Fractal Properties of Sympathetic Nerve Discharge

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Das, Mahasweta, Gerard L. Gebber, Susan M. Barman, and Craig D. Lewis. Fractal properties of sympathetic nerve discharge. J Neurophysiol 89: 833–840, 2003; 10.1152/jn.00757.2002. Fano factor analysis and dispersional analysis were used to characterize time series of single and multifiber spikes recorded from the preganglionic cervical sympathetic nerve and cardiac-related slow-wave activity of the whole postganglionic sympathetic vertebral nerve (VN) in anesthetized cats. Fluctuations in spike counts and interspike intervals for single preganglionic fibers proved to be fractal (i.e., time-scale invariant), as reflected by a power law relationship between indices of the variance of these properties and the window size used to make the measurements. Importantly, random shuffling of the data eliminated the power law relationships. Fluctuations in spike counts in preganglionic multifiber activity also were fractal, as were fluctuations in the height and of the area of cardiac-related slow waves recorded from the whole postganglionic VN. These fractal fluctuations were persistent (i.e., positively correlated), as reflected by a Hurst exponent significantly >0.5. Although fluctuations in the interval between cardiac-related VN slow waves were random, those in the interval between heart beats were fractal and persistent. These results demonstrate for the first time that apparently random fluctuations in sympathetic nerve discharge are, in fact, dictated by a complex deterministic process that imparts “long-term” memory to the system. Whether such time-scale invariant behavior plays a role in generating the fractal component of heart rate variability remains to be determined.

INTRODUCTION

Whereas the naturally occurring action potentials of single neurons in the cat rostral ventrolateral medulla (RVLM) are correlated to the cardiac-related and 10-Hz rhythmic components of postganglionic sympathetic nerve discharge (SND), these neurons miss firing in a variable number of rhythmic cycles and exhibit periods of quiescence lasting several seconds or longer (Lewis et al. 2001). As such, the interspike intervals (ISIs) of these RVLM-spinal presympathetic neurons are distributed exponentially or in a gamma-like fashion. Traditionally, these distributions have been modeled as random Poisson processes in which the ISIs are uncorrelated (Cox and Lewis 1966; Tuckwell 1988). Nevertheless, exponential and gamma-like distributions are also characteristic of time series in which long-range correlations exist (Teich 1989, 1992). Such time series are best described as fractal point processes. Fractal point processes are characterized by long-range correlations among events extending over multiple time scales (Bassingthwaighte et al. 1994; Liebovitch 1998; West 1990). Such statistical self-similarity or time-scale invariant behavior is revealed by methods that test for a power law relationship between the variance of some property and the resolution (e.g., window length) used to make the measurements. In a study from our laboratory (Lewis et al. 2001) on brain stem presympathetic neurons, we used Fano factor analysis to demonstrate such a relationship, as reflected by the proportionality to a power of fluctuations in spike counts measured over short periods (approximately 1 s) to those measured on longer time scales (≈100 s). The long-range correlations so revealed reflect a form of memory in that the current value of the measured property is dependent on events in the “distant past” (i.e., largest window size).

Long-range correlations are also characteristic of time series of the intervals between heart beats in healthy humans (Goldberger 1992; Goldberger et al. 1996; Ivanov et al. 1999). This has attracted the interest of cardiologists, since the fractal component of heart rate variability (HRV) is diminished with aging and in patients with congestive heart failure (Goldberger et al. 1996; Goldberger and Rigney 1991). Whereas it has been suggested that autonomic outflows to the sinoatrial node in some way contribute to fractal HRV (Goldberger et al. 1996; Yamamoto and Hughson 1994; Yamamoto et al. 1995), it is not known whether SND and/or cardiac vagal nerve activity themselves contain fractal components. The current study was designed to test this possibility for SND in view of our past findings on brain stem unit activity. Specifically, we have addressed the following questions. 1) Do long-range correlations exist among the ISIs of individual preganglionic sympathetic neurons (PSNs)? 2) Are fluctuations in activity recorded from populations of PSNs and whole postganglionic sympathetic nerves fractal in nature? 3) What is the nature of the long-range correlations in SND? In particular, is fractal activity characterized by positive (persistent) or negative (antipersistent) correlations? 4) Does fractal SND coexist with fractal HRV in the same cats?

METHODS

General procedures

The experimental protocols described below were approved by the All-University Committee on Animal Use and Care of Michigan State University. The experiments were performed on 11 spontaneously breathing, baroreceptor-intact cats anesthetized by intraperitoneal injection of a mixture of diallylbarbiturate (60 mg/kg), urethan (240 mg/kg), and monoethylurea (240 mg/kg). A surgical state of anesthesia was indicated by the failure of noxious stimuli (pinch, muscle
cauterization) to desynchronize spindles and delta-slow wave activity in the frontal-parietal electroencephalogram (Gebber et al. 1999; Steriade and Llinas 1988). Blood pressure was measured from a femoral artery, and 6% dextan in normal saline was infused into a femoral vein at a rate of 6 ml/h. Body temperature was maintained near 37°C with a heat lamp, and end-tidal CO₂ was in the range of 3.5 to 5% (Transverse Medical Monitors Capnometer, model 2200).

Nerve recordings

Multiunit activity was recorded from thin strands teased from the left preganglionic cervical sympathetic nerve using the method described by Koley et al. (1989). The recordings were made from the central end of the strand with bipolar platinum electrodes and a preamplifier band-pass of 300–3,000 Hz. On-line analog window discrimination was used to isolate multiunit spikes from background noise. Spike-sorting software (RUN Technologies, Mission Viejo, CA) was used off-line to separate the spikes of different preganglionic fibers making up the multiunit recording field. Spikes were grouped into separate files based on similarities in spike height, width, shape, depolarization velocity, and other characteristics. A minimum ISI of ≥60 ms was taken as an indication that the spikes in a file arose from a single fiber (Mannard and Polosa 1973).

Bipolar platinum electrodes were used to record monophonically from the central end of the cut whole preganglionic vertebral sympathetic nerve (VN) near its exit from the leftstellate ganglion. VN recordings were made with a preamplifier band-pass of 1–1,000 Hz. Bursts of multiunit activity (envelopes of spikes) appear as slow waves when this preamplifier band-pass is used (Cohen and Gootman 1970; Gebber et al. 1994).

Spike train analysis

The action potentials of single PSNs (spike-sorted files) or groups of preganglionic cervical sympathetic fibers were represented by standardized 5-V square-wave pulses (2 ms in duration). From time series of these pulses, we counted the number of spikes in bins of designated length (single and multiunit activity) and measured ISIs using software written in our laboratory by C. D. Lewis (Gebber et al. 1999). Tests were performed to determine whether fluctuations in these parameters were fractal or random in nature.

The first test involved calculation of the Fano factor for window sizes of different lengths. The Fano factor, \( F(T) \) as used by Teich (1992) and Lewis et al. (2001), is defined as the variance of the number of spikes divided by the mean number of spikes in a time window of length \( T \)

\[
F(T) = \frac{\text{var}[N(T)]}{\text{mean}[N(T)]}
\]

where \( N(T) \) is the number of spikes in the \( T \)th window of length \( T \). The Fano factor curve is constructed by plotting \( F(T) \) as a function of the window size on a log-log scale. For a data block of length \( T_{\text{max}} \), the window size, \( T \), is progressively increased from a minimum of a single bin (2 ms) to a maximum of \( T_{\text{max}}/10 \) so that ≥60 ms nonoverlapping windows are used for each measure of \( F(T) \). For a random process in which fluctuations in spike counts are uncorrelated, \( F(T) \) is 1 for all window sizes (Teich 1989, 1992). For a periodic process, the variance decreases and \( F(T) \) approaches 0 as the window size is increased. For a fractal process, \( F(T) \) increases as a power of the window size and may reach values > 1.0. This reflects the greater variance of spike counts with increasing window size. The power law relationship appears as a straight line with a positive slope, \( \alpha \). Alpha, the scaling exponent, is the power to which fluctuations in spike counts on one time scale are proportional to those on larger time scales. The correlation coefficient \( r \) value is used as a test for linearity on the log-log scale, and linear regression is used to calculate \( \alpha \).

Whether a power law relationship in the Fano factor curve truly reflects a fractal process, and thus long-range correlations of events, is tested by constructing surrogate data sets in which ISIs have been randomly shuffled. Specifically, we assigned random numbers to the ISIs in the original time series and then sorted the random numbers by size. This creates a randomized data set whose mean ISI, ISI variance, and ISI histogram are identical to those of the original spike train, but with no correlations among events (Teich and Lowen 1994). If shuffling of ISIs eliminates the power law relationship, then it can be concluded that the ISIs in the original time series were ordered and interdependent. We routinely compared the Fano factor curve for the original spike train with those for 10 or 20 surrogates, thereby approximating 90 or 95% confidence limits.

Dispersional analysis (DA) was also used to test for fractal properties of single-unit spike trains. The algorithm developed by Bassingthwaighte and Raymond (1995) involves calculation of the SD of the mean values of the ISI for groups of data points of a specified number \( m \). Specifically, the mean ISI for each group of data points is obtained and the SD of these values is calculated for the total number of groups. The process is repeated each time \( m \) is increased progressively from a minimum of one data point to a maximum of one-quarter of the total number of data points. SD is then plotted against \( m \) on a log-log scale yielding a straight line with a negative slope. The slope is used to calculate the Hurst \((H)\) exponent using the formula

\[
H = \text{slope} + 1
\]

The value of the \( H \) exponent (0 to 1.0 range) indicates whether the time series is fractal. As explained by Feder (1988) and Bassingthwaighte and Raymond (1995), the \( H \) exponent is 0.5 for a time series in which events are uncorrelated (i.e., random Poisson process). An \( H \) exponent ≠ 0.5 implies that the time series is fractal. When \( H > 0.5 \), the long-range correlations among events are positive (persistence; values larger (smaller) than the mean tend to be followed by values also larger (smaller) than the mean). When \( H < 0.5 \), the correlations are negative (antipersistence; values larger than the mean tend to be followed by values smaller than mean and vice versa). As with Fano factor analysis, the DA curve for the original time series is compared with those for surrogate data blocks \((H \sim 0.5)\).

Slow trends in the data may lead to erroneous conclusions when using DA. For example, a progressive increase or decrease in ISI would be interpreted as persistence \((H > 0.5)\) even when the spike train lacks true fractal properties. For this reason, we also performed DA on first differences derived from the original time series. In the case of ISIs, a new time series of the absolute differences between successive intervals is constructed. The first difference, \( D(I) \) takes the form

\[
D(I) = (I + 1) - I
\]

where \( I \) and \( I + 1 \) are successive ISIs in the original time series. This procedure removes slow trends due to nonstationarity of the data (Goldberger et al. 1996). This is ascertained by viewing the time series of first differences. We refer to DA of first differences as detrended DA in this paper.

HRV and VN activity

Ordinary and detrended DA were used as tests for fractal fluctuations of the intervals between heartbeats and for fractal fluctuations of the following properties of cardiac-related bursts (slow waves) of preganglionic VN activity: 1) interval between slow waves; 2) trough-to-peak slow-wave height (normalized on scale of 0 to 1.0); and 3) normalized slow-wave area. The cardiac interval was the interval (ms) between the peak systolic phases of successive femoral
arterial pulse waves. Time series of properties 1–3 were constructed after digital band-pass filtering of the original recordings of VN activity with software obtained from RC Electronics (Santa Barbara, CA). A symmetric, nonrecursive filter with a Lanczos smoothing function was used. The width of the band-pass was between 4 and 6 Hz, with the center frequency matched to that of the sharp peak at the frequency of the heartbeat in the autospectrum of SND (Gebber et al. 1999). The digital filter had a roll-off slope of 39%/Hz outside of the band-pass. As shown in Fig. 5, the digitally filtered records of VN activity are smoother than the originals, thus aiding in the accurate detection of peaks and troughs for time series analysis. Note that digital filtering produced minimal or no amplitude and phase distortion.

### Results

#### Preganglionic single fiber activity

The spike trains of 24 single fibers from the cervical sympathetic nerve were tested for fractal properties using Fano factor analysis and DA. These files were obtained from 13 multifiber preparations (6 cats) using the spike-sorting software. The number of spikes contained in these files ranged from 540 to 7,010. A time series was considered fractal irrespective of the number of spikes it contained providing that 1) a power law relationship was present in the Fano factor curve for the original data, but not in those for ≥10 surrogate data blocks and 2) the H exponent derived by detrended DA fell outside of the range of values for the surrogate data blocks. The spike train was considered not to have fractal properties if conditions 1 and 2 were not met when the number of spikes in the time series was ≥2,000. The rationale for using this number is based on our work with brain stem sympathetic neurons showing that the percentage of spike trains with fractal properties is dependent on sample size and reaches 100 when the time series contains ≥2,000 spikes. As such, we were able to classify 15 of 24 files of single-fiber activity as fractal. There were 9 files that could not be classified because the spike train contained <2,000 spikes and the Fano factor and detrended DA curves for the original spike train did not differ from those of the surrogates. There were no files containing ≥2,000 spikes (n = 7) that were nonfractal.

Figure 1 shows the results for the spike train of a single PSN with cardiac-related activity. The time series of ISIs was nearly 2,000 s in length (Fig. 1C) and contained 3,130 spikes, which are superposed in Fig. 1A. Note the clustering of relatively long intervals near the beginning of the time series. Clusters of long and/or short intervals are characteristic of fractal point processes (Teich 1989) and may appear at any position in the time series (compare Figs. 1C with 2C). Such clusters account for the increase in variance of spike counts with increasing window size, which, in turn, leads to a power law relationship in the Fano factor curve. The AP-triggered histogram of PSN activity is shown in Fig. 1B. Note that the probability of PSN discharge was highest during the diastolic phase of the AP. The ISI histogram was gamma-like in shape with a coefficient of variation (CV) of 0.74 (Fig. 1D). The minimum and modal ISIs were 136, 302, and 630 ms, respectively; resolution, 2 ms. The CV of the ISIs was 0.75. F. detrended dispersional analysis (DA) of real data (single black line) and 10 surrogate data blocks (gray region). Hurst (H) exponent derived from curve for real data is 0.88.

![Fractals spike train of single preganglionic cervical sympathetic fiber with cardiac-related activity.](image)

**FIG. 1.** Fractals spike train of single preganglionic cervical sympathetic fiber with cardiac-related activity. A: superposition of 3,130 naturally occurring unit action potentials isolated by spike sorting. Horizontal calibration is 1 ms. B: arterial pulse (AP)-triggered average of AP (top) and histogram of single fiber activity (bottom) based on 7,434 trials; histogram resolution, 10 ms. C: time series of interspike intervals (ISIs); resolution, 2 ms. D: ISI histogram. Minimum, modal, and mean ISIs were 136, 302, and 630 ms, respectively; resolution, 2 ms. E: Fano factor curves for original time series (single black line) and 10 surrogate data blocks (gray region). Scaling exponent, α, for real data is 0.75. F: detrended dispersional analysis (DA) of real data (single black line) and 10 surrogates (gray region). Hurst (H) exponent derived from curve for real data is 0.88.
window sizes less than the minimum ISI. This feature of the Fano factor curve is consistent with a Bernoulli process with a low probability of success (Teich 1992). This is explained by the fact that, for very small windows, the spike count can be either zero or one, with the former more likely to occur. For window sizes between the minimum ISI and approximately 3 s, $F(T)$ dipped below 1.0 and reached its lowest value near the modal ISI. The extent of the dip is related to skewness of the ISI histogram (Teich 1992). In general, the more symmetric the histogram, the greater the dip (compare Figs. 1, D and E, with 2, D and E). The skewed distribution of the Fano factors at large window sizes in the curves for the surrogates is more apparent than real because of the log-log scaling. Nonetheless, some skewness toward values $< 1.0$ is expected because the distribution of ISIs did not fit a pure exponential (Teich and Lowen 1994).

The results of detrended DA (Fig. 1F) also point to the fractal nature of the spike train of this PSN. Note that the slope of the curve for the real data (single black line) was relatively flat as compared with those of the superposed curves for 10 surrogates (gray region). The range over which the slopes of the curves for the real data and surrogates differed was for groups $(m)$ of between 10 and 280 data points. In this case, the $H$ exponent calculated from the negative slope of the curve for the real data was 0.88. The $H$ exponent for the surrogates ranged from 0.42 to 0.55.

The results in Fig. 2 are for the spike train of a PSN that lacked cardiac-related activity (Fig. 2B). For window sizes $\geq 1$ s, the slope of the power law relationship in the Fano factor curve for the real data was 0.71 (Fig. 2E, single black line). In contrast, the curves for 10 surrogate data blocks were flat, with $F(T)$ hovering near 1.0 (gray region). The $H$ exponent derived by detrended DA for the real data was 0.89 for $m$ of between 5 and 720 data points (Fig. 2F). The DA curve in this range clearly fell far from the curves for the surrogate data blocks. The number of spikes in this time series was 2,888 and the mean discharge rate was 1.7 Hz. The CV of the ISI histogram (Fig. 2D) was 1.2, and the minimum ISI was 72 ms. The highly asymmetric shape of the ISI histogram is consistent with the virtual absence of a dip in the Fano factor curve for window sizes $< 1$ s.

The properties of the fractal spike trains of 15 single PSNs, 8 with and 7 without cardiac-related activity, are summarized in Table 1. Note that the properties were generally similar for the two groups. However, mean blood pressure was significantly lower ($P < 0.05$; unpaired $t$-test) for the group of PSNs lacking cardiac-related activity. Also note that the $H$ exponents derived by detrended DA were not significantly different from those obtained using ordinary DA. The $H$ exponent was persistent in every case, indicating that the long-range correlations among ISIs were positive.

**Preganglionic multifiber activity**

Fano factor analysis was used to test for fractal fluctuations in spike counts recorded from 16 multifiber strands teased from the preganglionic cervical sympathetic nerve (6 cats). Each strand contained between two and five active units, some of which only occasionally emitted a spike. Fluctuations in spike counts were fractal for 13 of 16 multifiber fields. The smallest number of spikes in the 16 fields was 2,043. A case of fractal multifiber activity is illustrated in Fig. 3. This field had cardiac-related activity with peak counts occurring during diastole (Fig. 3A). The nearly 2,000-s-long time series in Fig. 3B shows the number of spikes counted in 20-s bins. In this case, there was a tendency toward increased multifiber activity during the recording period. The total number of spikes in the time series was 5,784. The Fano factor curve for the real data (Fig. 3C, single black line) shows a power law relationship with a slope $(\alpha)$ of 0.72 beginning at a window size of approximately 2 s. In contrast, after an initial dip below $F(T) = 1.0$, the curves for 10 surrogates data blocks were essentially flat (gray region). Thus shuffling of the ISIs in multifiber time series effectively randomized the number of spike counts in successive windows of specified length.

Three of 16 multifiber fields did not exhibit fractal fluctuations in spike counts despite the fact that these time series contained no less than 3,071 action potentials. An example is shown in Fig. 4. In this case, there was little or no cardiac-related activity (Fig. 4A). Note that the Fano factor curve for the original time series (Fig. 4C, single black line) fell within...
TABLE 1. Properties of fractal spike trains of single preganglionic cervical sympathetic fibers

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>Non-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of fibers</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Data length (s)</td>
<td>2,082 ± 592</td>
<td>1,499 ± 168</td>
</tr>
<tr>
<td>No. of spikes</td>
<td>1,856 ± 421</td>
<td>2,142 ± 928</td>
</tr>
<tr>
<td>Firing rate (Hz)</td>
<td>1.3 ± 0.4</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>CV (ISIH)</td>
<td>0.75 ± 0.11</td>
<td>0.61 ± 0.10</td>
</tr>
<tr>
<td>$\alpha$ (Fano)</td>
<td>0.70 ± 0.09</td>
<td>0.64 ± 0.04</td>
</tr>
<tr>
<td>Fano range (s)</td>
<td>5.6–208.2</td>
<td>4.0–149.9</td>
</tr>
<tr>
<td>$H$ exp (DA)</td>
<td>0.83 ± 0.06</td>
<td>0.79 ± 0.04</td>
</tr>
<tr>
<td>$H$ exp (DA-1$^a$)</td>
<td>0.79 ± 0.06</td>
<td>0.77 ± 0.04</td>
</tr>
<tr>
<td>$m$</td>
<td>4–468</td>
<td>4–536</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>113 ± 14</td>
<td>84 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SE. CR, fibers with cardiac-related activity; non-CR, fibers lacking cardiac-related activity; CV (ISIH), coefficient of variation of interspike interval histogram; $\alpha$ (Fano), scaling exponent of the power law relationship in the Fano factor curve; Fano range, range of grouped data points over which $H$ exponent was measured using DA-1$^a$; MBP, mean blood pressure.

The properties of the 16 multifer fiber spike trains are summarized in Table 2. Note that the majority of both the fractal and nonfractal time series exhibited cardiac-related activity. Mean firing rates were similar for the two groups. The slope of the power law relationship in the Fano factor curves for the 13 multunit fractal time series was not significantly different from those in the curves for single fiber activity (see Table 1).

![Figure 3](http://jn.physiology.org/)

**Figure 3.** Fano factor analysis of fractal multifer fiber spike train recorded from strand of preganglionic cervical sympathetic nerve. A: AP-triggered average of AP (top) and histogram of multifer activity (bottom) based on 7,513 trials; histogram resolution, 10 ms. B: time series showing number of spikes in 10-s bins. Total number of spikes is 5,784. C: fano factor curves for original time series (single black line) and 10 surrogate blocks (gray region); $\alpha = 0.72$ for real data.

![Figure 4](http://jn.physiology.org/)

**Figure 4.** Fano factor analysis of nonfractal multifer fiber spike train recorded from preganglionic cervical sympathetic nerve. A: AP-triggered average of AP and histogram of multifer activity (3,788 trials); histogram resolution, 10 ms. B: time series showing number of spikes in 10-s bins. Total number of spikes is 3,071. C: fano factor curve for original time series (single black line) falls within range of those for 10 surrogates (gray region).

DA of preganglionic multifer fiber activity was not performed so as to avoid dealing with “mixed” populations of ISIs. The intervals would include those between the spikes of the same unit (whether fiber 1, 2, or $n$) and those between the spikes of different sets of unit pairs (fibers 1 and 2, 2 and $n$, etc.). The sequence of such “mixed” intervals might be random even when fluctuations in spike counts for the total population of active fibers were proven to be fractal by Fano factor analysis.

**Postganglionic SND and HRV**

Femoral blood pressure and the activity of the whole postganglionic VN were recorded in five cats. As illustrated in Fig. 5, we made cycle-by-cycle measurements of the cardiac interval (CI), the interval between successive cardiac-related slow waves of VN activity (SWI), trough-to-peak normalized slow-wave height (referred to as SWH), and normalized slow-wave area (SWA). The measurements of VN activity were made

![Table 2](http://jn.physiology.org/)

**Table 2. Properties of spike trains of preganglionic cervical sympathetic multifer fiber activity**

<table>
<thead>
<tr>
<th></th>
<th>Fractal</th>
<th>Nonfractal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of fields</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Data length (s)</td>
<td>1,384 ± 239</td>
<td>693 ± 359</td>
</tr>
<tr>
<td>CR activity</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>No. of spikes</td>
<td>7,322 ± 1,521</td>
<td>3,843 ± 571</td>
</tr>
<tr>
<td>Firing rate (Hz)</td>
<td>7.9 ± 2.8</td>
<td>10.4 ± 9.8</td>
</tr>
<tr>
<td>$\alpha$ (Fano)</td>
<td>0.55 ± 0.05</td>
<td>—</td>
</tr>
<tr>
<td>Fano range (s)</td>
<td>4.2–138.4</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± SE. Abbreviations same as in Table 1.
from digitally filtered records (see METHODS). Time series containing ≥2,000 readings of these parameters were constructed, after which DA was performed.

The results of one of the five experiments are illustrated in Figs. 6 and 7. The time series in Fig. 6, A–D (left), are 900 s in length and contain 2,120 (CI and SWI) or 2,121 (SWH and SWA) measurements. The corresponding histograms (Fig. 6, A–D, right) show the distribution of these measurements. Values of the four parameters were distributed normally and mean CI and mean SWI were identical (425 ms). Because slow trends (decrease in CI and SWI, increase in SWH) appeared in the time series, the decision on whether momentary fluctuations in a particular parameter were fractal in nature was made on the basis of detrended DA rather than ordinary DA.

Figure 7 shows the results of detrended DA of the time series illustrated in Fig. 6. The slopes of the curves for CI, SWH, and SWA, but not SWI (real data; single black line) were flatter than those for 10 surrogate data blocks (gray region) over the following ranges of \( m \): 5–540 (CI); 40–540 (SWH); and 30–540 (SWA). \( H \) exponents derived from the negative slopes were 0.67 (CI), 0.67 (SWH), and 0.76 (SWA). \( H \) exponents for SWI and the surrogates for each of the parameters were close to 0.5. These results were typical of those observed in four of five cats. None of the parameters were fractal in the other cat.

The results of DA in the four cats showing fractal fluctuations are summarized in Table 3. The following points should be noted. 1) Fractal \( H \) exponents for CI, SWH, and SWA obtained with detrended DA were persistent, but lower than those obtained with ordinary DA. 2) The fractal range (detrended DA) began at a smaller value of \( m \) for CI than for SWH or SWA. 3) Although ordinary DA yielded highly persistent \( H \) for SWI, the \( H \) exponents derived with detrended DA were indistinguishable from those for the surrogates.

DISCUSSION

Various methods of fractal analysis have been used to test for time-scale invariant behavior of biological signals that appear to be either periodic or aperiodic (Bassingthwaighte et al. 1994; Goldberger et al. 1996; Ivanov et al. 1999; Teich 1992; Yamamoto and Hughson 1994). In the case of an apparently periodic signal such as the heart beat, the question entertained is whether relatively small fluctuations in CI occur
Fluctuations in spike counts were fractal for the majority (13 of 16) of time series of multifiber preganglionic activity. This observation raises the possibility that groups of PSNs share common fractal inputs possibly from the brain stem (Lewis et al. 2001) or that time-scale invariant behavior generated independently by individual neurons in the brain stem and/or spinal cord is somehow synchronized. These possibilities are deserving of future investigation since synchronization of the fractal discharges of populations of sympathetic neurons might play a role in explaining the fractal component of HRV.

HRV in awake humans is characterized not only by respiratory-related and slower third-order fluctuations, but also by a time-scale invariant component extending over a very low frequency (0.00003 to 0.1 Hz) range (Goldberger et al. 1996; Ivanov et al. 1999; Malliani et al. 1991; Yamamoto and Hughson 1994). In the current study, we found fractal fluctuations in CI recorded from cats anesthetized with dial-urethane. DA revealed persistent correlations among CIs for groups (m) of between 7 and 653 data points. Population activity recorded from the whole postganglionic VN in the same cats also exhibited persistent fractal properties over a somewhat shorter range of window sizes (see Table 3). Specifically, fluctuations in the height and area of cardiac-related VN slow waves were fractal. As was the case for CI, H exponents derived for these properties were persistent but lower in value when detrended DA was substituted for ordinary DA. Although ordinary DA yielded persistent H exponents for fluctuations in the interval between cardiac-related VN slow waves, those derived with detrended DA were not significantly different from 0.5. Thus it is likely that slow trends in the time series of SWI rather than true fractal behavior accounted for the persistent H derived by using ordinary DA.

The fractal component of HRV in humans is diminished with aging and in cardiovascular diseases such as heart failure (Goldberger 1992; Goldberger et al. 1996; Ivanov et al. 1999). As such, methods of fractal analysis have recently been introduced into the cardiology clinic. Because of the clinical implications attached to the loss of fractal HRV, it becomes even more important to identify the mechanisms responsible for time-scale invariant fluctuations in CI. There are conflicting views concerning the role played by autonomic outflows to the heart. Whereas Goldberger et al. (1996) have postulated that the fractal component of HRV in healthy humans arises from a nonlinear interaction of sympathetic and vagal influences on the SA node, Yamamoto and Hughson (1994) reported that the power law relationship in power spectrum of CI in humans is minimally affected by β-adrenergic blockade. Whether sym-

### Table 3. Properties of time series of CI and SWI, SWH, and SWA recorded from postganglionic vertebral sympathetic nerve in four cats

<table>
<thead>
<tr>
<th>Property</th>
<th>$H_{\exp} (\text{DA})$</th>
<th>$H_{\exp} (\text{DA}-1^\text{st})$</th>
<th>$m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>0.92 ± 0.05</td>
<td>0.67 ± 0.01</td>
<td>7–653</td>
</tr>
<tr>
<td>SWI</td>
<td>0.92 ± 0.03</td>
<td>Nonfractal</td>
<td>—</td>
</tr>
<tr>
<td>SWH</td>
<td>0.89 ± 0.06</td>
<td>0.68 ± 0.04</td>
<td>25–653</td>
</tr>
<tr>
<td>SWA</td>
<td>0.82 ± 0.07</td>
<td>0.74 ± 0.04</td>
<td>25–653</td>
</tr>
</tbody>
</table>

Values are means ± SE. Mean heart rate was 3.1 ± 0.3 beats/s and data length averaged 906 ± 11 s. Mean number of events was 2.689 ± 228. CI, cardiac interval; SWI, cardiac-related slow wave interval; SWH, slow-wave height; SWA, slow-wave area. Other abbreviations same as in Table 1.

The preganglionic cervical sympathetic nerve is functionally heterogeneous in that it contains fibers controlling blood vessel diameter, pupil size, nictitating membrane contraction, pilomotor, and sweating (Bishop and Heinbecker 1932; Eccles 1935). Whether the spike trains of each of these fiber types are fractal cannot be decided on the basis of the currently available data. Although PSNs governing vasoconstriction are reputed to have the strongest cardiac-related activity (Janig 1988), the fact that the spike trains of single PSNs were fractal independent of whether their discharges were cardiac related turned out not to be helpful. Regarding this issue, mean blood pressure was significantly lower in the cases in which the spike train did not contain cardiac-related activity (see Table 1). Thus these PSNs may not have been functionally distinct from those with cardiac-related activity. Rather, baroreceptor input may have been too weak to induce cardiac-related activity at lower blood pressures.

In a previous study (Lewis et al. 2001) on brain stem neurons with activity correlated to the cardiac-related or 10-Hz rhythmic component of SND, we found that the percentage of fractal spike trains ($n = 19$) reached 100 when the time series contained ≥2,000 spikes. On this basis, we proposed that all such neurons have fractal firing patterns. We are reticent to propose the same for PSNs because only a small sample of time series containing this number of spikes was obtained in the current study.

Fluctuations in spike counts were fractal for the majority (13 of 16) of time series of multifiber preganglionic activity. This observation raises the possibility that groups of PSNs share common fractal inputs possibly from the brain stem (Lewis et al. 2001) or that time-scale invariant behavior generated independently by individual neurons in the brain stem and/or spinal cord is somehow synchronized. These possibilities are deserving of future investigation since synchronization of the fractal discharges of populations of sympathetic neurons might play a role in explaining the fractal component of HRV.
pathetic outflow is involved in generating fractal HRV in the cat remains to be investigated. This possibility seems more attractive in the light of our finding that both pre- and post-
ganglionic sympathetic activities contain fractal components.

Fractal fluctuations in the height and area of cardiac-related bursts of postganglionic VN activity indicate that a time-scale invariant process is involved in determining the number of active neurons and/or their firing rate during each cardiac cycle. At first glance, the fact that fluctuations in the interval between cardiac-related bursts of VN activity were not fractal seems surprising since fluctuations in CI were fractal in the same cats. However, it should be remembered that the phase angle relating SND to the AP in the cat shows considerable variability on a heart beat-to-beat basis (Larsen et al. 2000; Lewis et al. 2000). This arises from the fact that the cardiac-related rhythm in SND is not the simple consequence of constant latency central inhibition of baroreceptor reflex origin. Rather, cardiac-related bursts are forced nonlinear oscillations whose timing relative to pulse-synchronous baroreceptor input can assume many different values (Larsen et al. 2000; Lewis et al. 2000). Thus CI might fluctuate in a time-scale invariant manner while fluctuations in the interval between cardiac-related bursts of SND occur randomly. At any rate, if fractal SND plays a role in generating fractal HRV, the properties of SND so responsible would apparently be SWH and SWA.

In summary, we have demonstrated that apparently random fluctuations in activity recorded from PSNs and the postganglionic VN are, in fact, fractal in nature. Such properties include spike counts, ISIs, and population burst height and area. Time series of these properties should not be modeled as random, stochastic processes comprised of uncorrelated events. Rather, the time-scale invariant fluctuations are dictated by a complex deterministic process that imparts a type of “long-
term” memory into the system responsible for SND, as re-
lected by long-range, positive correlations among events. Thus, for example, the current value of the ISI is determined not only by recent events, but also by those in the “distant” past (range over which a power law relationship appears in the Fano factor and DA curves). It remains to be investigated whether the fractal properties of SND play a role in generating the fractal component of HRV that is typical of the “healthy” cardiovascular state.

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