.05$) (Table 1). BNP continued to increase after 9 weeks of pacing before decreasing slightly after 12 weeks of pacing. The plots of QT against RR interval for the eighteen dogs at baseline (pre-pacing) and after 12 weeks of right ventricular pacing to induce heart failure were shown (Fig 4). The relationships

between QT and RR interval for normal and heart failure dogs were: QT = 152.4+0.08RR, having an r^2 of 0.43 and QT = 32.3(RR) 0.29, having an r^2 of 0.62, respectively. This reveals that 43% (normal dogs) and 62% (heart failure dogs) of the variability in QT can be explained by the RR interval, and the relationships between the two are highly significant (p<0.001). Plots of QTc versus RR interval using each of the 3 methods of correction for RR interval are shown, with their slopes and r^2 (baseline, Fig 5; dogs with heart failure, Fig 6). In normal dogs, plotting rate-corrected QT interval (QTcVW) against RR interval produced a regression line with a slope of zero, indicating that this correction removed the influence of heart rate. In dogs with HF, the Fridericia equation produced a regression line with a slope of 0.01, indicating that this equation was superior to the others.

Discussion

This study aimed to describe the induction of heart failure in dogs by rapid right ventricular pacing. The most suitable correction methods for the alterations of the RR interval on the QT interval of conscious normal dog and dog with HF were also evaluated. After 12 weeks of rapid ventricular pacing, the cardiac remodeling was markedly observed by the decrease in systolic function (FS and BP), increased heart rate and BNP levels, and lengthening of QT and QTc intervals. The relationship between RR and QT interval was significantly different between normal and heart failure dogs.

A pacing-induced heart failure model was first described by Whipple and colleagues (1962). Currently, several investigators have used this model to investigate left ventricular systolic dysfunction since the neurohormonal activation mimics the

Table 1 Effects of rapid ventricular pacing on male Beagles

Parameters	Time-points			
	Baseline	**Week 6**	**Week 9**	**Week 12**
PQ (msec)	93.5 ± 2.48	92.5 ± 2.96	93.4 ± 2.78	91.0 ± 3.36
QRS (msec)	45.1 ± 2.31	41.4 ± 1.09	42.7 ± 1.28	44.6 ± 1.27
RR (msec)	630.6 ± 18.58	477.1 ± 19.49***	475.7 ± 25.56***	462.6 ± 22.44***
QT (msec)	205.6 ± 2.40	194.0 ± 2.35***	194.1 ± 3.70***	192.5 ± 3.54***
QTcF (msec)	243.4 ± 2.12	250.1 ± 2.80***	250.9 ± 2.69***	250.9 ± 2.86***
QTcVW (msec)	237.7 ± 1.82	239.5 ± 1.95	239.7 ± 2.41	239.3 ± 2.37
QTcB (msec)	259.8 ± 3.04	283.0 ± 4.54***	284.4 ± 4.24***	285.7 ± 4.35***
FS (%)	34 ± 1.11	13 ± 0.93*	11 ± 1.04*	13 ± 1.17*
SAP (mmHg)	142 ± 3.68	119 ± 3.90**	122 ± 3.87**	129 ± 3.76**
DAP (mmHg)	79 ± 3.57	70 ± 3.38	68 ± 3.65	76 ± 3.77
MAP (mmHg)	98 ± 3.81	85 ± 3.59*	88 ± 3.75	92 ± 3.0
PP (mmHg)	63 ± 2.45	49 ± 3.65	53 ± 3.02	54 ± 4.62
BNP (pmol/l)	214 ± 57.19	1622 ± 176.32*	1885 ± 214.43*	1707 ± 224.44*

Values are presented as mean (±SEM); n=18. Pacing began after 14 days of recovery from pacemaker implantation surgery. Pacing protocols were 180 bpm for baseline to week 3, 200 bpm for week 3 to week 6, 220 bpm for week 6 to week 9, and 160-180 bpm for week 9 to week 12. *indicates p<0.05, **indicates p<0.01, ***indicates p<0.001 when compared with the baseline. QTcF: correct QT by Fridericia's formula, QTcVW: correct QT by Van de Water's formula, QTcB: correct QT by Bazett's formula, FS: Fractional shortening, SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure, PP: pulse pressure, BNP: brain natriuretic peptide, msec: millisecond, mmHg: millimeter of Mercury,pmol/l: picomolar per liter.

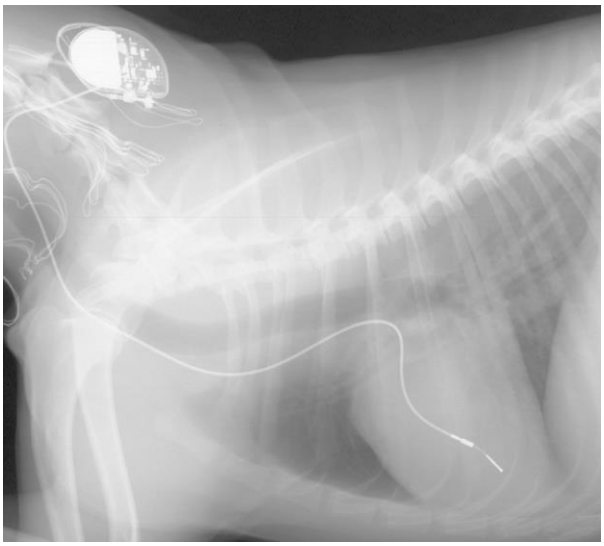

Figure 1 A left lateral thoracic radiograph showing placement of a pacing catheter with a bipolar electrode in contact with the right ventricular apical endocardium and a generator placed under the skin on the neck

2A 2B

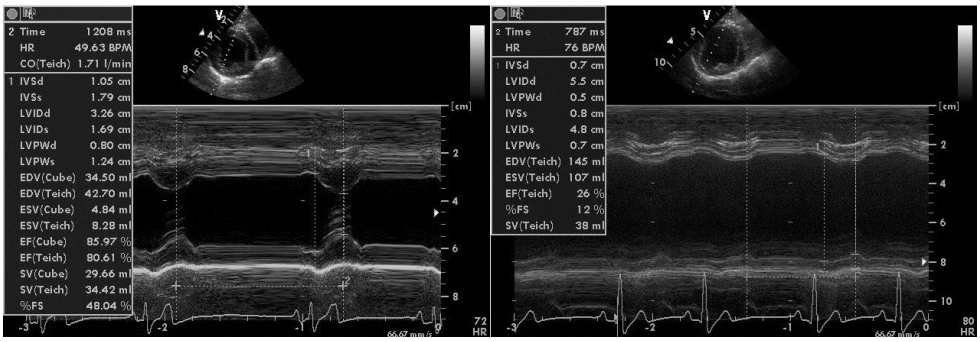

Figure 2 2D-M mode echocardiograms showing normal left ventricular dynamics (2A) before pacing and reduced wall motion (2B) after pacing for 12 weeks

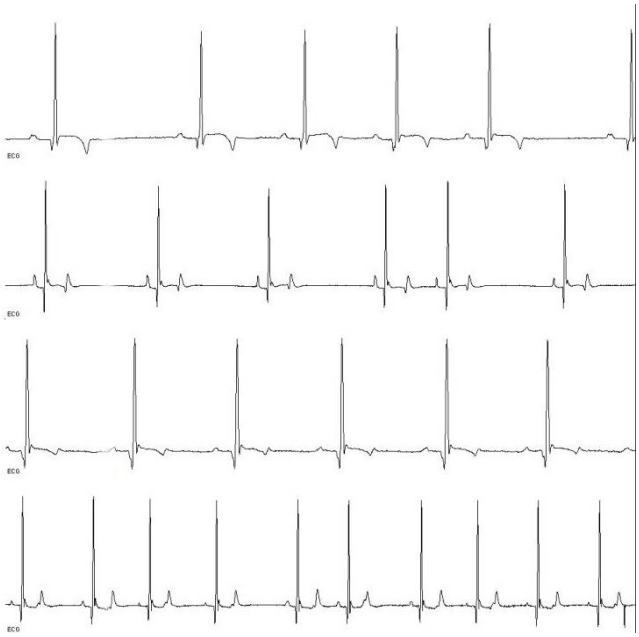

Figure 3 Examples of bipolar, transthoracic ECG, in conscious normal (top two panels) and heart failure (bottom two panels) dogs recorded after 12 weeks of pacing. Notice the absence of baseline artifacts, the ease of identification of the onset of QRS and the end of T wave

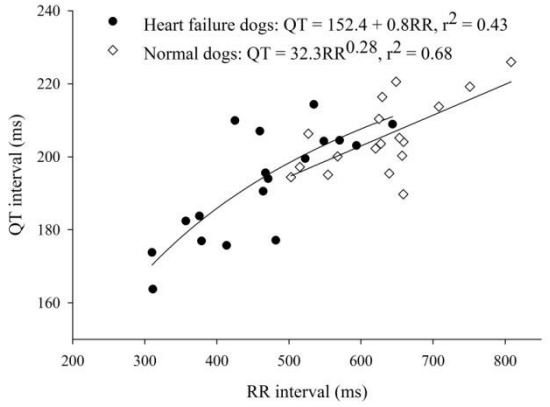

Figure 4 Plots of QT (ms) duration versus (preceding) RR (ms) interval from conscious normal and heart failure dogs. Regression lines and its equation with r^2 are shown. Each data point is an average of 60 consecutive cardiac cycles from a different dog (n= 18)

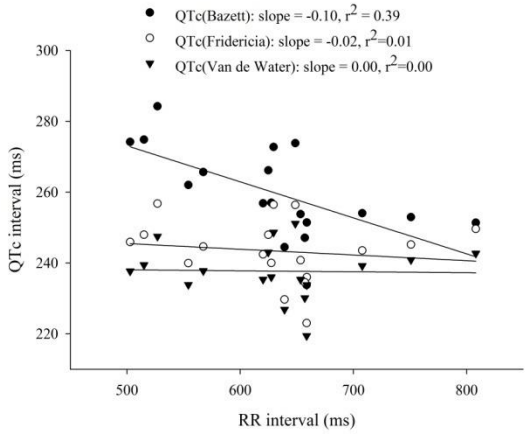

Figure 5 Plots of QTc, their slopes, and r^2, using three equations for removing influence of heart rate, versus RR (ms) interval for normal dogs. Notice that the slope for the Van de Water equation is zero with an r^2 of 0.00. Each data point is an average of 60 consecutive cardiac cycles from a different conscious dog (n=18)

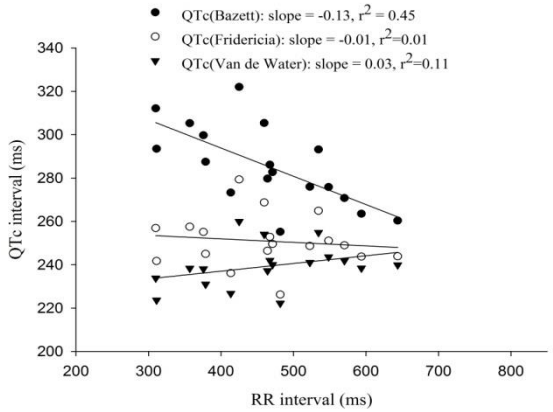

Figure 6 Plots of QTc, their slopes, and r^2, using three equations for removing influence of heart rate, versus RR (ms) interval for dog with heart failure. Notice that the slope for the Fridericia's equation is 0.01 with an r^2 of 0.01. Each data point is an average of 60 consecutive cardiac cycles from a different conscious dog (n=18)

pathophysiology of dilated cardiomyopathy (DCM) in humans (Redfield et al., 1993; Spinale et al., 1997; Roche et al., 2002; Zucker et al., 2007). In our study, the level of BNP was dramatically elevated at 6 weeks after pacing and remained elevated throughout the experiment. This finding is consistent with clinical observations in which elevated plasma BNP levels occurred in dogs with DCM (Oyama et al., 2007; Oyama et al., 2008; Noszczyk-Nowak, 2011). Furthermore, the level of BNP has been used as a diagnostic marker in dogs with heart failure and as a negative prognosis in dog with DCM (Noszczyk-Nowak, 2011).

Rapid right ventricular pacing in dogs produces cardiac remodeling for both structural and electrical alteration (Su et al., 1995; Hill, 2003; Umana et al., 2003). These changes begin with myocyte hypertrophy and apoptosis, increased interstitial collagen, and abnormal cardiac structure. As a consequence, progressive myocardial dysfunction and clinical symptoms occur. In this study, functional remodeling was observed and supported by significantly decreased FS, blood pressure, and lengthened QT and QTc intervals. This finding is consistent with previous reports by several investigators in which the FS and SAP were decreased and the action potential duration was increased in mongrel dogs subjected to rapid right ventricular pacing (230 bpm) for 3 weeks (Wilson et al., 1987; Brandle et al., 1985; Song et al., 2013). However, it should be recognized that when the pacing was discontinued the hemodynamic properties could be reversed to normal within a week and the structural remodeling might improve within 4 weeks (Howard et al., 1988; Moe et al., 1988).

In this study, the systolic function of left ventricle was evaluated by FS; however, the function may be assessed by other indirect methods (*e.g.* left ventricular ejection fraction, left ventricular pre-ejection period, etc.). FS measures the changes in size of the LV from M-mode echocardiography while EF is estimated from the change in volume of the LV (*i.e.* the Simpson method). Although the FS has some limitations for estimation of left ventricular (LV) systolic function, it is simple and accurate to assess the LV systolic function (Crippa et al., 1992). This is consistent with several publications which showed that FS correlated very well with plasma atrial natriuretic peptide concentration and NT-proBNP level in dogs (Aramaki et al, 2011; Ebisawa et al., 2013). Since there was no clinical sign presented in dogs used for this study except for one dog, the severity of heart failure in this model was estimated from the non-invasive methods. At the pacing rate of 200 bpm (6 weeks of pacing), RR, QT, QTc intervals, and BNP levels were increased from the baseline significantly. In addition, the FS was significantly decreased. As the pacing rate increased, these parameters remained stable from the values at 6 weeks. These data agree with our previous publications (Nishijima et al., 2005; Sridhar et al., 2009).

The relationship between QT interval and HR has been investigated for many years and several mathematical formulae have been proposed to correct QT for HR in order to allow comparisons between QT intervals at different HR. According to a previous report, about 41% of preclinical laboratories used Bazett formula for their studies (Hammond et al., 2001). It has been known that Bazett's formula was established from the QT and RR relationship of humans, therefore, it tends to over-correct the HR of dogs. This limitation is also applied to Fridericia's formula with a lesser degree. In the present study, Bazett's formula was inadequate to correct QT intervals for heart rates in both normal and HF dogs. On the other hand, Fridericia's formula is suitable for both normal and heart failure dogs to remove the effect of HR on QT interval. Van de Water's formula is favorable in normal dogs. This can be explained by the fact that the Van de Water's formula was derived from normal dogs (Van de Water et al., 1989). In dogs with HF used during this study, heart rates varied between 101 and almost 200 beats per minute, a wide range that we utilized to confirm the dependence of QT on the preceding RR interval and the independent of RR on QTc using Fridericia's equation.

In conclusion, the rapid pacing method of HF is reliable and reproducible as described by the non-invasive measures of echocardiography (*i.e*. FS), levels of BNP, and indirect sphygmomanometry (*i.e.* SAP). The severity of heart failure in this model may be expressed by the reduction in FS, MAP, and SAP as well as the markedly increased level of BNP in plasma. In HF dogs, the Fridericia formula appears to be valuable as a biomarker for evaluating the effect of drugs on ventricular repolarization whereas the Van de Water formula is suitable in normal dogs.

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บทคัดย่อ

ความสัมพันธ์ของระยะ RR และ QT ในสุนัขปกติ และสุนัขที่ถูกเหนี่ยวนำให้เกิดภาวะหัวใจล้มเหลวด้วยการกระตุ้นหัวใจ

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การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อหาผลของการกระตุ้นหัวใจห้องล่างให้เต้นด้วยอัตราเร็วสูงต่อการทำงานของหัวใจและความดันโลหิต เพื่อหาสมการที่ดีที่สุดในการคำนวณผลของระยะ RR ที่มีต่อระยะ QT ในสุนัขปกติ และมีภาวะหัวใจล้มเหลว สุนัขทั้ง 18 ตัวได้รับการตรวจคลื่นไฟฟ้าหัวใจ การตรวจหัวใจด้วยคลื่นความถี่สูง และการวัดระดับ BNP ในพลาสมา ก่อนเริ่มทำการทดลองและภายหลังการกระตุ้นหัวใจด้วยอัตราเร็วสูงนาน 6 9 และ 12 สัปดาห์ จากนั้นทำการวัดระยะ RR และ QT ทำการคำนวณระยะ QTc ด้วยสมการ 3 วิธีคือ Bazett Fridericia และ Van de Water เมื่อเปรียบเทียบกับก่อนเริ่มกระตุ้นหัวใจพบว่าภาวะหัวใจล้มเหลวทำให้เกิดการลดลงของการบีบตัวของหัวใจห้องล่างซ้าย ($p<0.05$) การเพิ่มขึ้นของอัตราการเต้นของหัวใจ ($p<0.001$) และการเปลี่ยนแปลงของระยะ QT และ QTc อย่างมีนัยสำคัญ ($p<0.001$) นอกจากนี้พบการลดลงของความดันโลหิตแดงสูงสุด ($p<0.01$) และการเพิ่มขึ้นของระดับ BNPในเลือดอย่างมีนัยสำคัญ ($p<0.05$) พบว่าความสัมพันธ์ระหว่าง RR และ QT intervalsในสุนัขปกติคือ QT =152.4+0.08RR และในสุนัขที่มีภาวะหัวใจล้มเหลวคือ QT =32.3 (RR) 0.29 ในสุนัขปกติพบว่าสมการของ Van de Waterทำให้ระยะของ QTc มีความเป็นอิสระต่อระยะ RR ดีที่สุด และในสุนัขที่มีภาวะหัวใจล้มเหลว สมการของ Fridericia เป็นสมการที่เหมาะสมที่สุดในการใช้ขจัดอิทธิพลของอัตราการเต้นของหัวใจได้

คำสำคัญ: บีเอ็นพี ประสิทธิภาพการทำงานของหัวใจ สุนัข ภาวะหัวใจล้มเหลว การกระตุ้น ระยะคิวที

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