Heart rate dynamics during accentuated sympathovagal interaction

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Heart rate dynamics during accentuated sympathovagal interaction. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H810–H816, 1998.—Concomitant sympathetic and vagal activation can occur in various physiological conditions, but there is limited information on heart rate (HR) behavior during the accentuated sympathovagal antagonism. Beat-to-beat HR and blood pressure were recorded during intravenous infusion of incremental doses of norepinephrine in 18 healthy male volunteers (mean age 23 ± 5 yr). HR and blood pressure spectra and two-dimensional Poincaré plots were generated from the baseline recordings and from the recordings at different doses of norepinephrine. The mean blood pressure increased (from 90 ± 7 to 120 ± 9 mmHg, P < 0.001), HR decreased (from 60 ± 9 to 48 ± 7 beats/min, P < 0.001), and the high-frequency spectral component of HR variability increased (P < 0.001) during the norepinephrine infusion as evidence of accentuated sympathovagal interaction. Abrupt aperiodic changes in sinus intervals that were not related to respiratory cycles or changes in blood pressure occurred in 14 of 18 subjects during the norepinephrine infusions. These fluctuations in sinus intervals resulted in a complex or parabola-shaped structure of the Poincaré plots of successive R-R intervals and a widening of the high-frequency spectral peak. In four subjects, the abrupt fluctuations in sinus intervals were followed by a sudden onset of fixed R-R interval dynamics with a loss of respiratory modulation of HR, resulting in a torpedo-shaped structure of the Poincaré plots. These data show that HR behavior becomes remarkably unstable during accentuated sympathovagal interaction, resembling stochastic dynamics or deterministic chaotic behavior. These features of HR dynamics can be better identified by dynamic analysis of beat-to-beat behavior of R-R intervals than by traditional analysis techniques of HR variability.

Heart rate variability; cardiovascular regulation

POWER SPECTRAL ANALYSIS of heart rate (HR) variability is a commonly used method in the measurement of sympathovagal interaction on sinus node (2, 24). Because traditional analysis techniques are insensitive to abrupt, aperiodic changes in HR dynamics, beat-to-beat analysis techniques and other dynamic methods have been developed to uncover stochastic or nonlinear features in HR behavior (9, 14, 20, 25).

Reciprocal changes in sympathetic and vagal activity have been observed in some physiological conditions, such as during passive tilt, which can be detected by typical changes in spectral components of HR variability (22, 26). In other physiological and pathological states, concomitant sympathetic and vagal activation can occur, leading to accentuated sympathovagal antagonism (6, 8, 16, 30). Acetylcholine and norepinephrine have a complex interaction at the level of the sinus node, resulting in a typical condition favoring the occurrence of complex HR dynamics (17, 18). The present research was designed to study the HR behavior during accentuated sympathovagal interaction by generating power spectra and Poincaré plots of successive R-R intervals at the baseline and during infusion of incremental doses of norepinephrine in young healthy males.

METHODS

Subjects and study protocol. HR dynamics were studied in 18 healthy male volunteers (mean age 23 ± 5 yr) at rest in the supine position under quiet baseline conditions and during incremental doses of intravenous norepinephrine. Subjects with atrial or ventricular ectopic beats or those with episodes of nodal rhythm during the experiment were excluded. The design was approved by the ethics committee of the institution, and all subjects gave their informed consent. All the tests were performed between 10:00 AM and 4:00 PM, and vigorous exercise, alcohol intake, or smoking were forbidden for 48 h before the testing days. The subjects lay in a supine position in a quiet room for 30 min before the data collection and became accustomed to breathing at a constant metronome-guided rate of 0.25 Hz for the duration of the experiment. The beat-to-beat R-R intervals were recorded with a wireless HR monitoring system having a sampling frequency of 1,000 Hz (Polar Electro, Kempele, Finland) (27). A continuous surface electrocardiogram was also recorded during the experiment to confirm the sinus origin of the beats. Beat-to-beat arterial blood pressure was measured by the Finapres finger-cuff method, the respiration was measured with a disposable screen-type flow transducer, and the data were stored by means of menu-driven software packages (1, 29). HR, blood pressure, and respiration signals were fed into an analog-to-digital converter and stored in a microcomputer for further analysis. The protocol included baseline recordings for 15 min and, during infusion of norepinephrine at constant rates of 50, 100, and 150 ng·kg⁻¹·min⁻¹, recordings of 15 min at each concentration. The doses of norepinephrine were based on previous studies (3) that have shown these doses to result in plasma concentrations of norepinephrine observed under various physiological conditions. If the blood pressure increased >180/110 mmHg or the subjects complained of any uncomfortable symptoms during the norepinephrine infusion, the infusion was stopped (6 subjects, see Table 1).

Analysis of R-R interval dynamics. Data analyses were performed as described in detail previously (13, 29). An autoregressive model was used to estimate the power spectrum densities of HR and blood pressure variabilities (see APPENDIX). The computer program automatically calculates the autoregressive coefficients to define the power spectrum density. The power spectra were quantified by measuring the area under two frequency bands: low-frequency power from
RESULTS

The mean blood pressure increased and mean HR decreased progressively with increasing doses of norepinephrine (Table 1). The high-frequency spectral component of HR variability increased during the initial dose of 50 ng·kg⁻¹·min⁻¹, but no additional increase occurred with higher doses. No significant changes were observed in the low-frequency component of HR variability during norepinephrine infusion.

Recordings of electrocardiogram, blood pressure, and respiration and corresponding R-R interval tachograms for one subject with typical HR dynamics at the baseline and with incremental doses of norepinephrine are presented in Fig. 1. Respiratory modulation of R-R intervals and blood pressure were observed under the baseline conditions with lengthening of R-R intervals and an increase in blood pressure during expiration and shortening of the R-R intervals and a decrease of blood pressure during inspiration, resulting in a discrete high-frequency spectral peak at 0.25 Hz. During the small dose of norepinephrine (50 ng·kg⁻¹·min⁻¹), a pattern with abrupt lengthening of the R-R intervals followed by gradual shortening to the baseline level (Fig. 1B) was observed without any concomitant abrupt changes in blood pressure. These sudden changes in HR occurred aperiodically and were not related to the frequency or depth of respiration. At a medium dose (100 ng·kg⁻¹·min⁻¹), abrupt shortenings of R-R intervals were observed that again occurred aperiodically and were not related to the respiration cycles (Fig. 1C).

At a high dose of norepinephrine (150 ng·kg⁻¹·min⁻¹), a periodic respiratory modulation of the R-R intervals reappeared at a slower HR without any abrupt changes in R-R intervals.

Abrupt changes in R-R intervals resulted in a significant widening of the high-frequency spectral peak toward a very high frequency area (see Fig. 3). The two-dimensional return maps showed a typical comet-shaped plot for the baseline R-R intervals (Fig. 2A). Abrupt episodes of HR slowing during norepinephrine infusion resulted in a complex or an inverted parabola-like plot for the Poincaré plot (Fig. 2B). The aperiodic shortenings of the R-R intervals typically resulted in a horseshoe- or parabola-like structure of the Poincaré plot (Fig. 2C). A comet-shaped or cirdlike Poincaré plot of R-R intervals reappeared during the high dose (150 ng·kg⁻¹·min⁻¹) of norepinephrine. The shape of the Poincaré plots of the blood pressure remained similar during the different doses of norepinephrine infusion (Fig. 2).

A comet-shaped Poincaré plot of R-R intervals was observed in 14 of the 18 subjects at the baseline, whereas 4 subjects already had a parabola-like structure before the norepinephrine infusion. This latter group had slower mean HR (51 ± 9 vs. 63 ± 9 beats/min, P < 0.05) and higher high-frequency spectral component (4.892 ± 1.209 vs. 1.277 ± 0.838 ms², P <

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Table 1. Effects of norepinephrine on HR, blood pressure, and HR variability

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>50 ng·kg⁻¹·min⁻¹</th>
<th>100 ng·kg⁻¹·min⁻¹</th>
<th>150 ng·kg⁻¹·min⁻¹</th>
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<tr>
<td>n</td>
<td>18</td>
<td>18</td>
<td>17</td>
<td>12</td>
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<tr>
<td>HR, beats/min</td>
<td>60 ± 9</td>
<td>53 ± 8†</td>
<td>51 ± 10†</td>
<td>48 ± 7†</td>
</tr>
<tr>
<td>BP, mmHg</td>
<td>90 ± 7</td>
<td>102 ± 10‡</td>
<td>110 ± 11‡</td>
<td>120 ± 9†</td>
</tr>
<tr>
<td>SD1, ms</td>
<td>48 ± 24</td>
<td>83 ± 43‡</td>
<td>82 ± 50</td>
<td>87 ± 52</td>
</tr>
<tr>
<td>SD2, ms</td>
<td>90 ± 37</td>
<td>111 ± 45*</td>
<td>106 ± 58</td>
<td>102 ± 46</td>
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<tr>
<td>SD1/SD2</td>
<td>0.53 ± 0.15</td>
<td>0.72 ± 0.21†</td>
<td>0.73 ± 0.26</td>
<td>0.78 ± 0.20</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>0.08 ± 0.05</td>
<td>0.199 ± 0.1276</td>
<td>1.787 ± 1.236</td>
<td>1.868 ± 1.364</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>1.290 ± 1.236</td>
<td>1.787 ± 1.236</td>
<td>1.787 ± 1.236</td>
<td>1.868 ± 1.364</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.77 ± 0.85</td>
<td>0.54 ± 0.65</td>
<td>0.55 ± 0.51</td>
<td>0.45 ± 0.38</td>
</tr>
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Data are means ± SD. HR, heart rate; BP, blood pressure; SD1, standard deviation of instantaneous beat-to-beat R-R interval variability measured from Poincaré plots; SD2, standard deviation of long-term R-R interval variability measured from Poincaré plots. HF, high-frequency component of HR variability; LF, low-frequency component of HR variability; LF/HF = ratio between low- and high-frequency components. *P < 0.05, †P < 0.01, ‡P < 0.001 compared with preceding value by analysis of variance of repeated measurements.

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0.04 to 0.15 Hz, and high-frequency power from 0.15 to 0.4 Hz.

Two-dimensional return maps or Poincaré plots were generated by plotting each R-R interval as a function of its previous R-R interval and each systolic blood pressure value as a function of its previous systolic blood pressure value, respectively, obtained at the baseline and with different levels of norepinephrine infusion. Two-dimensional vector analysis was used to quantify the shape of the plots as described previously (13, 29). In this quantitative method, short-term (SD1) and long-term R-R interval variability (SD2) and the ellipse area of the plot are separately quantified. The shapes of Poincaré plots were classified as 1) a normal, comet-shaped plot, in which increasing beat-to-beat R-R interval dispersion is observed with increasing R-R intervals (SD1/SD2 < 0.15); 2) a torpedo-shaped plot with small overall beat-to-beat dispersion (SD1) and without increasing dispersion at longer R-R intervals (SD1/SD2 < 0.15); or 3) a complex or parabola-like plot, in which two or more distinctive limbs are separated from the main body of the plot, with at least three points included in each limb.

Statistical methods. Analysis of variance for repeated measurements was used to compare the changes in HR, blood pressure, and normally distributed HR variability measures during the norepinephrine infusion. Normal Gaussian distribution of the data was verified by the Kolmogorov-Smirnov goodness-of-fit test. Whenever the data were not normally distributed (z value > 1.0 for all spectral components of HR variability), Friedman’s randomized block analysis of variance followed by post hoc analysis (Wilcoxon test) was used. Differences in baseline data between the subjects with different R-R interval dynamics during the norepinephrine infusion were analyzed by a Mann-Whitney U test.
0.01) than subjects with a comet-shaped plot at the baseline. During low or medium doses of norepinephrine infusion, a parabola-like plot was observed in 12 subjects, and in 2 subjects the parabola-like structure occurred during a high dose of norepinephrine. Only four subjects had a normal comet-shaped plot at the baseline and during all phases of norepinephrine infusion. When the baseline HR and blood pressure data were compared between those subjects with a parabola-like plot and those with a comet-shaped plot during the norepinephrine infusion, no significant differences were observed in any of these data (Table 2), nor did changes in mean HR or blood pressure differ between these subjects during the norepinephrine infusion.

In four subjects, the abrupt changes in R-R interval dynamics were followed by a sudden change into fixed R-R interval dynamics, resulting in a torpedo-shaped Poincaré plot (Fig. 3). No respiratory modulation of R-R intervals was observed during the fixed dynamics.

![Fig. 1](image1.png)  
**Fig. 1.** Heart rate (HR) and blood pressure (BP) dynamics of a healthy 19-year-old man at baseline resting condition (A) and during norepinephrine infusion of 50 (B) and 100 ng·kg⁻¹·min⁻¹ (C). Top at each condition shows R-R interval tachogram. The portion of electrocardiograms (ECG) with R-R interval lengths in milliseconds from segments indicated by lines in tachograms are shown below tachograms, BP recordings are below ECG, and respiration curve is at bottom. A: at baseline, a typical respiratory modulation of R-R interval and BP is observed. B: during norepinephrine infusion of 50 ng·kg⁻¹·min⁻¹, abrupt lengthening in R-R intervals (4 episodes in tachogram) without concomitant changes in BP are observed (e.g., from 2nd to 5th R-R interval in ECG). These abrupt changes are not related to respiration. C: during norepinephrine infusion of 100 ng·kg⁻¹·min⁻¹, abrupt aperiodic shortenings of R-R intervals are observed (5 episodes in tachogram; 3rd and 4th beats in ECG) that are not related to respiration or to concomitant changes in BP.

![Fig. 2](image2.png)  
**Fig. 2.** Poincaré plots of successive R-R intervals (R-Rn and R-Rn⁺₁; left) and systolic BP (BPn and BPn⁺₁; right) at baseline (A) and during norepinephrine infusion of 50 (B) and 100 ng·kg⁻¹·min⁻¹ (C). A: a typical comet-shaped Poincaré plot of R-R-intervals is observed at baseline. B: during a norepinephrine dose of 50 ng·kg⁻¹·min⁻¹, a typical pattern of Poincaré plot is observed (an inverted parabola). C: during a norepinephrine dose of 100 ng·kg⁻¹·min⁻¹, a typical parabola-like shape of the Poincaré plot of R-R-intervals is observed. Comet-shaped Poincaré plots of BP are observed throughout experiment (right).
Reproducibility. When HR and blood pressure dynamics were assessed twice under similar baseline conditions in four subjects with a parabola-like Poincaré plot at the baseline, all of them showed similar R-R interval dynamics during the second recording. However, in one subject who underwent four recording sessions at 1-wk intervals under similar external conditions, the parabola-like structure was not repeated during the last experiment, when completely different HR dynamics were observed (Fig. 4).

When norepinephrine was repeatedly infused in four subjects with occurrence of parabola-like structure during the first experiment, similar dynamics were repeated in two subjects, but in two cases the parabola-like structure did not reappear. In three cases without recurrence of nonlinear dynamics during the repeated test (one at the baseline and two during the norepinephrine infusion), the baseline measures of HR variability differed significantly (>20% difference for all measures) between the first and the repeated experiment (see e.g., Fig. 4), whereas in cases in which R-R interval dynamics showed similar behavior during the repeated experiments, the baseline measures of HR variability

<table>
<thead>
<tr>
<th>Comet-Shaped Poincaré Plot Both at Baseline and During Norepinephrine Infusion</th>
<th>Comet-Shaped Poincaré Plot at Baseline and Parabola-Like Structure During Norepinephrine Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>65±6</td>
</tr>
<tr>
<td>BP, mmHg</td>
<td>89±9</td>
</tr>
<tr>
<td>SD1, ms</td>
<td>32±10</td>
</tr>
<tr>
<td>SD2, ms</td>
<td>67±16</td>
</tr>
<tr>
<td>SD1/SD2</td>
<td>0.49±0.18</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>880±482</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>634±510</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.08±1.63</td>
</tr>
</tbody>
</table>

Values are means ± SD.

Fig. 4. Poincaré plots and R-R interval tachograms of a healthy subject with 4 experiments on different days with similar external conditions. Baseline tachograms (top), power spectra (middle), and corresponding Poincaré plots (bottom) are shown from 1st and 4th experiments. During trial 1, unstable R-R-interval dynamics with a parabola-like plot (bottom left) were observed. In trial 4, completely different dynamics of R-R intervals were observed without abrupt fluctuations. Baseline high- and low-frequency spectral components are smaller in trial 4 compared with those in trial 1 (middle).
were almost identical (~20% difference in all measures).

**DISCUSSION**

HR dynamics during accentuated sympathovagal interaction. The observations of this study show that atypical, abrupt changes occur in HR dynamics during norepinephrine infusion in young healthy males. These findings suggest that the HR may become remarkably unstable during stressful situations that result in accentuated sympathovagal antagonism.

Unstable behavior of HR may be explained by complex interaction of acetylcholine and norepinephrine at the presynaptic and postsynaptic level of sinus node (17, 18). Norepinephrine infusion causes baroreceptor-mediated vagal activation, resulting in accentuated sympathovagal interaction, as evidenced here by an increase in blood pressure, a decrease in HR, and an increase in high-frequency spectral component of HR variability. Norepinephrine and acetylcholine have different temporal influences on the basic R-R interval length; vagal effects on R-R intervals occur more rapidly than sympathetic influences (17, 18), and the beat-to-beat fluctuations in R-R intervals depend on summation and timing of the opposing effects of norepinephrine and acetylcholine on the sinus node. Abrupt changes in R-R intervals are most likely a result of sudden vagal bursts or withdrawals, respectively, during high sympathetic influences on sinus node firing. The physiological background for onset of fixed R-R interval dynamics and abrupt disappearance of respiratory modulation of HR may be explained by the saturation of the respiratory vagal modulation of sinus node during a very high tonic vagal activity (19, 21).

Present observations also show that incremental doses of norepinephrine infusion seldom result in a linear slowing of HR but that the HR behavior can be described as stochastic increases or decreases in R-R intervals followed by return to control. There are also some features of deterministic chaos in HR dynamics during this experimental condition. A parabola-like or ringlike structure rather than a random distribution of the successive R-R intervals was observed in the Poincaré plots during unstable HR behavior. This type of specific structure in the return maps of successive data points has been considered to provide evidence for deterministic chaos in the experimental animal models (5, 7, 10, 12, 15, 28). Also, the occurrence of fixed beat-to-beat R-R interval dynamics after abrupt fluctuations on R-R intervals represents another feature of deterministic chaos, i.e., abrupt temporal changes as cascades to fixed dynamics (7, 11, 15). Finally, completely different R-R interval dynamics were observed in the same subject in the similar external conditions when the baseline HR dynamics were different. Dependence of system dynamics on initial conditions is also one of the typical features of deterministic chaos (7, 15).

The present analysis of data may not provide definite evidence of whether the observed HR dynamics can be better described as stochastic or as having characteristics of deterministic chaos, but it nevertheless empha-

sizes the need for analysis of HR behavior with dynamic methods in addition to methods based on moment statistics.

Analysis methods of HR dynamics during sympathovagal interaction. Spectral analysis techniques have been most commonly used in assessment of the effects of sympathovagal balance on sinus node (2, 23, 24, 26). These analysis methods are based on the assumption that reciprocal changes occur in sympathetic and vagal activity under various physiological conditions (23, 24). Present findings demonstrate that traditional measures of HR variability are not specific for measurement of accentuated sympathovagal interaction. Abrupt changes in R-R intervals resulted in a widening of the high-frequency spectral peak without consistent changes in any numerical measure of spectral components. These changes in HR dynamics could be accurately described not by quantitative two-dimensional analysis of the Poincaré plots but only by visual inspection of the plots, suggesting that the visual interpretation of the shape of the Poincaré plot is more reliable than numerical methods in revealing the atypical HR behavior during accentuated autonomic interaction. These findings support the concept that beat-to-beat dynamic analysis methods may give important physiological information on HR behavior that cannot be detected by traditional methods of HR variability based on moment statistics. From a methodological point of view, it is also important to note that abrupt changes in sinus intervals can occur in various physiological and pathological states (4, 13, 30). These changes in R-R intervals may become deleted as artifacts or ectopic beats in automatic and visual editing of R-R interval tachograms and in analysis of HR variability by some geometric methods (22).

In conclusion, the results of this study show that unstable stochastic dynamics or deterministic chaos is involved in the genesis of HR variability during accentuated sympathovagal interaction. These features of HR behavior can be better observed by dynamic beat-to-beat analysis of R-R intervals than by traditional nonspectral and spectral HR variability methods. Dynamic analysis methods may importantly increase our understanding of the physiological background for the complex behavior of HR in various conditions.

**APPENDIX**

Spectrum estimation with autoregressive modeling of time series. The most popular of the time-series modeling approaches to spectral estimation is the autoregressive (AR) spectral estimation (15a). Other names by which the AR spectral estimator is known are the maximum entropy spectral estimator and the linear prediction spectral estimator. In AR(p) modeling of time series, it is assumed that a time series can be predicted with a linear combination of past p samples

\[ x[n] = - \sum_{k=1}^{p} a[k]x[n-k] \]  

(A1)

in which \( x[n] \) is the prediction at a time instant \( n \), \( x[n-k] \) is the data sample at \( n-k \), and \( a[k] \) is a coefficient to be
estimated from the data. The a[k] coefficients are estimated from time series by solving a set of linear equations, the so-called Yule-Walker equations. Usually a prediction at time instant n produces a small prediction error \( u(n) \), and \( x(n) = x'(n) + u(n) \).

Many methods have been developed for solving for the Yule-Walker equations, e.g., autocorrelation, covariance, and modified covariance methods. We apply the Burg method, which estimates reflection coefficients first and then uses the Levinson recursion to obtain the AR parameter estimates. The reflection coefficients are estimated by minimizing the average of the estimates of the forward and backward prediction error powers. The Burg estimate is the only one of a large class of estimates that maintains the minimum-phase property. A drawback is that line splitting in spectrum may occur if too large a model order \( p \) is used in the AR(\( p \)) model. It is therefore recommended that model order \( p \) should not exceed one-third of the data size. However, \( p \) should be at least twice the number of distinct frequency components in the time series.

After the data series is modeled, power spectral density can be computed straightforwardly from the model

\[
P(f) = \frac{\sigma^2}{1 + \sum_{k=1}^{p} a[k] z^{-k(n-k)^2}}
\]

in which \( f \) is a frequency variable, \( \sigma^2 \) is the variance of the driving noise of the model \( u(n) \), and \( z = \exp(j2\pi f) \), where \( j = \sqrt{-1} \).

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