Respiratory-related heart rate variability in progressive experimental heart failure

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Heart failure is associated with an autonomic imbalance, and this can be evaluated by a spectral analysis of heart rate variability. However, the time course of low-frequency (LF) and high-frequency (HF) heart rate variability changes, and their functional correlates during progression of the disease are not exactly known. Progressive heart failure was induced in 16 beagle dogs over a 7-wk period by rapid ventricular pacing. Spectral analysis of heart rate variability and respiration, echocardiography, hemodynamic measurements, plasma atrial natriuretic factor, and norepinephrine was obtained at baseline and every week. 30 min after pacing interruption. Progressive heart failure increased heart rate (from 91 ± 4 to 136 ± 5 beats/min; P < 0.001) and decreased absolute and normalized (percentage of total power) HF variability from week 1 and 2, respectively (P < 0.01). Absolute LF variability did not change during the study until it disappeared in two dogs at week 7 (P < 0.05). Normalized LF variability increased in moderate heart failure (P < 0.01), leading to an increased LF-to-HF ratio (P < 0.05), but decreased in severe heart failure (P < 0.044; week 7 vs. week 5). Stepwise regression analysis revealed that among heart rate variables, absolute HF variability was closely associated with wedge pressure, right atrial and pulmonary arterial pressure, left ventricular ejection fraction and volume, ratio of maximal velocity of mitral flow waves, left atrial diameter, plasma norepinephrine, and atrial natriuretic peptide (0.45 < r < 0.65, all P < 0.001). In tachycardia-induced heart failure, absolute HF heart rate variability is a more reliable indicator of cardiac dysfunction and neurohumoral activation than LF heart rate variability.

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HEART FAILURE is associated with an autonomic imbalance consisting of an increase in sympathetic drive (25) and a reduction of parasympathetic activity (5). In these patients, efferent sympathetic nerve traffic has been shown to be increased in proportion to functional impairment (16), norepinephrine plasma levels are associated with an increased risk of death (7), and β-blocker therapy improves survival (8). Thus autonomic imbalance with prominent sympathetic activation plays an important role in heart failure pathophysiology. Cardiac autonomic imbalance can be evaluated by the spectral analysis of R-R interval (RRI) variability (35). In normal humans and in dogs, RRI variability occurs predominantly at low frequency (LF, between 0.04 and 0.15 Hz) and at high frequency (HF, between 0.15 and 1.0 Hz) (29). LF oscillations are present in both sympathetic and vagal outflows (24, 30). However, within physiological conditions, sympathetic activation is associated with an increase in LF when expressed in normalized units (24, 26). HF oscillations occur with breathing and are known as respiratory sinus arrhythmia. Their quantification characterizes the response of the sinus node to fluctuations in vagal activity at the respiratory frequency and may correlate with the underlying mean level of that activity (11).

METHODS

Animal Preparation

The investigation was approved by the Institutional Animal Care and Use Committee of the Free University of Brussels and was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996).

Sixteen male beagle dogs were included in the study. After administration of cefazolin (20 mg/kg iv and 20 mg/kg sc) and premedication with midazolam (0.1 mg/kg iv) and methadone (0.3 mg/kg iv), the animals were anesthetized with intravenous propofol, 5 mg/kg followed by 5 mg·kg⁻¹·h⁻¹. During anesthesia, the dogs were intubated and ventilated with Elema B servo-ventilator (Siemens, Erlangen, Germany). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Germany), the fraction of inspired oxygen being 0.4, the respiratory rate at 12 breaths/min, and the tidal volume at 15 ml/kg. A bipolar pacemaker lead (Fineline II, model 4471, Guidant Brussels, Belgium) was surgically inserted in the right jugular vein and implanted in the right ventricular apex under fluoroscopic control. A multiprogrammable pulse generator (Insignia, Guidant) was inserted in the subcutaneous tissues of the cervical region and connected to the pacemaker lead.

**Experimental Protocol**

The experiment was a longitudinal repeated-measures study. The dogs underwent a modified pacing protocol with a stepwise increase of stimulation frequencies. The pacing was initiated after a 2-wk recovery period by activating the multiprogrammable pulse generator at 180 beats/min and continued during the first week, followed by 200 beats/min during a second week, 220 beats/min during a third week, and finally 240 beats/min during the final fourth week. The investigations were carried out at baseline (week 0) and once weekly throughout the pacing period (i.e., from week 1 to week 7) with exactly the same methods. Investigations were performed after a pacing interruption of at least 30 min and included blood sampling, hemodynamic and echocardiographic evaluation, as well as spectral analysis of RRI and respiration.

To exclude a possible impact of surgical intervention or the presence of inactivated pacemaker on cardiac function, preliminary experiments were performed on three sham-operated dogs. In these animals, clinical state, heart rate, and echocardiographic variables remained stable during 7 wk. It was therefore decided not to include a sham-operated control group in the present study.

**Measurements and Analytic Methods**

**Clinical examination.** The clinical examination included cardiac and lung auscultation, measurements of body weight, rectal temperature, and blood pressure. Systolic blood pressure was measured by Doppler sphygmomanometry (model 811-BTS, Parks Medical Electronics, Aloka, OR) on the forelimb of dogs placed in sternal recumbency and calculated as the mean of three consecutive measurements.

**Doppler echocardiography.** Doppler echocardiography (Pandion, Pie Medical Benelux, Zaventem, Belgium) was performed under continuous ECG monitoring using a 3.5- to 5-MHz mechanical sector probe, as previously described (27). Briefly, all the measurements were done in triplicate. A right parasternal window was used to evaluate systolic cardiac function and systolic and diastolic volume indexes. Left ventricular internal end-diastolic (LVIDd) and -systolic (LVIDs) diameters were determined in a right short-axis M-mode projection of the heart in a plane just below the mitral valves. From these data, left ventricular end-diastolic volume (EDV) and left ventricular ejection fraction (LVEF) were calculated by using the following formulas:

\[
EDV (\text{ml/m}^2) = \frac{(7 \cdot \text{LVIDd}^3)(2.4 + \text{LVIDd})}{\text{BSA}}
\]

\[
ESV (\text{ml/m}^2) = \frac{(7 \cdot \text{LVIDs}^3)(2.4 + \text{LVIDs})}{\text{BSA}}
\]

\[
\text{LVEF} (\%) = \left[ \frac{EDV - ESV}{EDV} \right] \cdot 100.
\]

A left apical long-axis view of the left ventricle was used to obtain images of the aortic flow and of the biventricular inflow (E and A wave) by pulsed-wave Doppler. Velocity spectra of aortic flow were used to measure the prejection period and left ventricular ejection time, whereas those of the mitral inflow were used to calculate the ratio of early-to-late diastolic flow velocities (E/A). Left ventricular isovolumic relaxation time (IVRT) was measured as the time period from the Doppler signal of aortic valve closure to the start of early diastolic flow.

**Hemodynamic evaluation.** Dogs were anesthetized and ventilated with the same anesthetic protocol as described in Animal Preparation and equipped with a fluid-filled systemic catheter and a 5-Fr Swan-Ganz catheter inserted in the left jugular vein. Heart rate, mean pulmonary arterial pressure (Ppa), occluded Ppa, and right auricular blood pressure were measured.

**Spectral analysis.** Ten-minute recordings of RRI period and respiration were made with dogs laying on a table in a conscious state. ECG electrodes were attached to forelimbs and hindlimbs while respiration was recorded with inductive plethysmography (spirotrace digital 100, Medical Electronic Construction, Brussels, Belgium) using a chest belt sensitive to both frequency and amplitude.

Analog-to-digital conversion was performed in real time at a rate of 200 Hz/channel with a six-channel recorder (model 2600S, Gould). The principles of the software for spectral analysis have been described elsewhere (29). In brief, a derivative-threshold algorithm provided the continuous series of RRI (tachogram) and the respirogram, derived from the ECG and the inductive plethysmography, respectively. All interpolated values were visually checked. Stationary segments devoid of arrhythmias were analyzed with autoregressive parametric spectral algorithms. This allowed a determination of total heart rate power (or variance), the power of the LF and HF oscillatory components in absolute units (ms²), and their center frequencies. In addition, the LF-to-HF ratio and LF and HF in normalized units were determined. Normalized units were obtained by dividing the power of each component by the total variance, from which the very LF (VLF) component had been subtracted, and this value was multiplied by 100. The respirogram underwent a similar analysis. The VLF component, which requires specific algorithms and longer data series, was not addressed in this study.

**Atrial natriuretic peptide.** Venous blood was drawn after each physical examination and collected into prechilled tubes containing EDTA (3 mM) and benzamidine (9 mM) for measurement of plasma atrial natriuretic peptide (NH₂-terminal portion). After centrifugation within 1 h, plasma was stored at −80°C until use. Atrial natriuretic peptide was measured on extracts by radioimmunoassay, as previously described (9), using commercially available specific antibodies and synthetic peptides from Peninsula (Belmont, CA), as well as tracers iodinated and HPLC purified in our laboratory.

**Plasma norepinephrine.** Venous blood was collected into hepati- natriuretic lithium tubes containing 200 µl of a solution of glutathion peroxidase (0.2 M) to avoid catecholamines degradation. Norepinephrine was measured by HPLC with intraassay and interassay coefficients of variation of 5% and 12.3%, respectively.

**Statistical Analysis**

All values are means ± SE. Echocardiographic and hemodynamic variables displayed a normal distribution. However, the distribution of the majority of the frequency domain heart rate variability variables was extremely skewed. Thus a log transformation of these measurements was applied to improve normality before the statistical analysis was performed. These measurements were back-transformed for presentation in the tables and figures. A repeated measures one-way ANOVA was first performed to calculate the P value for the trend of each variable over the time. When the F ratio of ANOVA reached a critical value of P < 0.05, modified t-tests, i.e., t-tests computed by using the residual mean square given by the ANOVA, were performed to compare specific situations (37). A forward stepwise regression analysis was used to investigate the correlation among echocardiographic, hemodynamic variables, and heart rate variability measurements (28).

**RESULTS**

The clinical examination showed a decrease in blood pressure and an increase in heart rate starting at the first week...
HEART RATE VARIABILITY IN EXPERIMENTAL HEART FAILURE

Table 1. Changes in hemodynamic variables, plasma atrial natriuretic peptide, and norepinephrine levels during progression of tachycardia-induced heart failure in dogs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (week 0)</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>sSAP, mmHg</td>
<td>156±6</td>
<td>138±6†</td>
<td>132±7*</td>
<td>124±5*</td>
<td>119±3*</td>
<td>124±6*</td>
<td>121±5*</td>
<td>122±5*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>91±4</td>
<td>104±3†</td>
<td>115±5*</td>
<td>115±5*</td>
<td>114±6*</td>
<td>129±5*</td>
<td>126±5*</td>
<td>143±3*</td>
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<td>ANF, pg/ml</td>
<td>55±7</td>
<td>67±6</td>
<td>79±6†</td>
<td>106±10*</td>
<td>139±11*</td>
<td>148±14*</td>
<td>162±16*</td>
<td>151±12*</td>
</tr>
<tr>
<td>NE, pg/ml</td>
<td>242±25</td>
<td>343±5†</td>
<td>389±5‡</td>
<td>384±4†</td>
<td>446±55*</td>
<td>594±81*</td>
<td>806±107*</td>
<td>921±153*</td>
</tr>
<tr>
<td>mPpa, mmHg</td>
<td>14±0.8</td>
<td>13±0.8</td>
<td>14±0.7</td>
<td>15±0.7</td>
<td>17±0.7</td>
<td>18±0.7*</td>
<td>20±1.8</td>
<td>22±2.2</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>9±0.6</td>
<td>8±0.7</td>
<td>9±0.5</td>
<td>10±0.5†</td>
<td>12±0.5*</td>
<td>14±0.6*</td>
<td>14±0.7*</td>
<td>16±0.8*</td>
</tr>
<tr>
<td>Pms, mmHg</td>
<td>5±0.3</td>
<td>4±0.2†</td>
<td>5±0.3</td>
<td>7±0.4‡</td>
<td>7±0.4*</td>
<td>8±0.4*</td>
<td>9±0.8*</td>
<td>10±0.7*</td>
</tr>
</tbody>
</table>

Values are means ± SE. sSAP, systolic systemic arterial blood pressure; HR, heart rate; ANF, atrial natriuretic factor; NE, norepinephrine; mPpa, mean pulmonary arterial pressure; Ppa, occluded Ppa; Pms, right atrial pressure. *P < 0.001 vs. baseline week; †P < 0.01 vs. baseline week; ‡P < 0.05 vs. baseline week.

Table 2. Echocardiographic changes during progression of tachycardia-induced heart failure in dogs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (week 0)</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>65.3±1.3</td>
<td>52.9±1.3*</td>
<td>47.7±2*</td>
<td>45.3±1.7*</td>
<td>40.2±2.2*</td>
<td>41.6±1.8*</td>
<td>37.8±2.2*</td>
<td>37.8±2.2*</td>
</tr>
<tr>
<td>PEPL/VLET Ao</td>
<td>0.31±0.01</td>
<td>0.42±0.01*</td>
<td>0.44±0.01*</td>
<td>0.46±0.01*</td>
<td>0.51±0.02*</td>
<td>0.56±0.02*</td>
<td>0.59±0.03*</td>
<td>0.61±0.03*</td>
</tr>
<tr>
<td>EDV, mℓ/ℓ²</td>
<td>99.6±4.4</td>
<td>99.5±3.8</td>
<td>116.1±6.5†</td>
<td>134.4±5.4*</td>
<td>146.0±6.6*</td>
<td>147.3±6.3*</td>
<td>157.0±12.8*</td>
<td>166.3±7.6*</td>
</tr>
<tr>
<td>LAD, cm</td>
<td>2.07±0.05</td>
<td>1.98±0.05</td>
<td>2.03±0.05</td>
<td>2.17±0.07</td>
<td>2.53±0.07*</td>
<td>2.68±0.10*</td>
<td>2.95±0.10*</td>
<td>3.05±0.07*</td>
</tr>
<tr>
<td>E/A</td>
<td>1.57±0.04</td>
<td>1.03±0.06*</td>
<td>1.16±0.04*</td>
<td>1.32±0.07‡</td>
<td>1.66±0.11</td>
<td>1.88±0.09†</td>
<td>1.97±0.12*</td>
<td>2.15±0.15*</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>60.3±2.0</td>
<td>68.8±2.3†</td>
<td>67.1±2.1‡</td>
<td>66.6±2.6β</td>
<td>64.5±2.4</td>
<td>63.8±1.3</td>
<td>59.4±1.6</td>
<td>55.5±2.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVEF, left ventricular ejection fraction; PEPL/VLET Ao, ratio of prejection period and left ventricular ejection time of aortic flow; EDV, end-diastolic volume; LAD, left atrial diameter; E/A, ratio of maximal velocity of E and A mitral flow waves; IVRT, isovolumic relaxation time. *P < 0.001 vs. baseline week; †P < 0.01 vs. baseline week; ‡P < 0.05 vs. baseline week.

The echo-Doppler examination of the heart showed a progressive decrease in LVEF and an increase in aortic ratio of prejection period to ejection time, starting at week 1, together with progressive increases in left ventricular volume and in left atrial diameter, which started at week 2 and 4, respectively (Table 2). Indexes of diastolic function, E/A and IVRT, showed a biphasic evolution with a decreased relaxation starting at week 1, a pseudonormal mitral inflow at the fourth week, and a restrictive pattern with elevated E/A at the fifth week, and a trend toward a shortened IVRT (Table 2).

The spectral analysis showed an early and drastic reduction of total and HF RRI power (from week 1; Table 3 and Fig. 1). Reductions in total RRI power were tightly correlated to absolute HF RRI variability changes (r = 0.96; P < 0.001). Absolute LF RRI variability decreased in week 7 (Fig. 1). During the progression of the disease, no significant differences were noted in the center frequency of the LF component of RRI variability, whereas the center frequency of the HF component, synchronous with the respiration, progressively increased from week 2 (Table 3). The percentage of HF in the spectral analysis of the respiratory signal was constant over the entire duration of the pacing protocol (Table 3).

The normalized HF RRI variability displayed a reduction from week 2 to 7 compared with the baseline week, but this reduction remained stable from week 5 to 7. As the normalized LF RRI increased (week 1), this led to an increased LF-to-HF ratio (week 2; Fig. 2). However, the normalized LF RRI decreased between week 5 and 7. The absolute and normalized LF component even disappeared in two dogs at week 7.

Mean Ppa increased from the fourth week, whereas occluded Ppa and right atrial blood pressure increased from the third week (Table 1). Mitral or tricuspid regurgitant murmurs were detected in 2, 9, 12, and 14 dogs from week 4, 5, 6, and 7, respectively. At week 5, 6, and 7, respectively, 3, 5, and 11 dogs presented with ascites.

Circulating atrial natriuretic peptide and norepinephrine were increased from week 2 and remained elevated until the end of the study (Table 1).

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Because LF variability could have been a predictor of some of the dependent variables up to the 5-wk point but failed to provide over all predictability because of a large fall at the end of the study, we repeated the multiple regression analysis after exclusion of the sixth- and seventh-week measurements. This did not change the significance of the results (data not shown). In addition, we calculated post hoc a simple linear correlation between the change in LVEF (ΔLVEF) and the changes in LF and HF variabilities (ΔLF and ΔHF, respectively) from baseline to week 7. The correlation between ΔLVEF and ΔLF was not significant (r = 0.11, P is not significant), whereas the correlation between ΔLVEF and ΔHF was significant (r = 0.30, P < 0.01). The results were exactly the same for calculated correlations between changes in LVEF and changes in LF and HF variabilities at week 5 (data not shown).

**DISCUSSION**

In the present model of progressive heart failure, spectral analysis of heart rate variability disclosed a biphasic evolution of LF variability, with initial increase followed by late decrease, whereas absolute HF variability showed a continuous decrease along with progressive alteration in systolic and diastolic indexes of ventricular function. This result suggests that absolute HF RRI variability may be superior to LF RRI variability as an indicator of heart failure severity.

The overpacing-induced congestive heart failure model is characterized by the rapid development (a few weeks) of a dilated cardiomyopathy with impaired systemic and regional hemodynamics, broad neurohumoral activation, and avid sodium and fluid retention (34). The model has been previously used to investigate the time course of sympathetic-vagal imbalance in progressive congestive heart failure (10, 20). However, in these studies, severe stages of the disease were induced in 1 or 2 wk with aggressive HF pacing (~250 beats/min), resulting in a subacute condition that might not be a sufficiently realistic reproduction of a chronic dilated cardiomyopathy clinical course. In the present study, the model was adapted with more progressive pacing, over a 7-wk observation period of time, allowing for heart rate variability analysis along with detailed echocardiographic and hemodynamic measurements at all stages of congestive heart failure severity (27).

In the present experiments, the baseline power density spectrum of heart rate was characterized by a predominance of the HF parasympathetically mediated region. This is in keeping with the known predominant resting vagal tone in resting dogs (32). With the onset of mild left ventricular systolic and diastolic dysfunction, there were major decreases of total RRI power and HF RRI variability, suggesting a significant contribution of decreased parasympathetic nervous system modulation in early heart failure pathophysiology. Rapid changes in RRI that occur at the start of muscular exercise, when standing up or lying down, are known to be parasympathetically mediated (3, 13, 14). A decrease in parasympathetic modulation is an integral component of cardiac autonomic imbalance (5) and, as such, is potentially implicated in ventricular arrhythmias and sudden cardiac death.

The HF spectral component of RRI variability continued to decrease during the progression of heart failure, whereas the
LF component and the LF-to-HF ratio increased gradually. This result is consistent with previous RRI variability studies (5, 10, 20) in patients or animals with moderate heart failure. There were also progressive increases in heart rate and in plasma norepinephrine, which is in keeping with previous reports (7, 36) on patients with advanced heart failure. The most obvious explanation for concomitant increases in LF RRI variability, resting heart rate, and plasma norepinephrine is a sympathetic nervous system activation.

However, in the present study, whereas the most advanced heart failure was, as expected, associated with tachycardia and increased plasma norepinephrine, a paradoxical decrease in the normalized LF component of RRI variability was observed, and this component in fact even disappeared in two of the animals. This biphasic evolution of the LF component of RRI variability was not observed in previous studies (10, 20) on the same canine overpacing heart failure model, probably because of too rapid evolution related to very aggressive pacing protocol.

An augmented LF oscillation of heart rate as a reflection of increased sympathetic drive is observed in healthy subjects during passive upright tilt (17, 26, 29), standing, mental stress, and moderate physical exercise or during moderate hypotension (24). Previous studies (1, 20, 21) of heart failure have also shown that the LF area of RRI spectrum is closely linked to the degree of sympathoexcitation. Indeed, a relationship between LF and microneurographic recordings of sympathetic activity (1, 21) or plasma norepinephrine (20, 21) has been demonstrated. However, in advanced stages of the disease the opposite is true (5, 18, 19, 33, 36) because the LF component present in RRI variability disappears in the presence of a markedly elevated sympathetic drive. The disappearance of this LF variability has distinct negative prognostic implications. La Rovere et al. (22) as well as Galinier et al. (18) have recently demonstrated that among the spectral measures of RRI variability, reduced power within the LF band was an independent predictor of sudden death in patients with stable congestive heart failure.

Heart rate variability parameters are affected not only by cardiac responsiveness to stimuli but also by variation and modulation in autonomic tone. Malik et al. (23) suggested that sympathetic activation that approaches maximal stimulation may be accompanied by a pattern of reduced LF variability. This could be explained by a progressive downregulation of LF component and the LF-to-HF ratio increased gradually. This result is consistent with previous RRI variability studies (5, 10, 20) in patients or animals with moderate heart failure. There were also progressive increases in heart rate and in plasma norepinephrine, which is in keeping with previous

Table 4. Associations between heart rate variability parameters and hemodynamic or neurohumoral dysfunction assessed by forward stepwise linear regression in a dog model of tachycardiomyopathy

<table>
<thead>
<tr>
<th>Dependent Parameters</th>
<th>1st Variable Included in Model</th>
<th>Others Variables Included in Model</th>
<th>Partial r</th>
<th>Multiple r</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPpa, mmHg</td>
<td>HF ms²*</td>
<td>HF nu</td>
<td>0.58</td>
<td>0.59</td>
</tr>
<tr>
<td>Ppao, mmHg</td>
<td>HF ms²*</td>
<td>Var RRI</td>
<td>0.64</td>
<td>0.65</td>
</tr>
<tr>
<td>Pra, mmHg</td>
<td>HF ms²*</td>
<td>Var RRI</td>
<td>0.62</td>
<td>0.63</td>
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<tr>
<td>LVEF, %</td>
<td>HF ms²*</td>
<td>LF ms²*</td>
<td>0.49</td>
<td>0.52</td>
</tr>
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<td>EDV, ml/m²</td>
<td>HF ms²*</td>
<td>RRI, LF ms²*</td>
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<td>0.54</td>
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<tr>
<td>LAD, cm</td>
<td>HF ms²*</td>
<td>RRI*</td>
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<td>E/A</td>
<td>HF ms²*</td>
<td>Var RRI*, HF nu</td>
<td>0.45</td>
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<td>NE, pg/ml</td>
<td>HF ms²*</td>
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<tr>
<td>ANF, pg/ml</td>
<td>HF ms²*</td>
<td>HF nu*, RRI</td>
<td>0.62</td>
<td>0.67</td>
</tr>
</tbody>
</table>
myocardial β-adrenergic receptors (6), a reduction in myocardial catecholamine stores (12), a baroreflex impairment (15), and by an alteration in central autonomic drive (36).

We excluded the possibility that the RRI oscillations were influenced by concurrent respiratory changes, which could not be recorded in previous studies (10, 20) using the same experimental model. Respiration is a powerful modulator of RRI variability (19). Changes in breathing frequency can confound the respective predominance of LF and HF oscillations in RRI variability. Recordings of respiratory activity that allowed us to rule out that reductions in HF oscillations in RRI were a result of irregular or slow breathing.

In the present study, the absolute HF component of RRI variability was better than the LF component related to echocardiographic and hemodynamic severity of heart failure and also to atrial natriuretic factor and norepinephrine concentrations. This could have been in part explained by a biphasic course with initial increase, followed by a decrease after the fifth week of evolution of the LF component of RRI variability. However, in this study, limiting the statistical analysis to the first 5 wk of evolution still did not disclose any significant correlation between LF RRI variability and severity of heart failure. Ishise et al. (20) reported that a parasympathetic withdrawal paralleled the decline in left ventricular contractility but did not describe the link between these variables. Our results showed that the total power of RRI variability is closely correlated to the absolute HF area of RRI variability and therefore suggest that the overall RRI variability is mainly influenced by cardiac vagal activity in dogs.

A limitation of the present study is that the variability of RRI was not investigated after the seventh week of evolution and until the death of the animals. Accordingly, heart rate variability analysis could not be related to cardiac events or to mortality. Another limitation is that RRI variability was analyzed on short-term recordings only. The analysis was impossible during HF pacing, and longer periods of interruption of overpacing could have affected the evolution of heart failure. Thus, despite the fact that the duration of the recordings appeared sufficient for meaningful readings, we cannot exclude that longer periods of recordings would have produced different variability profiles.

In conclusion, parasympathetic nervous system-related HF RRI oscillations appear to be more reliable than sympathetic nervous system-related LF heart rate oscillations as a measurement of congestive heart failure severity. We suggest that spectrum analysis of RRI variability in the evaluation of patients with heart failure takes into account the whole frequency spectrum with focus on the HF component.

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