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Heart Rate Variability in a Progressive Heart Failure Model with Rapid Ventricular Pacing

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ABSTRACT

Background: Heart rate variability (HRV) is an indicator of autonomic nervous system functionality and a recognized predictor of cardiac death; however, the changes in HRV occurring in progressive heart failure are not fully understood. The purpose of this study was to evaluate the progressive changes of autonomic system activity in progressive heart failure by rapid ventricular pacing in an animal model.

Methods: Heart failure was induced in 13 mongrel dogs (27.8 ± 3.7 kg) by rapid ventricular pacing (230 beats/min) for 4 weeks and maintenance of pacing at a reduced rate (190 beats/min) for 2 weeks. Time domain analysis and spectral analysis of HRV were performed with the MemCalc system after 30 minutes of pacing cessation every week. Hemodynamic and echocardiographic data were obtained before and after induction of heart failure.

Results: Cardiac output decreased significantly (3.6 L/min versus 1.6 L/min, $P < .001$) after 6 weeks of ventricular pacing. Significantly increased were the heart rate (126 beats/min versus 138 beats/min, $P < .05$), left ventricular end-diastolic pressure (9.1 mm Hg versus 30.9 mm Hg, $P < .001$), and pulmonary capillary wedge pressure (8.0 mm Hg versus 18.7 mm Hg, $P < .001$). High-frequency components progressively decreased. Low-frequency components progressively decreased except at 5 weeks after the pacing. A ratio of low- to high-frequency components increased in moderate heart failure and decreased in severe heart failure.

Conclusions: Changes in the high-frequency component and low-frequency component are important for assessing heart failure in progressive heart failure. Serial follow-up measurements of HRV might be helpful for patients with such disease.

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INTRODUCTION

Heart rate variability (HRV) is an indicator of the status of the autonomic nervous system. HRV contains some frequency components, which are divided into low- and high-frequency components by spectral analysis. The low-frequency component (LF) of HRV (0.04-0.15 Hz) is modulated by both the sympathetic nervous system and the parasympathetic nervous system, whereas the high-frequency component (HF) of HRV (0.15-0.4 Hz) is mainly modulated by the parasympathetic nervous system [Coumel 1991; Schwartz 1992]. The LF/HF ratio in HRV is used to assess a predominant shift in the sympatho-parasympathetic balance [Scalvini 1998]. Mild or moderate heart failure has been reported to be associated with reduced HF variability and increased LF variability [Casolo 1995]. LF variability has also been shown to decrease or even disappear in advanced congestive heart failure [Ponikowski 1996]. Depressed HRV has an independent prognostic value in patients with chronic heart failure [Ponikowski 1996, 1997; Galinier 2000]. However, the results about how HRV correlates to cardiac function during progressive aggravation of heart failure have not been fully assessed [Binkley 1991; Eaton 1995; Ishise 1998]. The hypothesis of the present study is that continuous measurements of HRV can detect the progression of heart failure.

The chronic rapid ventricular-pacing model has frequently been used in dogs because it induces severe heart failure. The resulting clinical, echocardiographic, hemodynamic, and neurohormonal changes are very similar to those found in patients with dilated cardiomyopathy [Takagaki 2002]. The purposes of this research were (1) to measure time courses of HRV changes during the progression of heart failure induced by rapid ventricular pacing and (2) to measure hemodynamic and echocardiographic data under anesthetized conditions before and after the induction of heart failure.

MATERIALS AND METHODS

Animal Model

Thirteen mongrel dogs (mean weight ± SD, 27.8 ± 3.7 kg) in sinus rhythm were used in this study. This study was

approved by the Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (http://www.nap.edu/catalog/5140.html).

Induction of Heart Failure

A venous catheter was placed in a peripheral vein to administer fluids. The animal was anesthetized with intravenous thiopental (20 mg/kg) and ventilated with a respirator (Servo Ventilator 900C; Siemens-Elema, Solna, Sweden) through an endotracheal tube. Anesthesia was maintained with isoflurane (1.5%). Electrocardiographic (ECG) leads were attached to the extremities to monitor cardiac vital signs. The carotid artery was cannulated with an 8F sheath to be used for a Millar catheter (Millar Instruments, Houston, TX, USA) to measure the left ventricular (LV) pressure. The side port of the sheath was used for monitoring the arterial pressure. The respirator setting was adjusted as required on the basis of arterial blood gas measurements. In addition, an 8F introducer sheath for a 7.5F Swan-Ganz catheter (Baxter Healthcare, Irvine, CA, USA) was inserted into the jugular vein to acquire hemodynamic data, including the arterial pressure, the right atrial pressure (RAP), the pulmonary arterial pressure (PAP), the pulmonary capillary wedge pressure (PCWP), and cardiac output (CO).

After acquisition of baseline hemodynamic data, the 8F and 7.5F sheaths were removed. A bipolar pacemaker lead (CapSureFix® Novus 5076; Medtronic, Minneapolis, MN, USA) was inserted under fluoroscopic guidance into the right ventricular apex via the right jugular vein and attached to a programmable pulse generator (Medtronic 8086) placed into a deep submuscular cervical pocket.

After recovery from anesthesia, the animal was returned to its housing, and it received a standard diet with free access to water and an antibiotic regimen of ampicillin (500 mg orally) for 5 days and cephalexin (500 mg orally) for 3 days. Rapid ventricular pacing at 230 beats/min in the asynchronous mode was initiated 2 or more days after pacemaker implantation and was maintained for 4 weeks, with maintenance pacing continuing at a reduced rate (190 beats/min), as we previously reported [Takagaki 2002]. No medications for congestive heart failure, including diuretics, were given during the ventricular-pacing period, and the animal was under careful observation for signs or symptoms of congestive heart failure.

Hemodynamic and Echocardiographic Data

Hemodynamic data were obtained at the time of pacemaker implantation and for 6 weeks after rapid ventricular pacing. Seven to 10 consecutive beats were recorded for analysis. The maximum rate of LV pressure change (LV *dp/dt* max) was determined as the first derivative of the LV pressure.

Transesophageal echocardiographic examinations were performed by means of a Sequoia 512 digital ultrasonographic system (Siemens, Mountain View, CA, USA) equipped with a high-frequency transducer (frequency, 5-7 MHz) and with the dog in an anesthetized condition. All Doppler echocardiographic images were obtained and recorded during 3 to 5 consecutive cardiac cycles in sinus rhythm. The LV end-diastolic volume (LVEDV) and the LV end-systolic volume (LVESV) were measured by the single-plane Simpson rule. The LV ejection fraction (LVEF) was calculated as follows: LVEF = 100 × (LVEDV – LVESV)/LVEDV.

HRV Analysis

Autonomic activities before and after induction of heart failure were quantified by wavelet analysis of HRV, as other investigators have reported elsewhere [Takusagawa 1999; Kanaya 2003]. In brief, time domain analysis and spectral analysis of HRV were performed with the MemCalc system (MemCalc Version 2.5; Suwa Trust Co, Tokyo, Japan) with each dog in an unanesthetized condition. The system continuously provides heart rate, HF, LF, and LF/HF data every 2 seconds. HRV data collection required approximately 11 minutes for each experimental subject. One minute was required to obtain a baseline reading, and HRV data were collected over a period of 10 minutes. The dogs were connected to the ECG machine by 3 ECG leads: 2 leads on the front limbs and 1 lead on a hind limb. They were placed in a calm, separate room. HRV data were collected in the morning, and the dogs did not eat prior to data collection. We measured HRV at baseline and every week for 6 weeks after initiating rapid ventricular pacing after 30 minutes of pacing interruption. The HF (0.15-0.5 Hz) was defined as a marker of parasympathetic nervous activity, and the LF (0.04-0.15 Hz) was related to a combination of parasympathetic and sympathetic nervous system activities. The LF/HF ratio was defined as an indicator of sympathetic nerve activity.

Atrial Natriuretic Peptide

Before pacemaker implantation and over 6 weeks after initiation of rapid ventricular pacing, venous blood was drawn and collected into tubes containing EDTA (3 mM) and benzamidine (9 mM) for measurement of plasma atrial natriuretic peptide (ANP) (NH_2-terminal portion). After centrifugation, plasma samples were stored at –80°C until measurements were taken. We measured ANP in extracts by radioimmunoassay with commercially available specific antibodies and synthetic peptides from Peninsula (Belmont, CA, USA) as well as tracers iodinated and purified by high-performance liquid chromatography in our laboratory.

Statistical Analysis

The hemodynamic variables were measured with a PowerLab data-acquisition system (ADInstruments, Mountain View, CA, USA) at 200 Hz and analyzed with a custom-made Visual Basic program on Excel software (Excel 2000; Microsoft Corporation, Redmond, WA, USA). All values were expressed as the mean ± SD. A paired Student *t* test was used to assess the differences between the baseline data and data obtained weekly after induction of heart failure. Differences with *P* values <.05 were considered statistically significant.

RESULTS

Hemodynamic and echocardiographic data such as heart rate (126 ± 17 beats/min versus 138 ± 21 beats/min, $P < .05$), mean RAP (3.5 ± 2.7 mm Hg versus 12.9 ± 4.5 mm Hg, $P < .001$), mean PAP (14.0 ± 4.2 mm Hg versus 31.1 ± 10.0 mm Hg, $P < .001$), PCWP (8.1 ± 3.2 mm Hg versus 20.6 ± 7.9 mm Hg, $P < .001$), end-diastolic LV pressure (8.2 ± 2.1 mm Hg versus 30.1 ± 11.7 mm Hg, $P < .001$), LVEDV (36.7 ± 10.5 mL versus 81.1 ± 17.6 mL, $P < .001$), and LVESV (21.4 ± 7.7 mL versus 63.8 ± 11.4 mL, $P < .001$) revealed significant increases by 6 weeks after initiation of rapid ventricular pacing (Table 1). Mean arterial pressure (113.3 ± 15.1 mm Hg versus 78.5 ± 19.7 mm Hg, $P < .001$), CO (3.6 ± 0.6 L/min versus 1.6 ± 0.4 L/min, $P < .001$), LV dp/dt max (1541 ± 242 versus 835 ± 252, $P < .001$), and LVEF (42.2% ± 11.6% versus 20.3% ± 8.5%, $P < .001$) had significant decreases after the pacing. Circulating ANP concentrations increased significantly, from 27.5 ± 34.8 pg/mL to 204.8 ± 146.0 pg/mL ($P < .05$).

The heart rate gradually increased during the induction of heart failure (Figure 1). The HF progressively decreased (Figure 2). The LF also progressively decreased, except at 5 weeks after the pacing (Figure 3). In contrast to the LF and HF, the LF/HF ratio showed a gradual increase by 4 weeks after the initiation of rapid ventricular pacing; however, the ratio decreased gradually at 5 and 6 weeks after the pacing (Figure 4).

Table 1. Hemodynamic and Echocardiographic Data before and after Initiation of Rapid Ventricular Pacing*

Variable	Baseline	6 Weeks
Heart rate, bpm	126 ± 17	138 ± 21
RAPm, mm Hg	3.5 ± 2.7	12.9 ± 4.5
PAPs, mm Hg	17.0 ± 4.3	34.8 ± 11.3
PAPd, mm Hg	11.5 ± 4.3	27.5 ± 8.5
PAPm, mm Hg	14.0 ± 4.2	31.1 ± 10.0
PCWP, mm Hg	8.1 ± 3.2	20.6 ± 7.9
LVPed, mm Hg	8.2 ± 2.1	30.1 ± 11.7
LV *dp/dt* max	1541 ± 242	835 ± 252
APs, mm Hg	126.9 ± 17.9	91.3 ± 19.5
APd, mm Hg	100.8 ± 13.1	70.3 ± 19.2
APm, mm Hg	113.3 ± 15.1	78.5 ± 19.7
CO, L/min	3.6 ± 0.6	1.6 ± 0.4
SV, mL	28.6 ± 4.4	11.3 ± 3.1
LVEDV, mL	36.7 ± 10.5	81.1 ± 17.6
LVESV, mL	21.4 ± 7.7	63.8 ± 11.4
LVEF, %	42.2 ± 11.6	20.3 ± 8.5

*Data are presented as the mean ± SD. Values of all variables measured at 6 weeks are significantly different from baseline values ($P < .05$). bpm indicates beats per minute; RAPm, mean right atrial pressure; PAPs, systolic pulmonary arterial pressure; PAPd, diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; LVPed, end-diastolic left ventricular pressure; APs, systolic arterial pressure; APd, diastolic arterial pressure; APm, mean arterial pressure; CO, cardiac output; SV, stroke volume; LVEDV, left ventricular end-diastolic pressure; LVESV, left ventricular end-systolic pressure; LVEF, left ventricular ejection fraction.

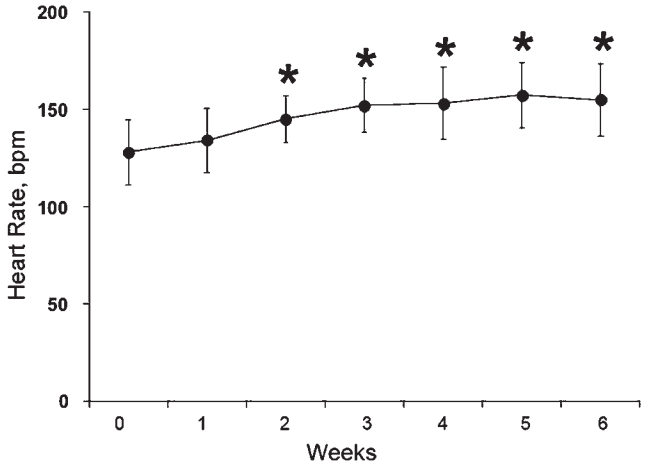

Figure 1. Heart rate after the initiation of rapid ventricular pacing. *$P < .05$, versus baseline (0 weeks). bpm indicates beats per minute.

DISCUSSION

Analysis of HRV after rapid ventricular pacing in our model revealed that (1) the HF decreased in accordance with the progression of severe heart failure and (2) the LF/HF ratio increased during the 4 weeks of rapid ventricular pacing at 230 beats/min. The LF/HF ratio decreased after that with the different pacing rate of 190 beats/min.

Changes in HRV have been widely reported in the presence of heart failure [Coumel 1991; Schwartz 1992; Scalvini 1998; Casolo 1995; Ponikowski 1996, 1997; Galinier 2000] or in response to several pharmacologic agents, such as an angiotensin-converting enzyme inhibitor [Petretta 2000], beta-blockers [Aronson 2001; Lampert 2003], and carvedilol [Bullinga 2005]. Hoffmann and associates reported that an analysis of time domain measurements indicated the reduction of HRV to be weakly correlated with impairment of the LVEF [Hoffmann 2000], whereas Nolan and associates reported no significant correlation [Nolan 1998]. From analyses

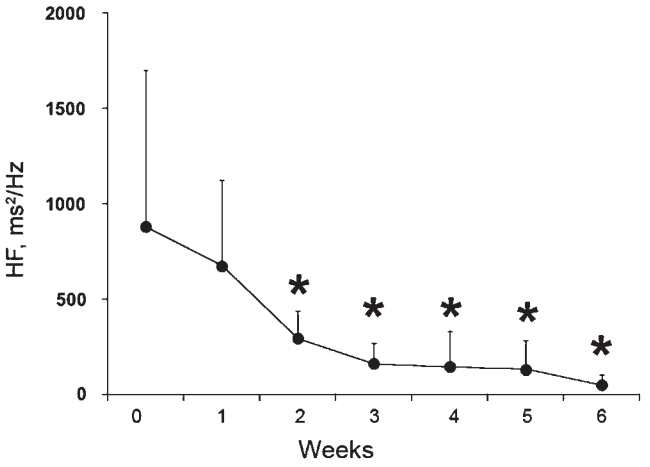

Figure 2. High-frequency component (HF) after the initiation of rapid ventricular pacing. *$P < .05$, versus baseline (0 weeks).

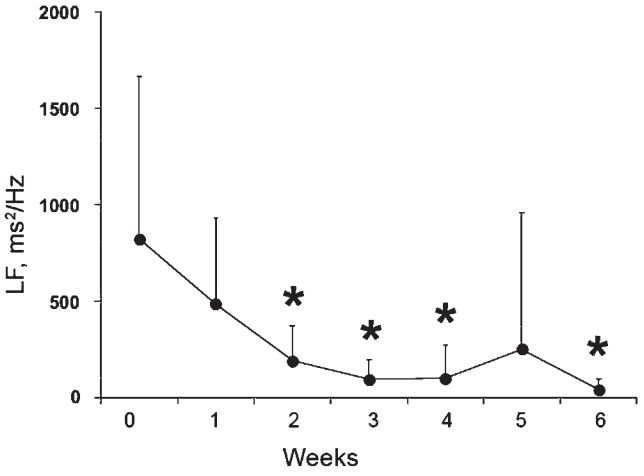

Figure 3. Low-frequency component (LF) after the initiation of rapid ventricular pacing. *$P < .05$, versus baseline (0 weeks).

of frequency domain measurements, the HF [Kawasaki 2003] and the LF [Galinier 2000] were revealed to be independent predictors of cardiac events; however, these studies were limited to assessing the changes in HRV in progressive heart failure, because several pharmacologic treatments should have been involved for the patients.

Rapid ventricular pacing was used to analyze HRV in progressive heart failure [Binkley 1991; Eaton 1995; Ishise 1998]. Although the study of Binkley and associates [1991] included a small number of animals (n = 4) and the time course of HRV was unclear, they reported that the HF area and the High/Low ratio had significantly decreased after induction of heart failure after 1 to 4 weeks of rapid ventricular pacing. Eaton and associates [1995] also reported that the HF and the High/Low ratio had significantly decreased and that the LF had significantly decreased after 7 days of rapid ventricular pacing. Ishise and associates [1998] reported that the LF and the HF had significantly decreased and that the LF/HF ratio had significantly increased after 2 weeks of rapid ventricular pacing [Ishise 1998]. Our results also revealed that the HF and the LF significantly decreased after 2 weeks of rapid ventricular pacing and that the results were similar to these previous results; however, a short duration of pacing did not induce symptomatic heart failure [Armstrong 1986]. The changes in HRV observed in the previous studies [Binkley 1991; Eaton 1995; Ishise 1998] might be relevant to mild or moderate heart failure.

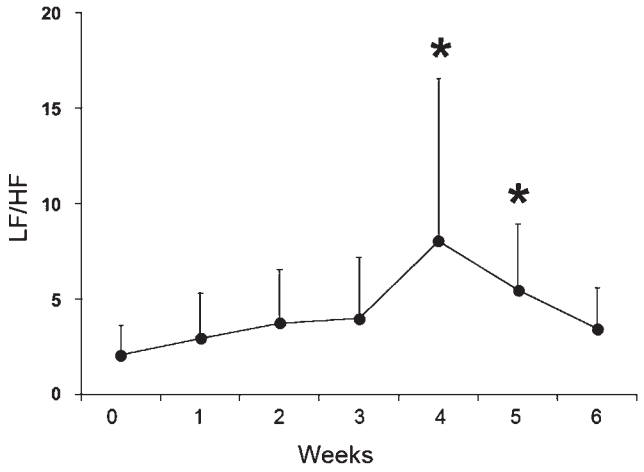

Figure 4. Ratio of low- to high-frequency components (LF/HF) after the initiation of rapid ventricular pacing. *$P < .05$, versus baseline (0 weeks).

Recently, Motte and associates [2005] reported the changes in HRV in a progressive experimental heart failure model that used rapid ventricular pacing for 7 weeks. These investigators reported that LVEF decreased from 65.3% to 37.7%, whereas we found that the LVEF decreased from 42.2% to 20.3%. Our result is possibly due to the anesthesia condition of the animals. Motte and associates reported that the HF decreased according to the progression of heart failure, whereas the LF/HF ratio increased in the beginning and then decreased at the end of heart failure induction. These results are very similar to our results. Lucreziotti and associates [2000] reported that a low LF/HF ratio was an independent predictor of cardiac events. Ponikowski and associates reported that LF variability decreased or even disappeared in advanced congestive heart failure [Ponikowski 1996]. LF values might be a more important predictor of cardiac events or even death in patients with severe heart failure. Because there was an elevation in LF and LF/HF values before heart failure was established, serial follow-up measurements of HRV also might be helpful for these diseased patients to distinguish the decreased LF/HF value with severe heart failure.

Nonphysiological rapid ventricular pacing may be a major limitation of this study with respect to extrapolating our result to human clinical cases; however, several investigators have reported the importance of a decreased LF or LF/HF ratio during severe heart failure [Ponikowski 1996; Lucreziotti 2000]. The second limitation of our study using rapid ventricular pacing is that each investigator needs to adjust the heart rate according to the progression of heart failure severity [Takagaki 2002; Motte 2005]. The change in the LF in our study was different from that reported by Motte and associates. It is possible that the different pacing protocol affected HRV. Further studies will be needed to investigate HRV in clinical patients with progressive heart failure.

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