Ventricular electrophysiology in congestive heart failure and its correlation with heart rate variability and baroreflex sensitivity: a canine model study

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Aims
This study investigated ventricular electrophysiological characteristics and the correlation between these parameters and heart rate variability (HRV) and baroreflex sensitivity (BRS) in a canine congestive heart failure (CHF) model.

Methods and results
Haemodynamics, HRV, BRS, and ventricular electrophysiological variables were measured 4–5 weeks after sham operation (control dogs) and pacemaker implantation, and rapid right ventricular pacing at 240 bpm (CHF group). In the CHF group, significant differences from the control group in ventricular effective refractory period (VERP), monophasic action potential (MAP) duration (MAPD90), ventricular late repolarization duration (VLRD), the ratio of VERP to MAPD90, dispersion of ventricular recovery time (VRT-D), and ventricular fibrillation threshold (VFT) were noted. Both BRS and the time and power domain parameters of HRV were significantly decreased in the CHF group compared with the control group, and a significant, positive correlation between HRV and BRS was identified in the CHF group. Heart rate variability and BRS were negatively and significantly correlated with VLRD and VRT-D, and were positively correlated with VERP/MAPD90 and VFT in the CHF group.

Conclusion
These results suggest that ventricular electrophysiological characteristics correlated with abnormal autonomic nerve function may have important effects on sudden cardiac death. Further research is warranted.

Keywords
Congestive heart failure • Electrophysiology • Heart rate variability • Baroreflex sensitivity

Introduction
Congestive heart failure (CHF) is a chronic medical condition affecting millions of people worldwide and is associated with a poor prognosis. Complex ventricular arrhythmias are encountered in ~90% of patients with CHF. Ventricular arrhythmias often result in sudden cardiac death, the leading cause of death in these patients.1

Changes in ventricular electrophysiological characteristics in CHF can lead to ventricular arrhythmias and cardiac sudden death.2,3 Experimental researches and clinical findings have demonstrated that ventricular monophasic action potential duration (MAPD90) and ventricular effective refractory period (VERP) are increased with CHF.4,5 Dysfunction of the autonomic nervous system has also been closely correlated with the occurrence of CHF and sudden cardiac death.6 It has been suggested that reductions in heart rate variability (HRV) and baroreflex sensitivity (BRS), which are markers of autonomic nerve function, could be used to predict risk of sudden cardiac death.7–10 Indeed, decreased HRV has been shown to be associated with an increased risk of cardiac death in a number of studies.11–14 In particular, BRS and HRV have been shown to be strong predictors of and important contributors to risk stratification for cardiac mortality after myocardial infarction.8,9 As early as 1988, it was suggested that decreased BRS is associated with the development of ventricular fibrillation and, therefore, sudden cardiac death.15 Further research has demonstrated that the measurement of BRS identified dogs at risk for sudden cardiac death.8,15
Based on the results from these studies, it was hypothesized that autonomic nerve dysfunction may increase the incidence of sudden cardiac death in patients with CHF by altering ventricular electrophysiology. However, in the assessment of risk of sudden cardiac death caused by CHF, clinical information about the association of the variation of cardiac electrophysiological parameters and the changes of HRV and BRS has never been reported. Therefore, the purpose of this study was to determine whether HRV and BRS were correlated with various cardiac electrophysiological parameters, particularly those that reflect the electric stability of the ventricles including ventricular recovery time dispersion (VRT-D), ventricular late repolarization duration (VLRD), VERP/MAPD90, and ventricular fibrillation threshold (VFT).

**Materials and methods**

**Subjects**

Healthy adult specific pathogen-free mongrel dogs (n = 22) weighing 13.8 ± 1.2 kg were obtained from the Sun Yat-Sen University Animal Laboratory. The dogs were randomly assigned into either a control (sham-operated) group (n = 10) or a CHF group (n = 12). Baseline haemodynamic parameters (described below) were obtained in all dogs prior to implantation surgery. This study was approved by the Institutional Review Board of the Sun Yat-Sen University Animal Laboratory.

**Induction of congestive heart failure**

Congestive heart failure was induced by rapid ventricular pacing as described by Armstrong et al. Briefly, 12 dogs in the CHF group were anaesthetized with an intraperitoneal injection of 3% sodium pentobarbital (30 mg/kg). Five per cent glucose in normal saline (500 mL) with penicillin (4.8 million IU) was administered intravenously. Under fluoroscopy, an endocardial pacemaker electrode (St Jude Medical, St Paul, MN, USA) was inserted into the right ventricular apex via the left external jugular vein. A pacemaker generator (Guangzhou Radio Research Institute, People’s Republic of China) was implanted in a small subcutaneous pocket created between the scapulas, and the pacemaker lead was connected to the generator through a subcutaneous canal. The pacing threshold was 0.3–1.5 V, the amplitude of the R-wave 4–10 mV, and the impedance 0.3–1.0 kΩ. The pacemaker frequency was set at 240 bpm with an output voltage of 5.0 V and a pulse width of 0.5 ms. Dogs in the control group underwent a sham surgery in which the pacemakers and electrodes were installed, but not connected.

Surgery was completed in an average time of 2–3 h, and all experimental procedures were performed in a central laboratory that had a consistent temperature control of 24–26 °C. Serum electrolyte concentrations (K⁺, Na⁺, Cl⁻, Ca²⁺, and Mg²⁺) were monitored in all dogs, and appetite, behaviour, activity status, and respiratory rate were recorded postoperatively. Rapid pacing in the experimental group was continued for 4–5 weeks, and during this period dogs in both experimental and control groups were trained to stand quietly in a sling for electrocardiographic (ECG) recording once a week to ensure that the cardiac pacing was stable and sustainable in the CHF group and that normal heart rate and rhythm were present in the control group.

Four to five weeks after the initiation of rapid pacing, electrophysiological and haemodynamic measurements were performed in both groups. Continuous 30 min ECG recordings were taken in conscious animals for the analysis of HR variation. The respiratory rate of each dog was also monitored during this period. In the CHF group, as described previously by others, rapid pacing was stopped 30 min prior to the ECG recording. After completion of ECG and respiratory rate recording, a phenylephrine injection protocol was used to measure BRS. Animals were subsequently anaesthetized for the measurement of haemodynamic parameters and cardiac electrophysiological characteristics, and then euthanized, so that morphological and histological examination could be performed.

**Measurement of heart rate variability**

Heart rate variability was measured from 30 min continuous ECG records (in the case of the CHF group, taken 30 min after discontinuation of pacing) using software from GE Medical Systems (Milwaukee, WI, USA). The time and frequency domain parameters of this variable were analysed using HRV analysis software.

Time domain parameters included the standard deviation (SD) of the RR intervals (SDNN, SD of all normal sinus rhythm RR intervals within a specified time in milliseconds), the root-mean-square of this SD (rMSSD, root-mean-square SD of the continuous normal sinus rhythm RR intervals within a specified time in milliseconds), and the percentage of long RR intervals (PNN50, percentage of the number of two adjacent >50 ms normal sinus rhythm RR intervals in the total number of all normal sinus rhythm RR intervals within a specified time in milliseconds).

Frequency domain parameters (expressed as ms²/Hz) included the following frequency bands: high-frequency (HF, >0.15 Hz), a band associated with the modulation of vagal tone, primarily breathing; low-frequency (LF, 0.04–0.15 Hz), a band associated with the modulation of baroreflex activity; very low frequency (VLF, 0.0033–0.04 Hz). In addition, the LF/HF ratio was calculated.

**Measurement of baroreflex sensitivity**

In all dogs, BRS was measured directly after HR variation data had been collected, using phenylephrine as the challenge substance. The femoral artery was catherized under local anaesthesia with 1% lidocaine on the day before the baroreflex measurement was taken, and the catheter filled with heparin saline and secured. During BRS testing, the catheter was connected to a pressure transducer attached to a multiple channel physiological recorder (Mingograf 7, Siemens-Elema AB, Solna, Sweden). During the test, arterial blood pressure (ABP) and limb lead ECG were simultaneously recorded at a paper speed of 100 mm/s. An initial dose of phenylephrine (5 µg/kg IV) was rapidly injected. If the increase of the ABP was <15 mmHg (1 mmHg = 0.133 kPa), phenylephrine was re-injected after 15 s. Doses of phenylephrine were then increased by 0.5 µg/kg per injection until a dose was reached that increased the artery systolic pressure 15–40 mmHg. Each dose was administered twice.

The change in pressure (mmHg) from the start of the increase in arterial systolic blood pressure until the maximum pressure was attained was the independent X variable. The RR intervals (milliseconds) seen after this increase were set as the dependent Y variables and at least 15 RR intervals were measured in each test. A linear correlation analysis using these data was then carried out. After plotting each arterial systolic blood pressure change and the RR intervals following this change, a regression coefficient ‘b’ and intercept ‘c’ were calculated. When the linear correlation coefficient (r) was greater than 0.8, a regression equation was calculated: Y = a + bX, the average value of three repetitions of the measurement of b was the BRS, and is shown as ms/mmHg.

**Measurement of haemodynamic parameters**

In all dogs, haemodynamic parameters were measured first in a closed-chest state before pacemaker implantation and again...
4–5 weeks later, at the end of the pacing period. For these measurements, dogs were anaesthetized, and the right femoral vein was catheterized for IV access. A Swan-Ganz catheter was passed into the right atrium, right ventricle, and pulmonary artery from the external jugular vein, and right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure were each measured using a Spectramed P23XL transducer on a Marquette Transcope 12 monitor (Marquette Co., USA).

Cardiac output (CO) was determined using the temperature dilution curve technique. Arterial blood pressure was measured from the femoral artery using a transducer (Spectramed P23XL). The cardiac index (CI, CI = CO/HR), and total peripheral resistance (TPR, TPR = mean ABP/CI x 100) were calculated from these data.16

Measurement of cardiac electrophysiology parameters
For cardiac electrophysiology measurements, the heart was exposed after anaesthesia through a median sternotomy and cradled in the pericardium. For electrical stimulation of the heart, a pair of stainless steel-wire electrodes (0.125 mm in diameter, 5 mm apart) were inserted into the right atrial appendage, using a 22 gauge injection needle. Additional electrode pairs were inserted into the right ventricular outflow tract, the right ventricular lateral wall, the left ventricular anterior wall, and the apex of the heart. A standard lead II surface electrocardiogram, ventricular bipolar electrograms, and ventricular epicardial monophasic action potentials (MAPs) were recorded synchronously using a multiple channel physiological recorder (Mingograph 7) at a paper speed of 100 mm/s. The ventricular MAP was recorded using unipolar contact electrodes (Guangzhou Radio Research Institute, People’s Republic of China). The range of the filter wave of the ventricular bipolar electrograms was 50–500 Hz.

Four parameters were derived from these records: VRT-D, ventricular late recovery time duration, the proportion of the action potential taken up by the effective refractory period (VERP/MAPD90), and the fibrillation threshold (VT).

Ventricular recovery time dispersion was the difference between the shortest and longest VRT recorded from the different ventricular sites (right ventricular outflow tract, right ventricular anterior wall, left ventricular lateral wall, left ventricular anterior wall, and the apex) at the same cardiac cycle length. Ventricular recovery time was the sum of ventricular activation time and VERP in the same cardiac cycle. Ventricular activation time was the interval from the onset of the standard lead II ECG QRS complex to the point where the rapid deflection of the local ventricular bipolar electrograms crossed the baseline.18 Ventricular effective refractory period was measured by S1S2 programmed stimulation (Medtronic 5323, Medtronic Co., USA). As the S1S2 interval decreased in 10 ms intervals, scanning was carried out until the S1S2 interval was so short that S2 was no longer able to evoke ventricular depolarization. Stimulation intensity was two times of the pacing threshold in the diastole, and pulse width was 1.8 ms. Ventricular effective refractory period was defined as the longest S1S2 interval that did not evoke ventricular depolarization.20

Ventricular late repolarization duration, the portion of the action potential subsequent to the effective refractory period, was measured as the difference between the local ventricular MAP (MAPD90) and the VERP at the same cardiac cycle length. Monophasic action potential duration was the interval, along a line horizontal to the diastolic baseline, from the onset of zero phase depolarization to the 90% repolarization level.21

The ratio of VERP to MAPD90 at the same cardiac cycle length was calculated (VERP/MAPD90). The above parameters were measured during atrial or ventricular pacing at 375 ms and 400 ms cardiac cycle length.

Finally, the VFT was determined. Ventricular fibrillation threshold was measured by a train of constant current pulses that scanned the T-wave at a stable atrial paced cycle length of 400 ms.22 Fibrillation threshold, VFT, was defined as the smallest amount of current required to elicit ventricular fibrillation. Within 15 s after ventricular fibrillation occurred, intrathorax non-synchronous DC cardiac defibrillation was performed at the energy of 5–15 J. Ventricular fibrillation threshold was assessed three times in each animal, and the mean value was calculated. The second and third assessments were done after defibrillation had been achieved and a normal sinus rhythm had returned for at least 15 min.

Gross and pathological examination of the heart
Pericardial effusion, pleural effusion, and the gross changes of the lungs were assessed at the time of thoracotomy. Then, after electrophysiological measurement had been taken, the heart was removed and heart weight, heart weight to body weight ratio, left and right ventricular free wall thickness, left ventricular longitudinal diameter, and right ventricular transverse diameter were each measured, and the left ventricular wall thickness was calculated.

The following definitions were employed for these measurements:16 left and right ventricular free wall thickness was measured at a point on the free ventricular wall half-way from the atroventricular valvular ring to the apex of heart; left ventricular longitudinal diameter was the length of the chamber from the left ventricular atroventricular valvular ring to the apex of heart. Right ventricular transverse diameter was the width of the chamber at half-way from the atroventricular valvular ring to the apex. Left ventricular volume was \( \pi \times \text{left ventricular long diameter} \times \text{right ventricular transverse diameter} \).16

Fresh left and right ventricular tissues were obtained from each heart and fixed for 12–24 h in a 10% formalin solution. The tissues were then embedded in paraffin and sectioned. The sections were observed under optical microscope using haematoxylin and eosin (H&E) staining.

Statistical analysis
Clinical parameters are expressed as mean and SD and compared using non-parametric methods. The differences between haemodynamic parameters before and after implantation surgery for the same dog were examined using the Wilcoxon Sign Rank test, and comparisons between the CHF and control groups were made using the Wilcoxon Rank Sum test. Pearson’s correlation was used to examine correlations between ventricular electrophysiological variables and HRV and BRS. The statistical analyses were performed using SAS 9.0 (SAS Institute Inc., Cary, NC, USA) and the significance level was set at 0.05.

Results
Four to five weeks after initiation of rapid right ventricular pacing, all dogs in the CHF group showed signs of congestive failure, such as anorexia, limb oedema, and hypokinetics. Moist rales could be heard bilaterally in their lungs. In addition, their respiratory rate had increased significantly \( (P < 0.01) \), from 18 ± 1 to 40 ± 3 breaths/min. Body weight, however, did not change \( (14.3 \pm 1.9 \text{ kg, } P > 0.05) \).
None of the above changes were seen in the control group. The respiratory rates of dogs in the control and CHF groups at the time of ECG recording for HRV analysis were 17.7 ± 2.2 and 40.3 ± 2.5 breaths/min, respectively ($P < 0.01$).

Congestion and oedema in both lungs were seen in all, pericardial effusion in most, and pleural effusion and ascites in some dogs in the CHF group. Gross anatomy of heart in the CHF group showed an enlarged heart: heart weight, heart weight/body weight, left ventricular longitudinal diameter, right ventricular transverse diameter, and left ventricular volume were all significantly increased compared with the control group, and right ventricular free wall thickness was significantly decreased (data not shown). Histological examination of the left and right ventricles in the CHF dogs showed vascular congestion in the endocardium and epicardium and an infiltration of neutrophils and lymphocytes. The myocardial cells showed oedema. Fatty degeneration, increase of cell fusion, and some necrosis and lysis were seen. Interstitial vasculitis with congestion was also observed. Occasionally, haemorrhagic foci could be found with substantial neutrophil and lymphocyte infiltration. Together, these data demonstrate that the model was successful in establishing CHF according to the diagnostic criteria suggested by Armstrong et al.$^{16}$

After 4–5 weeks of pacing, mean right atrial and ventricular pressures and pulmonary artery and capillary wedge pressures had significantly increased over pre-pacing values in the CHF group, and CO, CI, and SV were significantly decreased (all $P < 0.01$, Table 1). The control group showed no such changes during this period (data not shown). Total peripheral resistance in the CHF group at the end of pacing was significantly higher than that seen in the control group (78.4 ± 27.8 vs. 36.5 ± 11.4 mmHg min kg/mL, $P < 0.01$).

The CHF group, in addition to showing clear signs of congestive failure after pacing (see above), showed significant decreases in the two markers of autonomic function measured, HRV and BRS. Both the time and frequency domains of HRV were significantly lower, although LF/HF ratio was not (Table 2). Baroreflex sensitivity also decreased to 8.13 ± 2.50 ms/mmHg from a pre-pacing value of 15.85 ± 2.13 ms/mmHg ($P < 0.01$). Graphs of BRS are shown in Figure 1. No such decreases were seen in the control group.

In the myocardium itself, increase in action potential duration and effective refractory period in the ventricles accompanied the post-pacing signs of congestive failure and decrease in autonomic sensitivity seen in CHF dogs (Table 3). Monophasic action potential duration and VERP were 45 and 26% longer (respectively) in the CHF groups than in the control group ($P < 0.01$).

### Table 1

<table>
<thead>
<tr>
<th>Haemodynamic parameter</th>
<th>Pre-ventricular pacing</th>
<th>Post-ventricular pacing</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RAP (kPa)</td>
<td>0.189 ± 0.244</td>
<td>1.200 ± 0.461</td>
<td>0.0005</td>
</tr>
<tr>
<td>Mean RVP (kPa)</td>
<td>0.900 ± 0.607</td>
<td>2.000 ± 0.900</td>
<td>0.0015</td>
</tr>
<tr>
<td>Mean PAP (kPa)</td>
<td>1.144 ± 0.782</td>
<td>2.433 ± 1.137</td>
<td>0.0005</td>
</tr>
<tr>
<td>Mean PCWP (kPa)</td>
<td>0.244 ± 0.253</td>
<td>1.188 ± 0.671</td>
<td>0.0005</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.925 ± 0.746</td>
<td>1.425 ± 0.476</td>
<td>0.0005</td>
</tr>
<tr>
<td>CI (L/min/mmHg)</td>
<td>0.278 ± 0.044</td>
<td>0.120 ± 0.031</td>
<td>0.0005</td>
</tr>
<tr>
<td>SV (mL/beat)</td>
<td>0.025 ± 0.004</td>
<td>0.011 ± 0.002</td>
<td>0.0005</td>
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</tbody>
</table>

RAP, right atrial pressure; RVP, right ventricular pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; SV, stroke volume; TPR, total peripheral resistance.

### Table 2

<table>
<thead>
<tr>
<th>Time or frequency domain parameters</th>
<th>Control (n = 10)</th>
<th>CHF (n = 12)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (ms)</td>
<td>83.000 ± 15.699</td>
<td>52.333 ± 14.549</td>
<td>0.0025</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>41.600 ± 16.290</td>
<td>22.333 ± 7.426</td>
<td>0.0049</td>
</tr>
<tr>
<td>PNN50 (%)</td>
<td>9.330 ± 5.287</td>
<td>5.350 ± 2.616</td>
<td>0.0253</td>
</tr>
<tr>
<td>VLF (ms$^2$/Hz)</td>
<td>28.400 ± 9.192</td>
<td>17.250 ± 8.291</td>
<td>0.0231</td>
</tr>
<tr>
<td>LF (ms$^2$/Hz)</td>
<td>23.500 ± 5.893</td>
<td>10.750 ± 4.750</td>
<td>0.0016</td>
</tr>
<tr>
<td>HF (ms$^2$/Hz)</td>
<td>15.400 ± 4.526</td>
<td>6.250 ± 2.598</td>
<td>0.0009</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.555 ± 0.199</td>
<td>1.815 ± 0.625</td>
<td>0.2008</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; SDNN, standard deviation of all normal sinus rhythm RR intervals within the specified time; rMSSD, root-mean-square standard deviation of the continuous normal sinus rhythm RR intervals within the specified time; PNN50, percentage of number of every two adjacent >50 ms normal sinus rhythm RR intervals in the total number of all normal sinus rhythm RR intervals within the specified time; VLF, very low-frequency band; LF, low-frequency band; HF, high-frequency band; LF/HF, ratio of low- to high-frequency bands.
Action potentials became less uniform as well as longer. Variation in action potential recovery time, VRT-D, increased 164% \((P < 0.01)\) over control group values. Ventricular late repolarization duration, the portion of the action potential subsequent to the effective refractory period, was 360% longer \((P < 0.05)\). Because VLRD occupied a longer portion of the total action potential duration, the effective refractory period occupied a shorter fraction, and the VERP/MAPD\(_{90}\) ratio was smaller in the CHF group than in the control group \((P < 0.05)\).

Ventricular fibrillation was more easily produced in CHF dogs than in controls, and the threshold for fibrillation, VFT, was significantly lower \((P < 0.01)\).

In CHF dogs, HRV was negatively correlated with VLRD and VRT-D \((r = -0.861 \text{ to } -0.579, P < 0.01 \text{ and } P < 0.04, \text{ respectively})\). Table 4), that is, the lower the HRV, the greater the late repolarization duration, and the more variable the action potential recovery time in the ventricles. Heart rate variability was positively correlated with VERP/MAPD\(_{90}\) and VFT \((r = 0.626 - 0.854, P < 0.05 \text{ and } P < 0.01, \text{ respectively})\), that is, the lower the HRV, the smaller the fraction of the action potential occupied by the effective refractory period.

Like HRV, BRS, the other marker of autonomic function, was negatively correlated with VRT-D and VLRD \((r = -0.861 \text{ and } -0.781, \text{ respectively}, P < 0.01)\) and was positively correlated with VERP/MAPD\(_{90}\) and VFT \((r = 0.734 \text{ and } 0.777, \text{ respectively}, P < 0.01)\).

### Table 3 Changes in ventricular electrophysiological parameters 4–5 weeks after rapid ventricular pacing (congestive heart failure) or sham operation (control)

<table>
<thead>
<tr>
<th>Ventricular electrophysiological parameter</th>
<th>Control (n = 10)</th>
<th>CHF (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERP (ms)</td>
<td>169.00 ± 11.254</td>
<td>212.916 ± 38.106</td>
<td>0.0374</td>
</tr>
<tr>
<td>MAPD(_{90}) (ms)</td>
<td>179.00 ± 18.678</td>
<td>259.166 ± 43.632</td>
<td>0.0039</td>
</tr>
<tr>
<td>VRT-D (ms)</td>
<td>13.800</td>
<td>37.333 ± 14.163</td>
<td>0.0021</td>
</tr>
<tr>
<td>VLRD (ms)</td>
<td>10.000 ± 14.142</td>
<td>46.250 ± 35.170</td>
<td>0.0247</td>
</tr>
<tr>
<td>VERP/MAPD(_{90})</td>
<td>0.949 ± 0.076</td>
<td>0.831 ± 0.134</td>
<td>0.0357</td>
</tr>
<tr>
<td>VFT (mA)</td>
<td>33.750 ± 6.559</td>
<td>11.541 ± 8.993</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. CHF, congestive heart failure; VERP, ventricular effective refractory period; MAPD\(_{90}\), the interval, along a line horizontal to the diastolic baseline, from the onset of zero phase depolarization to the 90% repolarization level; VRT-D, ventricular recovery time dispersion; VLRD, ventricular late repolarization duration; VERP/MAPD\(_{90}\), the ratio of ventricular effective refractory period to the interval, along a line horizontal to the diastolic baseline, from the onset of zero phase depolarization to the 90% repolarization level; VFT, ventricular fibrillation threshold.

### Table 4 Summary of the Pearson’s correlations of ventricular electrophysiological variables and heart rate variability and baroreflex sensitivity in the congestive heart failure group of dogs after 4–5 weeks of rapid ventricular pacing

<table>
<thead>
<tr>
<th>HRV</th>
<th>BRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDNN</td>
</tr>
<tr>
<td>VRT-D</td>
<td>-0.61*</td>
</tr>
<tr>
<td>VLRD</td>
<td>-0.86**</td>
</tr>
<tr>
<td>VERP/MAPD(_{90})</td>
<td>0.85**</td>
</tr>
<tr>
<td>VFT</td>
<td>0.67*</td>
</tr>
<tr>
<td>BRS</td>
<td>0.63*</td>
</tr>
</tbody>
</table>

HRV, heart rate variability; BRS, baroreflex sensitivity; VRT-D, ventricular recovery time dispersion; VLRD, ventricular late repolarization duration; VERP/MAPD\(_{90}\), the ratio of ventricular effective refractory period to the interval, along a line horizontal to the diastolic baseline, from the onset of zero phase depolarization to the 90% repolarization level; VFT, ventricular fibrillation threshold; SDNN, standard deviation of all normal sinus rhythm RR intervals within the specified time; rMSSD, root-mean-square standard deviation of the continuous normal sinus rhythm RR intervals within the specified time; PNN50, percentage of number of every two adjacent > 50 ms normal sinus rhythm RR intervals in the total number of all normal sinus rhythm RR intervals within specified time; VLF, very low-frequency band; LF, low-frequency band; HF, high-frequency band.

*\(P < 0.05\), **\(P < 0.01\).
that is, the less sensitive the autonomic nervous system to blood pressure change, the more variable the recovery time of the action potential, the longer the post-effective refractory period portion of the action potential, and the smaller the electrical stimulus needed to evoke ventricular fibrillation. In the control group, no correlations between either HRV or BRS and these ventricular electrophysiological parameters were found. Representative correlation plots are shown in Figure 2. Baroreflex sensitivity was also positively correlated to the time and frequency parameters of HRV, that is, SDNN, rMSSD, PNN50, VLF, LF, and HF ($r = 0.603–0.814$, $P < 0.05$ and $P < 0.01$) (Table 4).

Ventricular fibrillation threshold was negatively correlated to action potential recovery variability (VRT-D, $r = -0.579$, $P < 0.05$) and to late repolarization duration (VLRD, $r = -0.749$, $P < 0.01$), and positively correlated to VERP/MAPD90 ($r = 0.674$, $P < 0.05$). In other words, ease of inducing fibrillation was linked to lower HRV, and shorter effective refractory portions and longer late refractory portions of the total action potential.

Discussion

Our pacing protocol was successful in establishing CHF, as has been previously reported by others.$^{23}$ Dogs in subjected to 4–5 weeks of rapid right ventricular pacing had decreased activity levels, oedema, increased intracardial pressures, reduced CO, and cardiac dilatation. Changes in clinical manifestations, haemodynamic, and cardiac pathology in these dogs were consistent with those reported for CHF in the literature.$^{16,22–25}$

The present study showed that both effective refractory period and action potential duration were increased in dogs with pacing-induced CHF compared with control dogs while the VERP/MAPD90 was decreased. This latter finding suggests that the increase in action potential duration was more significantly prolonged than the increase in effective refractory period in CHF.

The VLRD (the portion of the action potential that includes the relatively refractory period, vulnerable period, and super normal period) was significantly prolonged in CHF dogs. The VLRD prolongation can produce temporary conduction block in a portion of the myocardium, and, in this way, enable re-entry to occur. In addition, a prolonged VLRD or incomplete repolarization can result in early after-depolarizations which, if large enough, can become action potentials and cause triggered arrhythmias. Therefore, VLRD prolongation is thought to facilitate the genesis of ventricular arrhythmias. This hypothesis is further supported by the fact that early after-depolarizations have been recorded in both animal models of CHF and in isolated myocytes from human patients with heart failure.$^{19,26,27}$

The present study also found increased dispersion in action potential recovery time in the ventricles of CHF dogs. Myocardial cells with long recovery times are thought to be able to form a unidirectional block, and when electrical signals are conducted from myocardium with a short VRT to the myocardium with a long VRT, re-entry may occur and may result in the occurrence of sustained ventricular arrhythmias.$^{19}$

Bai et al.$^{28}$ have previously reported that the incidence of ventricular fibrillation is increased in dogs with CHF induced by rapid right ventricular pacing. In our study, the fibrillation threshold was lower in CHF than in control dogs. In addition, VRT-D and VLRD were significantly and negatively correlated with VFT, and VERP/MAPD90 was positively correlated with VFT. Together, our findings suggest that CHF-induced alterations in the electrophysiological properties of the myocytes lead to electrical instability and arrhythmia.

It has been suggested that significant reductions in HRV, and BRS that reflect autonomic nerve function, could be used to predict sudden cardiac death.$^{7–10}$ Prior researches have found that abnormal distribution of autonomic nerves innervating the ventricular muscles, excessive activation of the sympathetic nerve, and heterogeneity of sympathetic innervation of ventricular myocytes may result in uneven ventricular repolarization, an increase in dispersion of repolarization, and an increase in ventricular electric instability so that ventricular fibrillation is easy to induce.$^{29,30}$

Thus, indirect measurement of autonomic nervous system function via HRV and/or BRS may serve as a means of identifying CHF patients at risk for the development of cardiac arrhythmias and cardiac sudden death. As in previously reported studies,$^{8,9}$ it was
References

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References

22. Lu F, Zhang XM, Mei BY. Effects of propafenone, quinidine, and their combination on atrial repolarization parameters and with fibrillation threshold. These results support the contention that a relationship exists between autonomic nervous system function and sudden cardiac death, and that alterations in autonomic nervous system function correlate with ventricular electrophysiological characteristics. It is hoped that this and subsequent research will assist in the development of ways to minimize the development of cardiac arrhythmias and sudden cardiac death in patients with CHF.