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Implications of QRS Duration in Dogs with Pacing-induced Heart Failure

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Short title: **QRS duration in heart failure**

Summary

The objective of this study was to find out the implication of QRS duration in dogs with rapid pacing-induced heart failure. Sixteen Beagle dogs were implanted with transvenous cardiac pacemakers and underwent rapid right ventricular pacing for 3 weeks at 260bpm to induce heart failure. Dogs were divided into two groups according to the QRS duration: 9 with normal QRS duration (<100ms) and 7 with prolonged QRS duration (≥100ms). Cardiac systolic function and size was analyzed by real time 3-dimensional echocardiography and left ventricular dyssynchrony was assessed by speckle tracking strain imaging. Congestive heart failure developed 3 weeks after rapid right ventricular pacing. Dogs with prolonged QRS duration showed more extensive radial strain and circumferential strain dyssynchrony than dogs with normal QRS duration. At the end of 4-week recovery, greater improvement of left ventricular ejection fraction and left ventricular end-systolic volume was detected in dogs with normal QRS duration. The findings suggested that left ventricular dyssynchrony, indicated by a prolonged QRS duration, predicted an unsatisfying recovery in dogs with rapid pacing-induced heart failure. QRS duration had the potential to be a prognostic indicator for dogs with heart failure.

Keywords: Echocardiography; Dyssynchrony; Prognosis; Remodeling

Introduction

Rapid pacing-induced dilated cardiomyopathy was first described by Armstrong et al. in 1986 (Armstrong et al. 1986). In their experiment, dogs showed an increase in cardiac size and a fall in cardiac systolic function after 3 weeks of rapid right ventricular pacing (Damiano et al. 1987, Howard et al. 1988, Stambler et al. 2003, Vanoli et al. 2004). The hemodynamic and cardiac structural changes induced by rapid pacing generally recovered in a few weeks after the pacemakers were turned off. As a surrogate for electrical dyssynchrony in human, QRS duration prolonged in nearly half of patients with reduced left ventricular ejection fraction (Wang et al. 2008). Besides, a prolonged QRS duration in heart failure patients indicated a worse prognosis (Shamim et al. 1999, Shenkman et al. 2002). In animals, QRS duration also increased after rapid ventricular pacing (Akar et al. 2004, Nishijima et al. 2005) and correlated with enlarged cardiac size (Nakayama et al. 2001). So far, few data was available on the prognostic value of QRS duration in dogs with left ventricular systolic dysfunction. According to the criteria for dogs, prolonged QRS duration can be defined as ≥100ms (Birchard and Sherding 1994, Liu et al. 2002). Our study aimed to compare the outcome between dogs with prolonged and normal QRS duration during the recovery from rapid pacing-induced heart failure.

Materials and Methods

Surgical Preparation

The experimental procedures were approved by the Animal Welfare Committee of Zhongshan Hospital and complied with Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996).

Sixteen Beagle dogs received rapid right ventricular (RV) pacing (260 beats/min) continuously for 3 weeks and then were divided into two groups according to their QRS duration: prolonged QRS duration group (pQRSd group with QRS duration ≥100ms) and normal QRS duration group (nQRSd group with QRS duration <100ms) .

All dogs were anesthetized with sodium pentobarbital (30 mg/kg induction; intravenously 1.0 mg/kg/h with intermittent boluses as needed). RV pacing systems were implanted under fluoroscopic guidance. Bipolar endocardial pacing leads were positioned at RV apices through jugular vein and connected to the pacemakers (model 8084, Medtronic, Inc.).

Electrocardiography and Echocardiography

Dogs were studied at intrinsic sinus rhythm in conscious state during three periods: 1) at baseline before initiation of rapid pacing; 2) at the end of 3-weeks rapid pacing; 3) at the end of 4-weeks recovery.

Standard 12-leads electrocardiography (ECG) was acquired at a paper speed of 50 mm/s and a scale of 10 mm/mV, when the pacemaker was turned off. The longest QRS duration on surface lead was recorded by two experienced observers who were blinded to the echocardiography data.

Transthoracic two-dimensional images were acquired in a left lateral position with a 1.7MHz to 3.4MHz M3S probe (Vivid 7; General Electric Medical Systems, Horten, Norway). Short-axis images at the level of papillary muscles with the frame rate of 70-100 frames/s were acquired for speckle tracking strain analysis.

Real time 3-dimensional echocardiography (RT3DE) was performed with a 1.0MHz to 3.0MHz X-3 probe (IE33; Philips Medical Systems, Bothell, WA, USA) to derive left ventricular (LV) volumes and ejection fractions. The frame rate was above 40 frames/s. The offline analysis was

performed with the available software (QLAB, version 7.0, Philips Medical Systems, Bothell, WA, USA).

Speckle Tracking of Short-axis Two-dimensional Images

All mid-level short-axis images were analyzed by the 2D strain software (EchoPAC PC, version 7.0, General Electric Medical Systems, Horten, Norway). The speckles of interest were followed throughout the entire cardiac cycle and the parameters of myocardial radial and circumferential deformation were calculated automatically. Finally the 6 segmental time-strain curves for radial strain and circumferential strain were displayed. The mechanical dyssynchrony was assessed by the standard deviation of the time from the onset of QRS to the peak radial strain (Trs-6SD) and circumferential strain (Tcs-6SD).

The standard deviations of time to peak radial strain and circumferential strain were expressed by the percentage of the cardiac cycle (the beginning of one heart beat to the beginning of the next) length in order to adjust for different heart rates (Cui et al. 2010).

Reproducibility Assessment

Intraobserver agreement and interobserver agreement were assessed with Bland-Altman method and expressed as the mean percentage error (difference/mean).

Intraobserver variability: Limits of agreement were as follows: QRS duration (0.83 ±3.81ms), Trs-6SD (0.39 ±0.98 %) and Tcs-6SD (-0.37 ±1.53 %). The variability for each parameter was computed to be 4.2%, 6.3% and 6.8%, respectively.

Interobserver variability was determined by two independent observers: The limits of agreement and variability for QRS duration, Trs-6SD and Tcs-6SD were (1.04 ±4.16 ms) and 4.8%, (-0.46 ±1.11 %) and 7.9%, (0.49 ±1.39 %) and 8.3%, respectively.

Statistical Analysis

Analysis was performed with the SPSS 11.5 software (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean (SD). Data within the groups were compared by paired 2-tailed Student's t test. Data between groups were assessed by the one-way ANOVA or Mann-Whitney U-test as appropriate. Then covariance analysis was used to compare variables at the end of 4-week recovery between pQRSd Group and nQRSd Group with adjustment for the post-pacing values. The correlation between the QRS duration after rapid pacing and the change of LV ejection fraction (LVEF) during the recovery was assessed by Pearson's correlation coefficient. Statistical significance was defined as two-sided $p < 0.05$.

Results

Changes in dogs with pacing-induced heart failure

Sixteen Beagle dogs (50% male, 50% female; mean age 1.9 years, range 1.5-2.5 years; mean weight 10.8 kg, range 9.5-12.2kg) were included in the analysis. Basic characteristics and dyssynchrony parameters were summarized in Table 1. After 3 weeks of rapid pacing, all dogs developed dysphoria, anorexia, tachypnea and anesthetics intolerance. LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) increased, while LVEF decreased significantly compared with baseline (all $p<0.05$). In addition, a significant increase of QRS duration, Trs-6SD and Tcs-6SD ($p<0.05$, respectively) was present. A typical image of strain curves from a dog before and after rapid pacing indicated that posterior and lateral segments were activated later than other segments (Figure 1). During a recovery period of 4 weeks, LVEF and LVESV improved, while LVEDV remained enlarged ($p>0.05$). A decrease of Trs-6SD and Tcs-6SD could be observed in heart failure dogs during the recovery, but the QRS duration did not change ($p>0.05$).

Comparisons between dogs with prolonged and normal QRS duration

Of the 16 dogs with rapid pacing-induced dilated cardiomyopathy, 7 were classified as having a prolonged QRS duration of ≥100 ms (pQRSd group, n=7). The remaining 9 were classified as having a normal QRS duration and heart failure (nQRSd group, n=9). All features were comparable between two groups at baseline including age, gender and weight (Table 2). When heart failure was induced, Trs-6SD and Tcs-6SD were greater in the pQRSd group than those in the nQRSd group ($p<0.05$, Table 3). LVEF, LVEDV and LVESV were not different between two groups ($p>0.05$).

After 4 weeks of recovery, the QRS duration in the pQRSd group remained prolonged. LVEF improved in both groups, while the improvement was greater in the nQRSd group (52.5±2.2 vs. 42.6±2.9 %, $p<0.05$, Table 3). The QRS duration after rapid pacing was negatively correlated with the LVEF and the increase of LVEF ($r=0.94$, 0.93, respectively; both $p<0.001$, Figure 2). It was similar to the LVEF scenario that dogs with normal QRS duration displayed a more prominent improvement of LVESV (16.5±2.0 vs. 20.3±3.3ml, $p<0.05$, Table 3). Besides, LVEDV decreased in the nQRSd group only. Though Trs-6SD and Tcs-6SD shortened in both groups, they were still longer in the pQRSd group than in the nQRSd group (12.64±3.36 vs. 5.84±1.45 %, 8.73±0.50 vs. 7.08±0.82 %, both $p<0.05$, Table 3), which inferred that severe LV dyssynchrony among dogs in the pQRSd group still existed after the 4-weeks recovery course.

Discussion

Rapid ventricular pacing-induced heart failure is a reversible process. To the best of our knowledge, our study was the first report to demonstrate that the improvement of LV systolic

function and remodeling was greater in dogs with normal QRS duration than dogs with prolonged QRS duration.

LVEF is the most commonly used parameter to qualify LV systolic function (Serres et al. 2008). LVESV and LVEDV reduction has been recognized as the evidence for reverse remodeling in heart failure patients (St John Sutton et al. 2003, Yu et al. 2005). In order to assess LVEF, LVESV and LVEDV more accurately and objectively, we needed a feasible and reproducible method to qualify LV function and volumes. RT3DE permitted a rapid capture of the complete LV and an automatic detection of the endocardial border in a three-dimensional view. Therefore RT3DE, recommended by Jenkins et al (Jenkins et al. 2004) and Sugeng et al (Sugeng et al. 2006), was applied in the experiment. We observed that chronic rapid ventricular pacing led to severe LV dysfunction characterized by decreased LVEF and enlarged LVEDV and LVESV. Impaired myocardial contractility was able to recover after the pacemaker switched off.

QRS duration increased significantly after 3 weeks of rapid ventricular pacing. About 40% of the dogs with pacing-induced heart failure had a prolonged QRS duration of ≥100ms (Birchard and Sherding 1994, Liu et al. 2002) and the others had a normal QRS duration of <100ms. At 4-weeks follow-up of recovery, LVEF increased and LVESV decreased more significantly in dogs with normal QRS duration than dogs with prolonged QRS duration. LVEDV remained unchanged in dogs with prolonged QRS duration, but decreased significantly in dogs with normal QRS duration.

Previous study suggested that cardiac electrical properties were useful in preclinical evaluation of myocardial injury (Potácová et al. 2007). QRS duration is an accurate measure of ventricular activation time (Sutherland et al. 2008). But the implication of prolonged QRS duration in animals

with systolic dysfunction has hardly been referred to. After 3 weeks of rapid pacing, all parameters were comparable between dogs with prolonged and normal QRS duration except for Trs-6SD and Tcs-6SD derived from speckle tracking analysis. Speckle tracking was a novel technique to assess timing of regional wall strain (Schwarzwald et al. 2009) and qualify LV dyssynchrony (Suffoletto et al. 2006, Delgado et al. 2008). The accuracy of speckle tracking analysis as a Doppler angle independent method (Zemánek et al. 2010) was confirmed by MRI tagging as a reference method (Amundsen et al. 2006). Its superiority to tissue Doppler imaging (TDI) in detecting ventricular dyssynchrony was further proved by Arita et al (Arita et al. 2007). Moreover, LV dyssynchrony always led to inefficient LV contraction with a decreased cardiac output and was associated with a poor outcome (Bleeker et al. 2006). Given these results, the adverse implication of a prolonged QRS duration in dogs with heart failure was attributed to the presence of LV mechanical dyssynchrony.

As electrocardiography is a relatively cost-efficient, non-invasive and bedside test, the prognostic value of QRS duration is tempting (Schober et al. 2007, Santilli et al. 2008, Wess et al. 2010). LV dyssynchrony, indicated by a prolonged QRS duration, predicted an unsatisfying recovery in dogs with rapid pacing-induced heart failure. A negative correlation was found between the QRS duration after rapid pacing and the increase of LVEF during the recovery.

Our study has several limitations. It is uncertain whether the prognostic value of QRS duration could be extended to dogs with other kinds of remediable heart failure (Pirk 2009). Further investigation will be needed to evaluate the association between prolonged QRS duration and high mortality in dogs with idiopathic dilated cardiomyopathy. In human, QRS duration ≥120ms has been accepted as one of the established patient selection criteria for cardiac resynchronization

therapy (CRT) (Novák et al. 2008). Whether the outcome of dogs with prolonged QRS duration and heart failure can be improved by CRT requires further research.

In summary, myocardial contractility was severely impaired by supraphysiologic heart rates in Beagle dogs. About 40% of the dogs with pacing-induced heart failure demonstrated prolonged QRS duration. Prolonged QRS duration indicated left ventricular mechanical dyssynchrony. Dogs with normal QRS duration showed greater improvement in cardiac function and size than dogs with prolonged QRS duration during the recovery.

Abbreviations

RV - right ventricular, RT3DE - real time 3-dimensional echocardiography, LV - left ventricular, Trs-6SD - standard deviation of the time from the onset of QRS to the peak radial strain, Tcs-6SD- standard deviation of the time from the onset of QRS to the peak circumferential strain, LVEF - left ventricular ejection fraction, LVEDV - left ventricular end-diastolic volume, LVESV- left ventricular end-systolic volume, TDI - tissue Doppler imaging, CRT - cardiac resynchronization therapy

Conflict of Interest

There is no conflict of interest.

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Table 1. Basic characteristics and dyssynchrony parameters of 16 Beagle dogs

	Pre	HF	Post
LVEF, %	60.3 ±2.9	32.1 ±1.6*	48.1 ±5.6‡
LVEDV, ml	26.2 ±3.2	35.5 ±5.1*	34.8 ±4.5
LVESV, ml	10.4 ±1.7	24.1 ±3.6*	18.0 ±3.1‡
HR, bpm	109 ±14	123 ±13*	114 ±15‡
QRS, ms	60.9 ±11.3	84.1 ±25.0*	82.8 ±22.5
Trs-6SD, %	2.02 ±0.83	10.41 ±5.96*	8.82 ±4.22‡
Tcs-6SD, %	3.70 ±0.90	8.88 ±1.63*	7.80 ±1.09‡

Data are presented as mean ±SD. Pre: at baseline; HF: at the end of 3-weeks rapid ventricular pacing; Post: at the end of 4-weeks recovery; LVEF= LV ejection fraction; LVEDV= LV end-diastolic volume; LVESV= LV end-systolic volume; HR= heart rate; QRS= duration of QRS complex; Trs-6SD= SD of time to peak radial strain; Tcs-6SD= SD of time to circumferential strain; * $p<0.05$ Pre vs. HF; ‡ $p<0.05$ HF vs. Post.

Table 2. Baseline characteristics of both groups

	pQRSd	nQRSd	P Value
Number	7	9	
Age, years	1.9 ±0.3	2.0 ±0.4	NS
Gender, male/female	4/3	4/5	NS
Weight	10.7 ±0.9	10.9 ±1.0	NS
LVEF, %	59.6 ±2.6	60.9 ±3.1	NS
LVEDV, ml	26.5 ±3.2	25.9 ±3.3	NS
LVESV, ml	10.7 ±1.5	10.2 ±1.9	NS
HR, bpm	108 ±14	110 ±16	NS
QRS, ms	59.3 ±12.4	62.2 ±10.9	NS
Trs-6SD, %	1.98 ±1.04	2.06 ±0.69	NS
Tcs-6SD, %	3.83 ±0.62	3.60 ±1.10	NS

Data are presented as mean ±SD. LVEF= LV ejection fraction; LVEDV= LV end-diastolic volume; LVESV= LV end-systolic volume; HR= heart rate; QRS= duration of QRS complex; Trs-6SD= SD of time to peak radial strain; Tcs-6SD= SD of time to circumferential strain; NS= not significant.

Table 3. Comparisons between dogs with prolonged and normal QRS duration

	pQRSd (n=7)		nQRSd (n=9)	
	HF	**Post**	**HF**	**Post**
LVEF, %	31.9 ±2.1	42.6 ±2.9‡	32.4 ±1.1	52.5 ±2.2‡※
LVEDV, ml	34.2 ±4.4	34.8 ±5.0	36.5 ±5.6	34.7 ±4.5‡
LVESV, ml	23.3 ±3.2	20.3 ±3.3‡	24.7 ±3.9	16.5 ±2.0‡※
HR, bpm	125 ±12	117 ±13‡	122 ±14	112 ±17‡
QRS, ms	109.3 ±8.4	106.4 ±6.3	64.4 ±11.3※	64.4 ±7.3※
Trs-6SD, %	15.47 ±5.63	12.64 ±3.36‡	6.47 ±1.74※	5.84 ±1.45‡※
Tcs-6SD, %	9.97 ±0.93	8.73 ±0.50‡	8.03 ±1.58※	7.08 ±0.82‡※

Data are presented as mean ±SD. HF: at the end of 3-weeks rapid ventricular pacing; Post: at the end of 4-weeks treatment; LVEF= LV ejection fraction; LVEDV= LV end-diastolic volume; LVESV= LV end-systolic volume; HR= heart rate; QRS= duration of QRS complex; Trs-6SD= SD of time to peak radial strain; Tcs-6SD= SD of time to circumferential strain; ‡$p<0.05$ HF vs. Post; ※$p<0.05$ pQRSd group vs. nQRSd group.

Legends

Figure 1. A: radial strain curves, and B: circumferential strain curves obtained by speckle tracking strain imaging from the animal at baseline (Top) and the same animal with prolonged QRS duration and heart failure (Bottom). White arrow indicated the peak strain of the earliest and latest segments. LV dyssynchrony was present with later activation of posterior and lateral segments after rapid RV pacing (yellow=anterior septum; light blue=anterior segment; green=lateral segment; purple=posterior segment; dark blue=inferior segment; red=septum).

Figure 2. Correlation between the QRS duration after rapid pacing and LVEF after 4-weeks recovery (A) or the increase of LVEF during the recovery (B) in the 16 Beagle dogs.

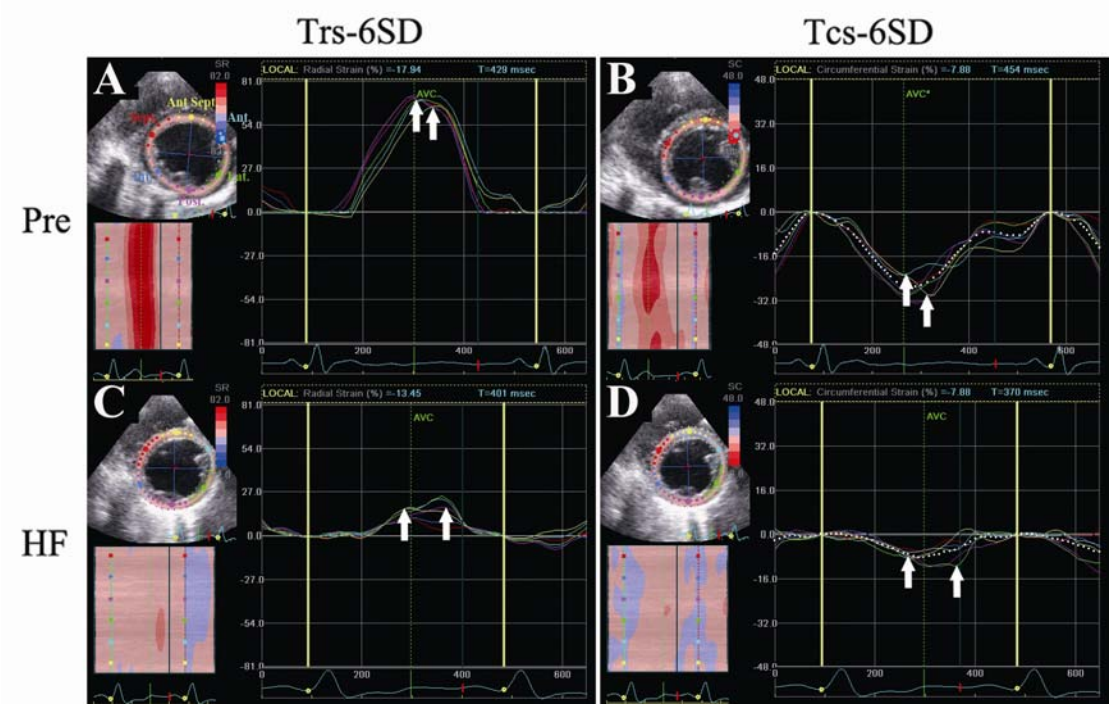
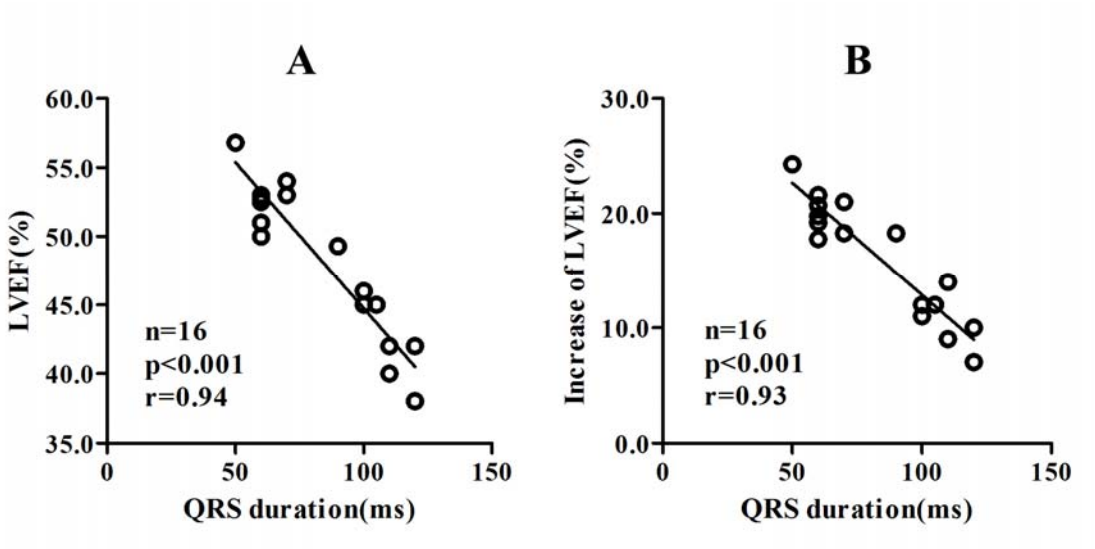


Fig. 1


A
LVEF(%)
60.0
55.0
50.0
45.0
40.0
35.0
n=16
p<0.001
r=0.94
0
50
100
150
QRS duration(ms)
B
Increase of LVEF(%)
30.0
20.0
10.0
0.0
n=16
p<0.001
r=0.93
0
50
100
150
QRS duration(ms)

1

2 Fig. 2