Time course of sympathovagal imbalance and left ventricular dysfunction in conscious dogs with heart failure

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Ishise, Hisanari, Hidetsugu Asanoi, Shinji Ishizaka, Shuji J oh o, Tomoki Kameyama, Katsumi Umeno, and Hiroshi Inoue. Time course of sympathovagal imbalance and left ventricular dysfunction in conscious dogs with heart failure. J. Appl. Physiol. 84(4): 1234–1241, 1998.—To elucidate the time course of sympathovagal balance and its relationship to left ventricular function in heart failure, we serially evaluated left ventricular contractility and relaxation and autonomic tone in 11 conscious dogs with tachycardia-induced heart failure. We determined a dynamic map of sympathetic and parasympathetic modulation by power spectral analysis of heart rate variability. The left ventricular peak +dP/dt substantially fell from 3,364 ± 338 to 1,959 ± 318 mmHg/s (P < 0.05) on the third day and declined gradually to 1,783 ± 312 mmHg/s at 2 wk of rapid ventricular pacing. In contrast, the time constant of left ventricular pressure decay and end-diastolic pressure increased gradually from 25 ± 4 to 47 ± 5 ms (P < 0.05) and from 10 ± 2 to 21 ± 3 ms (P < 0.05), respectively, at 2 wk of pacing. The high-frequency component (0.15–1.0 Hz), a marker of parasympathetic modulation, decreased from 1,928 ± 1,914 to 62 ± 68 × 10³ ms² (P < 0.05) on the third day and further to 9 ± 12 × 10³ ms² (P < 0.05) at 2 wk. Similar to the time course of left ventricular diastolic dysfunction, plasma norepinephrine levels and the ratio of low (0.05- to 0.15-Hz) - to high-frequency component increased progressively from 135 ± 50 to 532 ± 186 pg/ml (P < 0.05) and from 0.06 ± 0.06 to 1.12 ± 1.01 (P < 0.05), respectively, at 2 wk of pacing. These cardiac and autonomic dysfunctions recovered gradually toward the normal values at 2 wk after cessation of pacing. Thus a parallel decline in left ventricular contractility with parasympathetic influence and a parallel progression in left ventricular diastolic dysfunction with sympathoexcitation suggest a close relationship between cardiac dysfunction and autonomic dysregulation during development of heart failure.

Heart rate variability; autonomic tone; contractility; relaxation

Heart failure is characterized by marked imbalance of the neurohumoral axis, which is considered an aggravating factor in circulatory failure (1, 4, 7, 8, 13, 20). A large number of studies have provided evidence for an alteration in arterial and cardiopulmonary baroreflexes in patients with various stages of congestive heart failure (1, 4, 9, 11). Such abnormalities may initially be subtle but could result in a diminished tonic inhibitory influence on sympathetic nerve activity. The level of sympathetic activity is closely linked to severity of symptoms and hemodynamic derangement seen in heart failure (7). However, all subjects with left ventricular dysfunction do not always have increased sympathetic activity, and changes in parasympathetic control of the heart might precede sympathetic activation during the development of heart failure. Some of the key issues that still remained uninvestigated in this area are the relationship between time course of development of the sympathovagal imbalance and that of left ventricular dysfunction in each individual with congestive heart failure. Clinical study requires a long-term follow-up and has been limited by the lack of an in vivo technique applied easily for serial measurements of both sympathetic and vagal drives. A conscious dog model of heart failure induced by rapid ventricular pacing provides a unique opportunity to study reflex autonomic regulation of the cardiac function at the various stages of cardiac dysfunction (3, 8, 13). Spectral analysis of heart rate variability has emerged as a unique, noninvasive, and sensitive tool that provides insights into autonomic balance (21, 24, 25, 30, 33). Specific frequency bands of heart rate variability permit the simultaneous assessment of sympathetic and parasympathetic modulation, thereby providing a dynamic map of autonomic nervous activities. By using this heart failure model and spectral analysis, Eaton et al. (8) have recently reported that the autonomic abnormalities appear early during 7 days of rapid ventricular pacing. However, serial changes in autonomic profile and its relationship to left ventricular contractility and relaxation remain unclarified during the development and the recovery of heart failure in subjects under unanesthetized conditions.

To elucidate the time course of changes in sympathetic and parasympathetic modulation in relation to the changes in left ventricular contractility and relaxation, we serially examined left ventricular function and autonomic profile in conscious dogs with tachycardia-induced heart failure.

Methods

Chronic instrumentation. The surgical procedure used has been described in detail elsewhere (2, 3, 29). Briefly, under anesthesia 11 mongrel dogs (15–19 kg) underwent thoracotomy via the left fifth intercostal space with 1% halothane inhalation after induction with pentobarbital sodium (25 mg/kg iv). The pericardium was opened widely, and a high-fidelity micromanometer (Kornigsberg P-7) was inserted into the left ventricular cavity through a stab incision at the ventricular apex. The micromanometer was calibrated by comparison with a fluid-filled catheter connected to a transducer (Gould, Statham P23DB). A conductance catheter was also advanced from the apex so that its tip passed through the aortic valve. To determine the instantaneous ventricular volume serially, we modified the original conductance catheter introduced by Baan et al. (5) so that it could be implanted for a long period. Validity of this modified catheter system has

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been reported previously (2). The catheter system consisted of a 4-Fr polyvinyl catheter with eight ring electrodes mounted equidistantly at its tip, thereby obtaining an electrical field distribution similar to that achieved with a conventional catheter inserted retrogradely from the ascending aorta (2). Conductance catheters with a distance of 5, 6, or 7 cm between the first and the last electrodes were selected, depending on the size of the left ventricle in the dog under study. The position of the most distal electrode was verified by two-dimensional echocardiography (Toshiba SSH-60A) together with monitoring of segmental volume signals. Another polyvinyl catheter was placed in the pulmonary artery for infusion of hypertonic saline to determine parallel conductance by decreasing the resistivity of the blood pool in the left ventricular chamber (5). Pacing electrodes (Medtronic model 6500) were sutured to the left ventricular epicardial surface and left atrial appendage to pace the ventricle rapidly to induce heart failure and to record the electrocardiogram (3, 4). All wires and tubes were exteriorized to the back. The dogs were placed on an anesthetic regimen (buprenorphine hydrochloride, 0.216 mg/day im) for the first 3 days after the surgery and on an antibiotic regimen (piperacillin sodium, 2 g/day iv) while they were febrile. Experiments were started at least 10 days postoperatively, when the dogs had recovered from the surgery.

Study protocol. All measurements were made while the dogs lay on a table in a conscious and unrestrained state. After the dogs had completely recovered, baseline values were determined and blood samples were withdrawn from the pulmonary artery. After the control study, stimulation of the heart was initiated at a rate of 260 beats/min by using an external pacemaker (Biotronic EDP20). To elucidate the time course of changes in autonomic activation during the progression of heart failure, left ventricular pressure and power spectra of heart rate variability were serially determined on days 3, 7, 10, and 14 during the pacing period. Each measurement was made during sinus rhythm when a steady state was established after a 1-h interruption of rapid pacing. Seven of the eleven dogs were followed up during the recovery phase on days 3, 7, 10, and 14 after cessation of rapid pacing. The remainder were killed, to confirm that the catheter was correctly positioned in the left ventricle after heart failure developed. Left ventricular volume was determined in animals in the baseline condition, at 2 wk of pacing, and at 2 wk after cessation of pacing. In six of eleven dogs, blood samples for the measurement of plasma norepinephrine levels were withdrawn from the pulmonary artery via the polyvinyl catheter on days 3, 7, 10, and 14 during the pacing period.

After completion of the study, the animals were killed with an overdose of pentobarbital sodium to confirm that the instrumentation was properly positioned and that neither fibrin nor red blood cells coated the conductance catheter. All experiments were performed in accordance with the “Guide for the Care and Use of Laboratory Animals” DHEW Publication No. (NIH) 86–21, Revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20892.

Left ventricular pressure and volume measurements. Data of micromanometer pressure and conductance catheter volume were digitized by an online analog-to-digital converter at a sampling rate of 333 Hz by using a computer system (NEC, PC-9801 RX), and pressure-volume loops were obtained on a beat-to-beat basis. Volume measurements with the conductance catheter have been described in detail in previous reports from our laboratory and other laboratories (2, 5, 29). In brief, an alternating current (20 kHz, 0.07 mA) was passed between the driving electrode in the ventricular apex and that in the base by using a signal conditioner-processor (Leycom model Sigma-5). The five potential differences generated between each sensing electrode spanning the left ventricular cavity were measured continuously. Dividing the current by each of these potential differences gave five segmental conductances, and the sum of these five conductances [G(t)] was linearly related to the ventricular volume [V(t)] by the equation (5)

\[ V(t) = \frac{1}{L} \int \frac{1}{a} G(t) - V_c \]

where \( a \) is a dimensionless slope constant for the V(t)/G(t) relationship, L is the distance between electrodes 1 and 8, \( \sigma \) is the conductivity of blood surrounding the catheter in the ventricular cavity, and \( V_c \) is the volume signal error of parallel conductance formed by tissues surrounding the left ventricular cavity (myocardium, right ventricular contents, and so on). The value of the parallel conductance was determined in each experiment by injecting 3 ml of hypertonic saline (6 mol/l) through a catheter in the pulmonary artery.

The time constant of left ventricular isovolumic pressure decay (\( T_d \)) was calculated by the derivative method of Raff and Glantz (27): \( T_d = -1/\text{slope of a linear fit of the negative } \mathrm{dP}/\mathrm{dt}\text{ vs. the left ventricular pressure over the same interval.} \)

This method allows for a non-zero-pressure asymptote. To eliminate the effect of changes in intrathoracic pressure due to respiration, steady-state measurements obtained during expiration were averaged over a 12-s recording period that spanned multiple respiratory cycles.

Analysis of heart rate variability and plasma norepinephrine. An electrocardiogram was recorded continuously for a 10-min period from the pacing electrodes placed on the left atrial appendage and left ventricle. Online analysis was performed with use of a personal computer (NEC, PC-9801 RX). The electrical circuit for variable-threshold peak detection was employed to introduce pulse signals corresponding accurately to the peak of each QRS wave into the computer. Stable sections of data were selected for analysis. The computer program first calculated R-R intervals with a clock timer in the computer and restored them in the memory. Selected data segments of 400 heartbeats were sampled at 4 Hz. The computer program automatically calculated the power spectra by using a maximal entropy method. Derived parasympathetic spectral density of R-R interval variability contained two major components in power: a low-frequency (0.05- to 0.15-Hz) and a high-frequency (0.15- to 1.0-Hz) band. A very-low-frequency component (<0.05 Hz) was not examined in this study because of a small sample size. Power of the analyzed bands was expressed as absolute values and units normalized to total power (21, 25, 33). High-frequency power was used as an index of parasympathetic modulation, and the ratio of low- to high-frequency band was used as an index of sympathovagal balance. The prechilled tubes of collected blood samples were immediately placed in ice and then centrifuged at 4°C. Norepinephrine levels were assayed by using a high-performance liquid chromatographic technique. Duplicate measurements of plasma norepinephrine by use of this method in our laboratory have a coefficient of variance of <2%.

Statistical analysis. Group data are summarized as means ± SD unless otherwise indicated. The differences in the serial changes in hemodynamic and power spectral variables and plasma norepinephrine levels were examined with an analysis of variance for repeated measures. When a significant overall effect was present, a Scheffé’s correction was employed for multiple comparisons. A paired t-test was used to compare cardiac indexes at baseline with those at 2 wk of rapid pacing and to compare cardiac indexes at 2 wk of
pacing with those at 2 wk after cessation of pacing. A probability level < 0.05 was considered significant.

RESULTS

Signs of congestive heart failure, including ascites, respiratory distress, and a third heart sound, emerged in 7–10 days in all dogs after beginning of rapid pacing.

Changes in hemodynamic variables. Left ventricular pressures, their first derivatives (dP/dt), and left ventricular pressure-volume loops obtained from a representative dog are shown in Fig. 1. Rapid ventricular pacing resulted in a substantial decline in left ventricular systolic pressure, peak + dP/dt, and peak – dP/dt, with a parallel reduction in the area within the pressure-volume loop that was displaced rightward. These abnormalities were restored toward the control condition after cessation of pacing.

Serial hemodynamic changes are summarized in Tables 1 and 2. After 2 wk of rapid ventricular pacing, un paced heart rate increased by 44 beats/min, and left ventricular systolic pressure fell by 28 mmHg, along with a marked increase in end-diastolic and minimum pressures. Left ventricular end-diastolic and endsystolic volumes were increased by 35 and 117%, respectively, resulting in 36% reduction in stroke volume and 50% decline in ejection fraction. In the first 3 days of pacing, left ventricular peak + dP/dt fell substantially by 41%. After the symptoms became overt in 7–10 days, left ventricular peak + dP/dt declined gradually (Fig. 2). In contrast to the early dramatic changes in left ventricular systolic function, left ventricular diastolic function, as reflected by end-diastolic and minimum pressures and the time constant of left ventricular pressure decay, showed a gradual deterioration as the

Table 1. Changes in hemodynamic variables, power spectral components, and plasma norepinephrine levels during progression of heart failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>86 ± 11</td>
<td>119 ± 16*</td>
<td>123 ± 18*</td>
<td>128 ± 13*</td>
<td>130 ± 13*</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>41 ± 5</td>
<td>89 ± 12*</td>
<td>18 ± 3*</td>
<td>21 ± 3*</td>
<td>88 ± 11*</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>20 ± 3</td>
<td>18 ± 4*</td>
<td>18 ± 3*</td>
<td>21 ± 3*</td>
<td>88 ± 11*</td>
</tr>
<tr>
<td>EF, %</td>
<td>52 ± 7</td>
<td>42 ± 10*</td>
<td>42 ± 10*</td>
<td>42 ± 10*</td>
<td>42 ± 10*</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>116 ± 12</td>
<td>92 ± 15*</td>
<td>89 ± 12*</td>
<td>89 ± 13*</td>
<td>88 ± 11*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>10 ± 2</td>
<td>14 ± 3*</td>
<td>17 ± 4*</td>
<td>18 ± 3*</td>
<td>21 ± 3*</td>
</tr>
<tr>
<td>Pmin, mmHg</td>
<td>1 ± 1</td>
<td>4 ± 2</td>
<td>6 ± 4*</td>
<td>8 ± 4*</td>
<td>10 ± 4*</td>
</tr>
<tr>
<td>Peak + dP/dt, mmHg/s</td>
<td>3.364 ± 338</td>
<td>1.959 ± 318*</td>
<td>1.801 ± 327*</td>
<td>1.755 ± 364*</td>
<td>1.783 ± 312*</td>
</tr>
<tr>
<td>Peak – dP/dt, mmHg/s</td>
<td>2.761 ± 250</td>
<td>1.797 ± 369*</td>
<td>1.770 ± 315*</td>
<td>1.750 ± 265*</td>
<td>1.747 ± 288*</td>
</tr>
<tr>
<td>( T_d ), ms</td>
<td>25 ± 4</td>
<td>34 ± 6*</td>
<td>36 ± 4*</td>
<td>39 ± 4*</td>
<td>47 ± 5*</td>
</tr>
<tr>
<td>Total power, ( \times 10^3 ) ms²</td>
<td>2,037 ± 1,872</td>
<td>73 ± 70*</td>
<td>27 ± 26*</td>
<td>25 ± 29*</td>
<td>15 ± 16*</td>
</tr>
<tr>
<td>HF, ( \times 10^3 ) ms²</td>
<td>1,928 ± 1,914</td>
<td>62 ± 68*</td>
<td>21 ± 22*</td>
<td>18 ± 24*</td>
<td>9 ± 12*</td>
</tr>
<tr>
<td>nu</td>
<td>95 ± 5</td>
<td>78 ± 11*</td>
<td>67 ± 16*</td>
<td>60 ± 20*</td>
<td>54 ± 16*</td>
</tr>
<tr>
<td>LF, ( \times 10^2 ) ms²</td>
<td>48 ± 48</td>
<td>11 ± 9*</td>
<td>7 ± 6*</td>
<td>6 ± 6*</td>
<td>5 ± 4*</td>
</tr>
<tr>
<td>nu</td>
<td>5 ± 5</td>
<td>22 ± 11*</td>
<td>33 ± 16*</td>
<td>40 ± 20*</td>
<td>46 ± 16*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.06 ± 0.06</td>
<td>0.31 ± 0.19</td>
<td>0.61 ± 0.54</td>
<td>0.91 ± 0.84*</td>
<td>1.12 ± 1.01*</td>
</tr>
<tr>
<td>NE, pg/ml</td>
<td>135 ± 50</td>
<td>197 ± 50</td>
<td>329 ± 100*</td>
<td>391 ± 132*</td>
<td>532 ± 186*</td>
</tr>
</tbody>
</table>

Values are means ± SD, \( n = 11 \) dogs, expect for norepinephrine (\( n = 6 \) dogs). HR, mean heart rate; EDV and ESV, left ventricular end-diastolic and end-systolic volumes, respectively; EF, ejection fraction; LVSP and LVEDP, left ventricular systolic and end-diastolic pressures, respectively; \( P_{\text{min}} \), minimum left ventricular pressure; \( T_d \), time constant of isovolumic left ventricular pressure decay; HF, high-frequency power; nu, normalized units; LF, low-frequency power; LF/HF, low-to-high-frequency power ratio; NE, plasma norepinephrine level. * \( P < 0.05 \) vs. control.
AUTONOMIC IMBALANCE IN HEART FAILURE

Table 2. Changes in hemodynamic variables and power spectral components during recovery from heart failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pacing</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>134 ± 10</td>
<td>106 ± 21*</td>
<td>102 ± 18*</td>
<td>95 ± 20*</td>
<td>88 ± 23*</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>55 ± 10</td>
<td>48 ± 6*</td>
<td>27 ± 4*</td>
<td>38 ± 6*</td>
<td>48 ± 6*</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>41 ± 11</td>
<td>24 ± 4*</td>
<td>18 ± 4*</td>
<td>15 ± 2*</td>
<td>14 ± 2*</td>
</tr>
<tr>
<td>EF, %</td>
<td>26 ± 7</td>
<td>8 ± 4*</td>
<td>7 ± 4*</td>
<td>5 ± 3*</td>
<td>3 ± 3*</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>90 ± 10</td>
<td>2,242 ± 95*</td>
<td>2,287 ± 110*</td>
<td>2,242 ± 110*</td>
<td>2,287 ± 110*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>22 ± 3</td>
<td>20 ± 3</td>
<td>20 ± 3</td>
<td>20 ± 3</td>
<td>20 ± 3</td>
</tr>
<tr>
<td>Pmin, mmHg</td>
<td>14 ± 4</td>
<td>8 ± 4*</td>
<td>7 ± 4*</td>
<td>5 ± 3*</td>
<td>3 ± 3*</td>
</tr>
<tr>
<td>Peak +dP/dt, mmHg/sec</td>
<td>1,712 ± 140</td>
<td>2,267 ± 210*</td>
<td>2,302 ± 219*</td>
<td>2,242 ± 214*</td>
<td>2,302 ± 219*</td>
</tr>
<tr>
<td>T1, ms</td>
<td>48 ± 6</td>
<td>38 ± 7*</td>
<td>35 ± 8*</td>
<td>33 ± 7*</td>
<td>29 ± 5*</td>
</tr>
<tr>
<td>Total power, 10³ ms²</td>
<td>9 ± 8</td>
<td>157 ± 193*</td>
<td>111 ± 122*</td>
<td>404 ± 444*</td>
<td>700 ± 676*</td>
</tr>
<tr>
<td>HF × 10³ ms²</td>
<td>4 ± 3</td>
<td>116 ± 172*</td>
<td>110 ± 104*</td>
<td>245 ± 217*</td>
<td>648 ± 639*</td>
</tr>
<tr>
<td>LF × 10³ ms²</td>
<td>48 ± 15</td>
<td>73 ± 9*</td>
<td>78 ± 8*</td>
<td>80 ± 10*</td>
<td>86 ± 9*</td>
</tr>
<tr>
<td>nu</td>
<td>4 ± 3</td>
<td>28 ± 6</td>
<td>27 ± 19</td>
<td>41 ± 24*</td>
<td>62 ± 41*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.36 ± 1.19</td>
<td>0.42 ± 0.20*</td>
<td>0.30 ± 0.12*</td>
<td>0.27 ± 0.17*</td>
<td>0.18 ± 0.13*</td>
</tr>
</tbody>
</table>

Values are means ± SD, n = 7 dogs. Norepinephrine levels were not determined during recovery phase. *P < 0.05 vs. pacing.

Pacing period progressed and became prominent with heart failure symptoms. After cessation of pacing, all of these abnormalities recovered gradually.

Autonomic profile during progression and regression of heart failure. R-R intervals and power spectral densities obtained from the same dog as in Fig. 1 are shown in Fig. 3. In the control condition before the initiation of pacing, a marked periodic fluctuation of R-R intervals corresponding to the respiratory cycle was seen, and the power spectrum of this oscillation was reflected in predominant high-frequency power. Data of power spectra of heart rate variability are summarized in Tables 1 and 2. The most distinct profile of heart rate variability in heart failure was a substantial reduction in total power, with a greater attenuation of the absolute power of the high-frequency component. During the early asymptomatic phase of cardiac dysfunction, high-frequency power, a marker of parasympathetic modulation, decreased markedly, the time course of which was similar to that of left ventricular peak +dP/dt, as shown in Fig. 2 (Fig. 4). In contrast to the high-frequency component, the ratio of low- to high-frequency power, normalized units of low-frequency power, and plasma norepinephrine concentration showed a gradual increase as pacing progressed. There were positive correlations between plasma norepinephrine levels and the ratio of low- to high-frequency component (r = 0.46, P < 0.01) and between plasma norepinephrine levels and normalized units of low-frequency component (r = 0.43, P < 0.05) during the pacing period (Fig. 5). The time course of these indexes of sympathetic modulation resembled those of left ventricular end-diastolic pressure and of the time constant of left ventricular pressure decay. After the cessation of pacing, the high-frequency fluctuation reappeared, and the ratio of low- to high-frequency compo-

Fig. 2. Serial changes in LV function. Values are means ± SE. Signs of congestive heart failure, including ascites, respiratory distress, and a 3rd heart sound, appeared in 7–10 days (shaded area). LV peak +dP/dt (peak +dP/dt) fell substantially in first 3 days of pacing. This change became smaller as ventricular pacing continued. In contrast to time course of peak +dP/dt, LV end-diastolic pressure (EDP) increased gradually as pacing continued. During recovery phase after cessation of pacing, systolic and diastolic dysfunction were restored toward normal. *P < 0.05 vs. control and #P < 0.05 vs. pacing day 14 for LV peak +dP/dt. *P < 0.05 vs. control and †P < 0.05 vs. pacing day 14 for LV EDP.
The present longitudinal data obtained from the same dog are consistent with our previous cross-sectional observations in clinical settings that impaired parasympathetic control of the heart precedes sympathetic activation in patients with heart failure (4). The early deterioration in parasympathetic function is also documented in asymptomatic patients with anterior myocardial infarction or dilated cardiomyopathy (1, 19). The high-frequency component of heart rate variability, a marker of parasympathetic modulation, declined markedly from the early asymptomatic stage of pacing-induced heart failure in our dog model. The new
findings of the present study are as follows. The parasympathetic withdrawal occurred rapidly in a parallel fashion with the decline in left ventricular contractility. In contrast, plasma norepinephrine levels and the normalized units of low-frequency component increased gradually as left ventricular diastolic function worsened. After pacing cessation, the autonomic and cardiac dysfunction recovered toward baseline values, suggesting that these abnormalities are reversible with time.

Systolic dysfunction and parasympathetic withdrawal. Precise mechanisms for a parallel decline in left ventricular contractility and high-frequency power remain unknown. Nolan et al. (22) showed that reduced heart rate variability was related to resting left ventricular ejection fraction in patients with cardiac dysfunction. The principal stimuli to afferent discharge from the baroreceptors are systolic blood pressure, pulse pressure, and the rate of rise in arterial pressure (14). Therefore, a substantial reduction in left ventricular peak +dP/dt and systolic pressure caused by a depressed contractility, as observed in the present study, results in attenuated stimuli to the carotid sinus baroreceptor. These diminished inputs to baroreceptors could potentially inhibit tonic vagal efferent activity (parasympathetic withdrawal) to the heart, thereby decreasing heart rate variability. Although abnormal baroreflex responsiveness could be another potential mechanism for decreased heart rate variability, this seems unlikely to be involved in the early stage of heart failure in the present model. Grima et al. (13) have documented that the baroreflex sensitivity assessed by the phenylephrine-induced slope of the R-R interval-systolic pressure relationship was preserved within the first week after rapid pacing in the heart failure model was started. In addition to the afferent abnormality, there is some evidence suggesting that attenuated vagal outflow seen in heart failure results, at least in part, from abnormalities within the central nervous system (26). Whatever mechanisms are responsible for the relationship between left ventricular systolic dysfunction and parasympathetic withdrawal, heart rate variability diminished from the early asymptomatic stage of tachycardia-induced canine heart failure.

Diastolic dysfunction and sympathetic activation. The present study demonstrated that during the progression of the pacing period, plasma norepinephrine concentration and normalized units of low-frequency component rose gradually, with a parallel deterioration of left ventricular diastolic pressure and relaxation rate. These autonomic and cardiac abnormalities resemble those observed in human congestive heart failure in that sympathetic nerve activity correlated well with cardiac filling pressure rather than with systolic indexes (17). Left ventricular diastolic dysfunction, a major cause of a rise in cardiac filling pressure, results in a sustained distention of atrial wall and pulmonary vasculature. These cardiopulmonary stretches could diminish sympathoinhibitory input to the vasomotor center by desensitizing low-pressure baroreceptors (11). However, Malliani and Pagani (18) have proposed an alternative hypothesis of positive-feedback sympathetic reflexes in cardiovascular control. A sympathosympathetic spinal reflex originating from a stretching of the atria and the pulmonary veins could produce the observed increase in sympathetic activity in pulmonary congestive states (18). Conversely, the high level of sympathetic activity could shift the blood from systemic to pulmonary circulation by decreasing systemic venous capacitance, thereby raising the filling pressure and limiting diastolic reserve of the ventricle. Irrespective of the mechanisms for the relationship between sympahtoexcitation and left ventricular diastolic dysfunction, these abnormalities together could contribute to the worsening of heart failure by reinforcing the vicious cycle.

Therapeutic implications. The parallel changes in autonomic imbalance and left ventricular dysfunction during progression and regression of heart failure offer some therapeutic implications. Drugs for treatment of heart failure not only improve hemodynamics but also
influence the autonomic nervous system (6). Some of the direct arterial vasodilators clinically introduced for the treatment of chronic heart failure exacerbate heart failure while unloading the heart for a short period (10, 12). These adverse reactions are assumed to be related to reflex-mediated sympathoexcitation. Unlike these vasodilators, angiotensin-converting enzyme inhibitors have been documented to improve sympathovagal imbalance and to exert beneficial influences on hemodynamics and long-term clinical outcome in patients with chronic heart failure (6, 28, 31, 32). Recently, several large clinical trials have demonstrated that direct intervention with the sympathetic nervous system by using a β-blocker improves symptoms and cardiac function in patients with dilated cardiomyopathy (23, 34). Carvedilol, a β- and α-blocking agent, reduced the risk of death as well as the risk of hospitalization for cardiovascular causes in patients with ischemic and nonischemic heart diseases who had already received digitalis and angiotensin-converting enzyme inhibitors (23). These findings suggest that a parallel improvement in autonomic balance and cardiac function might provide a rational basis to predict long-term efficacy of therapeutic agents for heart failure.

Limitations. Several limitations must be considered in the present study. First, there is not complete agreement as to whether spectral analysis of heart rate variability might provide an optimal estimate of autonomic influence on the heart. Power spectral density of heart rate variability does not necessarily reflect average levels of autonomic tone but reflects its variation. However, Hayano et al. (15) have demonstrated that atropine-induced reduction in mean R-R interval was accompanied by a parallel reduction in high-frequency fluctuation. Furthermore, the high-frequency component is completely abolished by the administration of atropine, suggesting a prevalent parasympathetic contribution to the genesis of high-frequency fluctuation. Recently, Pagani et al. (25) and Van de Borne et al. (33) examined the relationship between spectral components of cardiovascular variabilities and direct measurements of muscle sympathetic nerve activity in humans. They found that the use of normalized units of low-frequency component or the ratio of low- to high-frequency component provides the strongest correlation with attendant spectral changes in muscle sympathetic nerve activity. Our data were concordant with their findings in that these spectral variables changed in parallel with plasma norepinephrine concentrations during progression of heart failure. Second, when heart failure is severely decompensated, the sympathovagal balance could not be assessed by means of heart rate variability because the neuroeffector balance fails to respond to autonomic drive (16). For this reason, we employed a rather short-term pacing period, i.e., 2 wk, compared with that reported previously, and followed up the heart rate variability until a moderate degree of heart failure developed. Third, there are striking differences between the rapid ventricular pacing model of heart failure and clinical heart failure in humans in terms of duration of the symptoms and underlying etiologies. However, as shown in previous studies by us and other investigators, hemodynamic and neurohumoral characteristics in this experimental model resemble those in human heart failure (13, 20).

Conclusions. The present study revealed a parallel and early decline in left ventricular contractility and parasympathetic influence on the heart and a gradual progression of sympathoexcitation along with left ventricular diastolic dysfunction in tachycardia-induced heart failure. Although it is unclear whether these chronological relationships hold true for heart failure from other causes, a close relationship between cardiac dysfunction and autonomic imbalance would potentially guide a new design of therapeutic strategies for the management of congestive heart failure.

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