Chaotic behavior of renal sympathetic nerve activity: effect of baroreceptor denervation and cardiac failure

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DiBona, Gerald F., Susan Y. Jones, and Linda L. Sawin. Chaotic behavior of renal sympathetic nerve activity: effect of baroreceptor denervation and cardiac failure. Am J Physiol Renal Physiol 279: F491–F501, 2000.—Nonlinear dynamic analysis was used to examine the chaotic behavior of renal sympathetic nerve activity in conscious rats subjected to either complete baroreceptor denervation (sinoaortic and cardiac baroreceptor denervation) or induction of congestive heart failure (CHF). The peak interval sequence of synchronized renal sympathetic nerve discharge was extracted and used for analysis. In control rats, this yielded a system whose correlation dimension converged to a low value over the embedding dimension range of 10–15 and whose greatest Lyapunov exponent was positive. Complete baroreceptor denervation was associated with a decrease in the correlation dimension of the system (before 2.65 ± 0.27, after 1.64 ± 0.17; P < 0.01) and a reduction in chaotic behavior (greatest Lyapunov exponent: 0.201 ± 0.008 bits/data point before, 0.177 ± 0.004 bits/data point after, P < 0.02). CHF, a state characterized by impaired sinoaortic and cardiac baroreceptor regulation of renal sympathetic nerve activity, was associated with a similar decrease in the correlation dimension (control 3.41 ± 0.23, CHF 2.62 ± 0.26; P < 0.01) and a reduction in chaotic behavior (greatest Lyapunov exponent: 0.205 ± 0.048 bits/data point control, 0.136 ± 0.033 bits/data point CHF, P < 0.02). These results indicate that removal of sinoaortic and cardiac baroreceptor regulation of renal sympathetic nerve activity, occurring either physiologically or pathophysiologically, is associated with a decrease in the correlation dimensions of the system and a reduction in chaotic behavior.

nonlinear dynamics; chaos; congestive heart failure; aortic baroreceptor denervation; renal sympathetic nerve activity

REGULATION OF HEART RATE and arterial pressure exhibits complex transitions in both normal and diseased states. Normal heartbeat (i.e., R-R intervals) and arterial pressure time series display complex nonlinear dynamics, including deterministic chaos. In normal dogs subjected to total sinoaortic and cardiopulmonary baroreceptor denervation, the regulation of arterial pressure became more simple, with significant reductions in two indexes of chaotic behavior, the correlation dimension and greatest Lyapunov exponent (28–30). Similarly, the heartbeat of patients with congestive heart failure (CHF), compared with normal subjects, showed marked reduction in chaotic behavior (20). This is of interest because animals and human subjects with CHF have impaired sinoaortic and cardiac baroreflex regulation of heart rate, arterial pressure, and sympathetic nerve activity (3).

Based on initial studies, it was speculated that synchronized renal sympathetic neural discharge observed in multifiber recordings may represent a nonlinear dynamic system with high dimensionality (34). Determining the chaotic characteristics of a nonlinear dynamic system with high dimensionality is problematic inasmuch as the currently applied mathematical approaches have been based on consideration of low-dimensional nonlinear dynamic systems. Therefore, the renal sympathetic nerve activity signal was reduced to a simpler form in an effort to make it possible to understand some important characteristics of the underlying dynamic system. This was achieved by measuring one variable of the synchronized renal sympathetic nerve discharge, the peak interval sequence, to provide a major component enabling important information about the entire system to be extracted from a single variable.

Heart rate, arterial pressure, and efferent (renal) sympathetic nerve activity are under arterial and cardiac baroreflex regulation, suggesting that the chaotic behavioral characteristics observed in heart rate and arterial pressure might also be observed in renal sympathetic nerve activity.

Synchronized renal sympathetic nerve discharge consists of bursts or peaks of activity in multifiber recordings. With the use of the Sympathetic Peak Detection Program, these peaks may be further characterized as to their height, duration, and frequency (13–15, 17). The height of the peak is a function of the number of active nerve fibers. The duration of the peak depends on the degree of synchronization of firing of the active nerve fibers. The interval between peaks is dependent on central rhythm oscillators that are influenced by afferent input from peripheral reflex mechanisms, e.g., arterial and cardiac baroreflexes.

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The defects in arterial and cardiac baroreflex function observed in patients or animals with CHF are similar to those after disruption of the arterial or cardiac baroreflex in normal subjects or animals; for any given increase in arterial pressure sensed at the level of the arterial baroreceptor or in cardiac filling pressure at the level of the cardiac baroreceptor (afferent input), there is a lesser decrease in heart rate (systemic), arterial pressure, and renal sympathetic nerve activity (3). Thus these results suggest that differences in the chaotic behavior of heart rate and arterial pressure between normal patients or animals and those with CHF may be similarly reflected in renal sympathetic nerve activity.

The purpose of the present study was to examine the chaotic behavior of renal sympathetic nerve activity in normal rats before and after complete baroreceptor (sinoaortic and cardiac baroreceptor) denervation and in rats with CHF.

**METHODS**

Adult male Sprague-Dawley rats, 200–250 g, allowed free access to normal sodium rat pellet diet (Teklad) and tap water, were used for all experiments. All animal procedures were performed in compliance with the University of Iowa Policies and Guidelines Concerning the Use of Animals in Research and Teaching and the National Research Council Guide for the Care and Use of Laboratory Animals (Washington, DC: Natl. Acad. Press, 1996).

**Anesthesia**

Rats were anesthetized with 50 mg/kg ip methohexital or 50 mg/kg ip pentobarbital sodium.

**Sinoaortic and Cardiac Baroreceptor Denervation**

Sinoaortic and cardiac baroreceptor denervation were performed using methods previously used and validated in this laboratory (3, 12). Sinoaortic baroreceptor denervation was verified by noting the absence of decreases in integrated renal sympathetic nerve activity (IRSNA) after the intravenous administration of 3 μg/kg phenylephrine. Cardiac (vagotony) baroreceptor denervation was verified by noting the absence of decreases in IRSNA after the intravenous administration of 50 μg/kg 2-methylserotonin (19).

**CHF**

With the use of techniques previously described and validated for this laboratory, left coronary ligation was performed to produce chronic CHF (see Refs. 2–4). Control rats were handled identically except that left coronary artery ligation was not performed (sham). After recovery from anesthesia, CHF and control rats were returned to individual metabolism cages with free access to normal sodium rat pellet diet and tap water. All subsequent studies were performed between 3 and 4 wk thereafter at a time when ongoing renal sodium retention and edema formation are present in the CHF rats.

**Procedures**

**Catheterization.** Catheters were placed in the right carotid artery and jugular vein for the measurement of mean arterial pressure (MAP) and heart rate (HR) and infusion of solutions (0.9% NaCl at 0.05 ml/min) or drugs, respectively; they were filled with heparinized 0.9% NaCl, tunneled to the back of the neck, exteriorized, and plugged with stainless steel pins.

**Renal sympathetic nerve activity electrode.** The left kidney was exposed through a left flank incision via a retroperitoneal approach. With the use of a dissecting microscope, a renal nerve branch from the aorticorenal ganglion was isolated and carefully dissected free. The renal nerve branch was then placed on a recording electrode. IRSNA was amplified (20,000–50,000 times) and filtered (low, 30 Hz; high, 3,000 Hz) via a Grass HIP511 high-impedance probe that led to a Grass P511 band-pass amplifier. The amplified and filtered neurogram signal was channeled to a Tektronix 5113 Oscilloscope and Grass model 7D polygraph for visual evaluation and to an audio amplifier/loudspeaker (Grass model AM 8) for aural evaluation. The quality of the IRSNA signal was assessed by its pulse synchronous rhythmicity; the signal-to-noise ratio ranged between 3:1 and 5:1. A further assessment was made during an intravenous injection of norepinephrine (3 μg); as MAP increased, IRSNA decreased. When an optimal IRSNA signal was observed, the recording electrode was fixed to the nerve preparation with a silicone cement (Wacker Sil-Gel). The electrode cable was sutured to the back muscles and tunneled to the back of the neck where it was exteriorized. The rat was returned to its home cage (situated in a room with controlled light, temperature, and humidity) with free access to food and water and was allowed to recover from anesthesia and surgery.

**Experimental Protocol**

Sinoaortic and cardiac baroreceptor denervation in normal rats (anesthetized). Normal rats were anesthetized, and surgical insertion of the arterial and venous catheters and implantation of the renal sympathetic nerve activity recording electrode were performed using methods described above. Thereafter, 1 h was allowed to elapse for stabilization. Next, during continuous measurement of MAP, HR, and IRSNA, a 60-min control period was made. Thereafter, sinoaortic and cardiac baroreceptor denervation were performed using methods described above. After a 1-h stabilization period, a second 60-min experimental period was made. The rat was killed, and postmortem IRSNA was recorded for 30 min; this value was subtracted from all experimental values of IRSNA.

**CHF (conscious).** CHF and control rats were anesthetized, and surgical insertion of the arterial and venous catheters and implantation of the renal sympathetic nerve activity recording electrode were performed using methods described above. CHF and control rats were allowed to regain consciousness, and the acute conscious study began 6–8 h thereafter at the same time each day. With the rat conscious and freely moving in its home cage, the jugular vein catheter was connected to an infusion pump set to deliver 0.9% NaCl at 0.05 ml/min, the carotid arterial catheter was connected to an electronic pressure transducer (Statham 23Db), and the IRSNA electrode was connected to the Grass HIP511 high-impedance probe. After 1 h further equilibration, a 60-min recording of MAP, HR, and IRSNA was made. The rat was killed, and postmortem IRSNA was recorded for 30 min; this value was subtracted from all experimental values of IRSNA. At autopsy, both pleural spaces and peritoneal cavity were inspected for evidence of fluid collection. The heart was removed, blotted, and weighed.

**Analytic**

The amplified and filtered renal neurogram was full-wave rectified and integrated (20-ms time constant; Grass 7P3 Resistance-Capacitance Integrator) and stored as IRSNA on...
videotape (Vetter 4000A PCM) along with the neurogram, MAP, and HR (Grass 7P4 Tachograph) signals for later off-line analysis, as described below.

**Sympathetic peak detection program.** The steady-state IRSNA displayed positive deflections that were proportional to the frequency discharge in the original neurogram and generally occurred with each cardiac cycle. Individual nerve bursts, still observable in the IRSNA record, were smoothed by subsequent filtering at 35 Hz. This smoothed IRSNA was used for analysis of synchronized renal sympathetic nerve discharge characteristics. With the use of an analog-to-digital converter (Lab-PC+) and standard data acquisition software (LabVIEW), the steady-state IRSNA was sampled at 200 Hz over the identical 60-min periods, as used above. The characteristics of IRSNA were determined with a statistically based computerized algorithm, the Sympathetic Peak Detection Program (2, 4, 13–15, 17). The Sympathetic Peak Detection Program allows the simultaneous determination of the amplitude (height), duration, and periodicity (peak interval) of synchronized sympathetic discharges or peaks. The minimum acceptable peak height was set at >25% of the maximum peak height in the data series. Because peak height depends on the number of active fibers, this choice indicates that a sufficient number of fibers are active so as to generate a peak whose height is >25% of the peak generated by the maximum number of fibers active in the data series, i.e., the maximum peak height. After the synchronized peaks had been identified for each data series, data on interpeak interval (ms), individual peak height (μV), MAP, and HR were extracted.

**Analytic Procedures**

**Data.** Each original data set consisted of ~24,000–26,000 interpeak intervals. The data sets were continuous without artifacts. For assessment of stationarity, the original data set was divided into two equal portions. The values of correlation dimension and greatest Lyapunov exponent determined in each of these portions and in the original data set were compared. The determinations of correlation dimension and greatest Lyapunov exponent were made in subsets (1,024 peak intervals each) of the original data set and in the original data set. For the Chaos Detection Algorithm, the original data set was divided into 24 subsets of 1,000 peak intervals each. The original data set size of ~25,000 agrees well with estimates of the minimal number of data points necessary to identify nonlinear structures: 102 ± 0.44 (16, 27) or 104 (24), where d is the dimension of the structure under study.

**Correlation dimension.** The Grassberger-Procaccia (6, 7) algorithm was used to determine the correlation dimension, defined as a dimension with noninteger values. The correlation dimension is an estimate of the least number of independent variables that characterize the system (given sufficient fine scale resolution). With each pass through the data, a new data point is taken, and a hyperdimensional sphere of embedding dimension D and radius r is centered on that point. The fraction of subsequent data points in the record within that sphere [C(r)] is then calculated for various values of r (length scale), and a plot is made of the log C(r) vs. the log r for a range of embedding dimensions. The slope of this relation is the correlation dimension. These slopes were plotted against r to identify values of the correlation dimension that were independent of both r and the embedding dimension. The correlation dimension was calculated over a wide range of embedding dimensions (1–15) to enable the detection of a plateau of the values of the calculated correlation dimension with increasing values of the embedding dimension. The time delay was determined from the first zero of the autocorrelation function (8, 10, 11) or from the minimum of the time-delayed mutual information (8, 10, 11), which were in close agreement for all data sets. The minimal sufficient embedding dimension was determined by the false nearest neighbor method (8, 10, 11). The length scale and its upper and lower limits were kept constant for the analysis of control and experimental original data sets as well as the matched surrogate data sets.

**Lyapunov exponent.** This is a measure of the exponential rate at which nearby trajectories in phase space diverge (given sufficient fine scale resolution). The Lyapunov exponent, λ, is directly related to the magnitude of chaos in the system. Periodic processes have λ = 0, wherein trajectories eventually converge, whereas uncorrelated random data (i.e., noise) have λ = ∞. Chaotic systems have 0 < λ < ∞, indicating that the trajectories diverge, i.e., insignificant differences in the initial conditions become significant over time, which is a defining feature of chaos. The greatest Lyapunov exponent was selected by the fixed evolution time program of Wolf et al. (33) and the algorithm of Hegger et al. (8) and Kantz et al. (9–11) over the similar ranges of embedding dimensions as used for determination of correlation dimension. The length scale and its upper and lower limits were kept constant for the analysis of control and experimental original data sets and the matched surrogate data sets.

**Chaos Detection Algorithm.** This algorithm detects nonlinear determinism in a time series by iteratively generating a family of polynomial autoregressive models (1, 20). The null hypothesis (i.e., that the time series is stochastic with linear dynamics) is rejected if there is at least one nonlinear model that provides a significantly better fit to the data in a parsimonious manner than linear autoregressive models of all dynamic order. The statistical test is highly robust and sensitive in that it is resistant to noise contamination and is applicable to short time series (<1,000 data points). The technique provides a highly specific test for deterministic chaos in that the null hypothesis is not readily rejected in the presence of random noise unless the underlying system is chaotic. The level of noise corruption that can be tolerated is directly related to the magnitude of the greatest positive Lyapunov exponent, a measure of the degree of chaos in the underlying noise-free data. The best linear and nonlinear models are obtained for both the original and the surrogate data series. This is defined as the model that minimizes the cost function, C(p) = log_e(εp) + p/N, where ε(p) is the residual error, p is the number of polynomial terms, and N is the length of the time series. Chaos is established when the best nonlinear model from the original data series is significantly more predictive than both the best linear model from the original data series and the best linear and nonlinear models obtained from the surrogate data series. This is determined by statistical comparison of the residual errors for the models using the F-ratio test at the 1% significance level. The algorithm was applied to each of the 1,000 data point subsets of the original data set, and the frequency of linear and nonlinear model selection was tabulated.

**Surrogate data.** Iterative fast-Fourier transform surrogate data sets (26) were generated (surrogates program in Refs. 8–11, 22, 26) using a subsequence of the original data set with negligible end point mismatch and minimal loss of data (end-to-end program in Ref. 8). The surrogate data sets have the same Fourier amplitudes and distribution of values. The linear properties (i.e., mean, SD, power spectra, autocorrelation function) of the surrogate data sets are identical to those of the original data set. The null hypothesis being tested is
that the original data set arises from a stationary, possibly rescaled, linear Gaussian random (stochastic) process. As a measure of nonlinearity, a nonlinear prediction error statistic (predict program in Ref. 8) was used with similar parameters of embedding dimension, time delay, and radius for both the original and surrogate data sets. For a one-sided test to detect a significantly smaller error with a residual probability of a false rejection, corresponding to a level of significance of 100% (1 - α), then 1/1 - α surrogate data sets are required; for α = 0.99, 100 surrogate data sets were constructed. The assessment of nonlinearity is important because, although deterministic chaos implies nonlinearity, the reverse is not true; thus not all nonlinear systems are chaotic.

**Computer software.** The following computer software programs were used: Chaos Data Analyzer (professional version) from the American Institute of Physics [Physics Academic Software, Box 8202, North Carolina State University, Raleigh, NC 27695 (25)]; FET, a program that quantifies chaos in a time series (33); Chaos Detection Algorithm, algorithm for detection of nonlinear dynamics in short, noisy time series (1); Time Series Analysis (TISEAN; Refs. 8–11, 22).

To assess concordance between the various analytic approaches to the identification of chaotic behavior, the greatest Lyapunov exponents were determined using the Chaos Data Analyzer, FET, and the algorithm of Kantz (9) on two benchmark experimental Lorenz-like chaotic series [Series A.dat (1,000 points) and Series A.cont (10,000 points) from Ref. 32]. The Chaos Detection Algorithm was also applied to these same two experimental series.

**Statistics**

Statistical analyses were conducted with ANOVA and Scheffé’s test for pair-wise comparisons among means and t-test for comparison between groups (31); statistical significance was taken at a value of P < 0.05. Statistical comparison of the residual errors for the models in the Chaos Detection Algorithm was performed using the F-ratio test, with statistical significance taken at a value of P < 0.01. Data in text, Table 1, and Figs. 1–10 are means ± SE.

**RESULTS**

The values of correlation dimension and greatest Lyapunov exponent calculated for each half of the original record agreed with each other and with the values calculated from the entire original record to within 5%. This was the case for each of the control rats before and after

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**Fig. 1.** A: 2-dimensional time delay phase space representation for one rat before sinoaortic and cardiac baroreceptor denervation. The coordinates of each point were calculated as PIS(t) and PIS(t + τ) where t = 1, . . . , 1,024 and the time delay τ = 1; PIS, peak interval sequence. B: estimate of correlation dimension by the method of Grassberger and Procaccia (6, 7). The slope of the linear segment in a plot of log correlation sum C(r) vs. log radius r is taken as the correlation dimension d(r). Each curve refers to a different value of the embedding dimension, with the uppermost curve being 7 and the lowermost curve being 15 in steps of 1. The curves contain a linear segment whose slope converges to a constant value as embedding dimension is increased. C: relation between the correlation dimension, d(r), and r for the same range of embedding dimensions. A plateau (i.e., scaling range) is identified around an intermediate value of r ~ 1e + 1 where the correlation dimension, d(r), is independent of changes in either the embedding dimension or r.
sinoaortic and cardiac baroreceptor denervation in the first experiment and for each of the control and CHF rats in the second experiment.

In both benchmark experimental series, the values for the greatest Lyapunov exponent determined by FET, the algorithm of Kantz, and Chaos Data Analyzer were within 8% of each other. The Chaos Detection Algorithm also showed a significant nonlinear component in both benchmark experimental series.

Effect of Sinoaortic and Cardiac Baroreceptor Denervation in Normal Rats

The rats weighed 387 ± 9 g, heart weight was 1.50 ± 0.05 g, and heart weight-to-body weight ratio was 0.39 ± 0.03%. Left ventricular end-diastolic pressure was 2.4 ± 0.3 mmHg. Before sinoaortic and cardiac baroreceptor denervation, intravenous administration of 3 μg/kg phenylephrine increased MAP by 62 ± 4 mmHg and decreased IRSNA by 92 ± 5%, and intravenous administration of 50 μg/kg 2-methylserotonin decreased IRSNA by 72 ± 4%. After sinoaortic and cardiac baroreceptor denervation, phenylephrine decreased IRSNA by 3 ± 3%, and 2-methylserotonin decreased IRSNA by 2 ± 3%. These results indicated effective sinoaortic and cardiac baroreceptor denervation.

Figure 1A shows a two-dimensional time delay phase space representation for one rat before sinoaortic and cardiac baroreceptor denervation. This degree of unfolding displays a recognizable structure resembling an attractor. Figure 1B shows the relation between the logarithm of the correlation sums, \( C(r) \), and the logarithm of the radius, \( r \), for this data set. Each curve signifies a different embedding dimension (from 7 to 15) whereby the correlation dimension, \( d(r) \), is given by the slope of the linear segment in these curves

\[
d(r) = \frac{d \log C(r)}{d \log r}
\]

It can be seen that the curves contain a linear segment in which the slope converges to a constant value as the embedding dimension increases. Figure 1C shows the relation between the correlation dimension, \( d(r) \), and \( r \) for the same range of embedding dimensions. A plateau (i.e., scaling range) is identified around a value of \( r \approx 1e + 1 \) where the correlation dimension, \( d(r) \), is independent of changes in either the embedding dimension or \( r \). For values of \( r \) greater or less than this scaling range, the correlation dimension, \( d(r) \), shows dependence on both the embedding dimension and \( r \). The nonlinear prediction error for the original data set was 2.54, whereas those for the 100 surrogate data sets ranged from 2.58 to 2.85 so that the null hypothesis that the original data set arises from a stationary, possibly rescaled, linear Gaussian random process was rejected at the 99% level of significance.

Figure 2 shows the correlation dimension calculated as a function of embedding dimension before and after sinoaortic and cardiac baroreceptor denervation. The mean correlation dimension approached a plateau value (i.e., converged) at increasing values of the embedding dimension. The mean correlation dimension over the plateau range of embedding dimensions from 10 to 15 was 2.65 ± 0.27 before and 1.64 ± 0.17 after sinoaortic and cardiac baroreceptor denervation \((P < 0.01)\).

Figure 3 shows the greatest Lyapunov exponents for each of the eight rats. The greatest Lyapunov exponent decreased in each rat after sinoaortic and cardiac baroreceptor denervation. The mean greatest Lyapunov exponent was 0.201 ± 0.008 bits/data point before and 0.177 ± 0.004 bits/data point after sinoaortic and cardiac baroreceptor denervation \((P < 0.02)\).

The correlation dimension and the greatest Lyapunov exponent for each of the eight rats, both before and after sinoaortic and cardiac baroreceptor denervation, were compared with the respective values for the matched surrogate data sets. Figure 4 shows the correlation dimensions (top) and greatest Lyapunov exponents (bottom) for each rat before (A) and after (B)
sinoaortic and cardiac baroreceptor denervation compared with the range of correlation dimensions and greatest Lyapunov exponents for the respective matched surrogate data sets (100 each). The correlation dimension and greatest Lyapunov exponent for each rat were outside the range of correlation dimensions and greatest Lyapunov exponents for the respective surrogate data sets both before and after sinoaortic and cardiac baroreceptor denervation. In addition, the ranges of correlation dimensions and greatest Lyapunov exponents for the surrogate data sets were overlapping.

As seen in Fig. 5, the nonlinear prediction errors for each of the eight rats before (A) sinoaortic and cardiac baroreceptor denervation were outside the range of those derived from the respective matched surrogate data sets, supporting nonlinearity. After sinoaortic and cardiac baroreceptor denervation (B), the nonlinear prediction errors were within the range of those derived from the respective matched surrogate data sets in three of the eight rats and quite close to the lowest value of the range in five of eight rats.

Figure 6 shows the results of application of the Chaos Detection Algorithm to 1,000-point data subsets from one rat before and after sinoaortic and cardiac baroreceptor denervation. The cost function, C(p), and the F-test yielded a nonlinear model before and a linear model after sinoaortic and cardiac baroreceptor denervation. In this rat (no. 5 in Fig. 7), 24 out of 24 data subsets (100%) were best fitted by a nonlinear model before sino-

![Fig. 4. Correlation dimensions (top) and greatest Lyapunov exponents (bottom) before (A) and after (B) sinoaortic and cardiac baroreceptor denervation. ● Values for the original data set in each rat; ▼ and ▲, range between the upper (▼) and lower (▲) values for the matching 100 surrogate data sets.](image)

![Fig. 5. Nonlinear prediction errors before (A) and after (B) sinoaortic and cardiac baroreceptor denervation. ● Values for the original data set in each rat; ▼ and ▲, range between the upper and lower values, respectively, for the matching 100 surrogate data sets.](image)
aortic and cardiac baroreceptor denervation compared with only 12 of 24 data subsets (50%) after sinoaortic and cardiac baroreceptor denervation. Figure 7 shows histograms of linear and nonlinear model selection for all data subsets before and after sinoaortic and cardiac baroreceptor denervation. Before sinoaortic and cardiac baroreceptor denervation, there was a 100% detection rate for the nonlinear model in each rat. After sinoaortic and cardiac baroreceptor denervation, only five rats showed a greater detection rate for the nonlinear compared with the linear model. The three rats that showed a greater detection rate for the linear compared with the nonlinear model (nos. 1, 5, and 7) were the same rats whose nonlinear prediction errors were not significantly different from the range of nonlinear prediction errors of the matched surrogate data sets (Fig. 5).

**CHF**

In Table 1, CHF rats had significantly greater body weight, heart weight, heart weight-to-body weight ratio, left ventricular end-diastolic pressure, and HR but significantly lower MAP than control rats. Mean IRSNA and peak height but not peak frequency were significantly greater in CHF than in control rats.

Figure 8 shows the correlation dimension calculated as a function of embedding dimension for the control and CHF groups. The correlation dimension approached a plateau value (i.e., converged) at increasing values of the embedding dimension. The mean correlation dimension over the plateau range of embedding dimensions from 10 to 15 was 3.41 ± 0.23 for control and 2.62 ± 0.26 for CHF rats ($P < 0.01$).
Table 1. Summary of data for control and congestive heart failure rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CHF</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>345 ± 6</td>
<td>365 ± 7*</td>
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<td>Heart weight, g</td>
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<td>Heart weight/body weight, %</td>
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<td>0.50 ± 0.02*</td>
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<td>MAP, mmHg</td>
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<td>103 ± 3*</td>
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<td>HR, beats/min</td>
<td>340 ± 8</td>
<td>360 ± 8*</td>
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<td>IRSNA, µV</td>
<td>1.01 ± 0.08</td>
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<td>Average peak height, µV</td>
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<tr>
<td>Average peak frequency, Hz</td>
<td>5.49 ± 0.14</td>
<td>5.56 ± 0.11</td>
</tr>
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</table>

Data are means ± SE. CHF, congestive heart failure; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; HR, heart rate; IRSNA, integrated renal sympathetic nerve activity. *P < 0.05.

Figure 9 shows the greatest Lyapunov exponents for the control and CHF groups. The mean greatest Lyapunov exponent was 0.205 ± 0.048 bits/data point for control and 0.136 ± 0.033 bits/data point for CHF rats (P < 0.02).

As with the sinoaortic and cardiac baroreceptor denervation protocol, the correlation dimension and the greatest Lyapunov exponent for each rat in the control and CHF group were compared with the respective values for the matched surrogate data sets (100 each). The correlation dimension and greatest Lyapunov exponent for each rat were outside the range of correlation dimensions and greatest Lyapunov exponents for the respective surrogate data sets (data not shown). In addition, the ranges of correlation dimensions and greatest Lyapunov exponents for the surrogate data sets were overlapping.

The nonlinear prediction errors for the nine control rats were outside the range of those derived from the respective matched surrogate data sets in three of the eight rats and quite close to the lowest value of the range in five of eight rats (data not shown).

The nonlinear prediction errors were within the range of those derived from the respective matched surrogate data sets in three of the eight rats and quite close to the lowest value of the range in five of eight rats (data not shown).

Figure 10 shows histograms of linear and nonlinear model selection for all data subsets in both control and CHF rats. In nine control rats, there was 100% detection rate for the nonlinear model in each rat. In eight CHF rats, there was a greater detection rate for the nonlinear compared with the linear model in five rats and greater detection rate for the linear compared with the nonlinear model in three rats. The three rats that showed a greater detection rate for the linear compared with the nonlinear model (nos. 2, 5, and 8) were the same rats in which nonlinear prediction errors were not significantly different from the range of nonlinear prediction errors of the matched surrogate data sets (data not shown).

DISCUSSION

The major findings of this study are 1) that interruption of afferent input from the sinoaortic and cardiac baroreceptors results in a decrease in the correlation dimension and the sensitivity to initial conditions of the nonlinear dynamic characteristics of synchronized renal sympathetic nerve discharge; and 2) similar changes are seen in CHF, a pathological condition characterized by impaired sinoaortic and cardiac baroreflex function.

Another study of the chaotic behavior of the peak interval sequence of synchronized renal sympathetic nerve activity compared normotensive Wistar with hypertensive stroke-prone spontaneously hypertensive rats (SHRSP; see Ref. 34). In the basal state, the correlation dimension was 3.11 ± 0.30 in Wistar rats, significantly greater than that of 2.36 ± 0.16 in SHRSP rats; the greatest Lyapunov exponents were positive and similar between the two groups. These results
indicated that the system was of low dimensionality and that chaos was present. Of interest, brachial nerve stimulation, to simulate somatic afferent receptor stimulation, significantly decreased both the correlation dimension and greatest Lyapunov exponent in Wistar rats but had no effect on these measurements in SHRSP rats. Thus clear differences could be observed between normal and pathological rats (i.e., hypertensive) both in the basal state and in response to a standard reflex intervention. Of interest, the pathological condition was characterized by a system with lower values for both the correlation dimension and the greatest Lyapunov exponent.

Similar results were obtained herein as normal rats had systems that were characterized by low dimensionality and positive greatest Lyapunov exponents. In comparison, the values for these two parameters were decreased after sinoaortic and cardiac baroreceptor denervation and in rats with CHF, characterized by sinoaortic and cardiac baroreflex impairment. Similarly, the pathological condition was characterized by a system with smaller values for the correlation dimension and the greatest Lyapunov exponent.

Previous examinations of the effect of sinoaortic and cardiac baroreceptor denervation on the nonlinear dynamic aspects of cardiovascular variables have been made on arterial pressure in conscious dogs (28, 30). The correlation dimension decreased from 3.05 ± 0.23 in a group of six control dogs to 1.74 ± 0.20 in another group of seven sinoaortic and cardiac baroreceptor denervated dogs (embedding dimensions 2–8), whereas the greatest Lyapunov exponent was decreased from 1.85 ± 0.18 to 0.74 ± 0.08 (embedding dimension 12). It was concluded that, after sinoaortic and cardiac baroreceptor denervation, arterial pressure control is less complex and less sensitive to initial conditions, i.e., less chaotic and more predictable.

Our results extend these observations to renal sympathetic nerve activity in the rat wherein acute sinoaortic and cardiac baroreceptor denervation decreased both the correlation dimension and the greatest Lyapunov exponent. Analysis using the Chaos Detection Algorithm yielded similar results demonstrating a shift from a uniform nonlinear model selection before sinoaortic and cardiac baroreceptor denervation to approximately equal linear and nonlinear model selection after sinoaortic and cardiac baroreceptor denervation. Although the studies on the effect of acute sinoaortic and cardiac baroreceptor denervation were performed under anesthesia, this approach permitted the use of a paired experimental design in which each rat served as its control, thus eliminating between-group variance.

It is widely appreciated that CHF is associated with impaired sinoaortic and cardiac baroreceptor function (3), including regulation of arterial pressure, HR, and renal sympathetic nerve activity. Several investigators have examined the nonlinear dynamic behavior of heartbeat intervals in normal human subjects and patients with CHF (summarized in Ref. 20). Most, but not all, have observed a significant chaotic component in normal human subjects. Furthermore, the suggestion that cardiac disease may decrease the degree of chaos in the heart rhythm is supported by the finding of a decrease in the correlation dimension of the heartbeat interval time series preceding ventricular fibrillation in human subjects (23). One of the difficulties in the analysis of physiological time series is the inevitable presence of random noise, which can lead to false positive or negative identification of chaos with the usual methods of nonlinear dynamic analysis. The effect of noise may be lessened somewhat by using long data records, but this approach is limited by the possible nonstationarity in long physiological time series, such as arterial pressure and heartbeat intervals. Herein, background noise represented by the postmortem signal was subtracted off, and there was agreement between short data subsets (minimizing
nonstationarity but increasing likelihood of noise effect) and original long data sets (decreasing noise effects but increasing likelihood of nonstationarity). A nonlinear system identification technique, the Chaos Detection Algorithm, has been developed and is capable of robust and highly sensitive statistical detection of chaotic dynamics in experimental time series (1, 20). It is based on the comparison of the predictive power of linear vs. nonlinear polynomial autoregressive models of the data. This technique has several advantages over other approaches when applied to short time series (<1,000 points), even when contaminated with noise or in the presence of strong periodicity. Thus original long data sets can be subdivided into short time series suitable for assessment, thus providing a composite analysis of the original long data set. With this approach, a reduction in the chaotic behavior of heartbeat intervals in patients with CHF compared with normal human subjects was detected.

Our results extend these observations to renal sympathetic nerve activity in the conscious rat wherein CHF rats had values for correlation dimension and greatest Lyapunov exponent that were less than those in control rats. As with the human studies noted above, the Chaos Detection Algorithm yielded similar results, demonstrating a shift from a uniform nonlinear model selection in the control rats to approximately equal linear and nonlinear model selection in the CHF rats.

In summary, normal rats subjected to sinoaortic and cardiac baroreceptor denervation exhibit a decrease in the chaotic behavior of synchronized renal sympathetic nerve discharge. When compared with normal rats, a similar decrease in the chaotic behavior of synchronized renal sympathetic nerve discharge is observed in rats with CHF, a pathological condition characterized by impaired sinoaortic and cardiac baroreceptor function.

Perspectives

It appears that loss of sinoaortic and cardiac baroreflex regulation of multiple cardiovascular variables results in a situation where control of these variables is less complex and less sensitive to initial conditions. This occurs after disruption of these reflexes in normal rats and by disease-acquired reflex impairment in rats with CHF. This reduction in chaotic behavior implies a shift to a more limited, stable, and predictable behavior. Such quantitative analysis may provide unique insight into important differences between physiological regulatory mechanisms and those that occur in pathophysiological conditions.


