Dynamic Behavior of Heart Rate in Ischemic Stroke
Juha T. Korpelainen, MD, PhD; Kyösti A. Sotaniemi, MD, PhD; Anne Mäkikallio, MD; Heikki V. Huikuri, MD, PhD; Vilho V. Myllylä, MD, PhD

Background and Purpose—Traditional spectral and nonspectral methods have shown that heart rate (HR) variability is reduced after stroke. Some patients with poor outcome, however, show random-like, complex patterns of HR behavior that traditional analysis techniques are unable to quantify. Therefore, we designed the present study to evaluate the complexity and correlation properties of HR dynamics after stroke by using new analysis methods based on nonlinear dynamics and fractals (“chaos theory”).

Methods—In addition to the traditional spectral components of HR variability, we measured instantaneous beat-to-beat variability and long-term continuous variability analyzed from Poincaré plots, fractal correlation properties, and approximate entropy of R-R interval dynamics from 24-hour ambulatory ECG recordings in 30 healthy control subjects, 31 hemispheric stroke patients, and 15 brain stem stroke patients (8 medullary, 7 pontine) in the acute phase of stroke and 6 months after stroke.

Results—In the acute phase, the traditional spectral components of HR variability and the long-term continuous variability from Poincaré plots were impaired ($P<0.01$) in patients with hemispheric and medullary brain stem stroke, but not in patients with pontine brain stem stroke, in comparison with control subjects. At 6 months after stroke, measures of HR variability in hemispheric stroke patients were still lower ($P<0.05$) than those of the control subjects. Various complexity and fractal measures of HR variability were similar in patients and control subjects. The conventional frequency domain measures of HR variability as well as the Poincaré measures showed strong correlations (Pearson correlation coefficient, $r=0.68$ to $r=0.90$) with each other but only weak correlations ($r=0.09$ to $r=0.56$) with the complexity and fractal measures of HR variability.

Conclusions—Hemispheric and medullary brain stem infarctions seem to damage the cardiovascular autonomic regulatory system and appear as abnormalities in the magnitude of HR variability. These abnormalities can be more easily detected with the use of analysis methods of HR variability, which are based on moment statistics, than by methods based on nonlinear dynamics. Abnormal HR variability may be involved in prognostically unfavorable cardiac complications and other known manifestations of autonomic failure associated with stroke. (Stroke. 1999;30:1008-1013.)

Key Words: autonomic nervous system n cerebral infarction n heart rate

Cardiac complications such as arrhythmias and ischemic heart damage are related to an impaired prognosis during the acute phase of stroke. Although the pathogenesis of these complications is still incompletely understood, they are obviously associated with central autonomic cardiovascular dysregulation involving both the sympathetic and the parasympathetic nervous systems.

Heart rate (HR) variability reflecting autonomic cardiovascular dysfunction has been shown to be reduced as a consequence of both hemispheric and brain stem cerebral infarction by using conventional time and frequency domain measuring techniques based on the linear fluctuation of HR variability. However, there is increasing evidence to suggest that the heart is not a periodic oscillator under normal physiological conditions, and commonly used measures of HR variability are insufficient in outlining the changes in HR dynamics. Therefore, a number of new methods based on nonlinear dynamics and fractal analysis (“chaos theory”) have recently been developed to quantify complex HR dynamics and to complement conventional measures of HR variability. These new methods have already provided clinically useful information on patients with impaired left ventricular function, as well as on patients vulnerable to life-threatening arrhythmias, but their prognostic value has not been definitively proven in the risk stratification of patients with other cardiological or neurological diseases.

The present prospective 6-month follow-up study was designed to assess quantitatively the effects of brain infarction on the dynamics of HR fluctuation by using new complexity and fractal measures of HR variability, ie, 2-dimensional vector analysis of a Poincaré plot, fractal-like correlation properties, and approximate entropy (ApEn).
and to study correlations between various traditional and new complexity and fractal measures of HR variability in ischemic stroke.

Subjects and Methods
Forty-six consecutive patients (33 men and 13 women; mean ± SD age, 52.1 ± 11.2 years; range, 19 to 67 years) with acute first-ever brain infarction were included in the study. In 31 patients the infarct was located at the hemispheric level (19 in the right hemisphere and 12 in the left) and in 15 patients at the brain stem level (8 medullary and 7 pontine). Patients with manifestations of other nervous system lesions and patients with any other disease or medication known to affect the autonomic nervous system were excluded. Patients with acute congestive cardiac failure as well as patients with previous cardiac or pulmonary diseases were also excluded.

Thirty of the 31 patients with hemispheric infarction had unilateral signs of pyramidal tract lesion; most also had sensory deficits, and 1 patient had only aphasia. Six of the 15 patients with brain stem infarction had the lateral medullary syndrome of Wallenberg. Two additional patients with medullary infarction had ipsilateral Horner’s syndrome, bulbar paresis, dizziness, and contralateral sensory deficits of the body and the limbs. Seven patients had pontine infarction resulting in either contralateral hemiparesis or impaired pain and thermal sensation, associated with bulbar paresis, external ophthalmoplegia, or ipsilateral facial sensory deficits.

Cerebral CT verified a hemispheric infarction in 24 cases and a brain stem infarction in 3 cases. Even the repeated CT with contrast remained normal in 7 cases in the group of patients clinically classified as having hemispheric infarction and in 12 patients classified as having brain stem infarction. The first CT was performed within 24 hours after the infarction and the second CT 2 weeks later.

The control group consisted of 30 healthy subjects (21 men and 9 women; mean ± SD age, 51.8 ± 10.8 years; range, 19 to 67 years) without clinical manifestations of any cardiac, pulmonary, or nervous system disease and who were taking no medication known to affect these systems. The protocol of the study was approved by the Ethics Committee of the Medical Faculty, and informed consent was obtained from each subject.

A 2-channel 24-hour ambulatory ECG recording (Delmar Avionics electroscanner) was performed in the hospital on all the patients.
from 1 to 7 days (median, 3 days) after the onset of stroke and repeated 6 months later and on the control subjects at home. Recordings of the control subjects were not repeated because the repeatability of the 24-hour measurements of HR variability was shown to be good in this population.15 Two patients with large cortical infarction died as a result of increased intracranial pressure a few days after the first recording. Two patients (1 hemispheric and 1 pontine lesion) were excluded from the study after the first recording because of treatment with a β-adrenergic blocking agent needed for hypertension. Other patients were not taking any medication known to affect the autonomic nervous system during the 6-month follow-up period.

The ECG data from the recordings were sampled digitally and transferred from the Oxford Medilog scanner to a microcomputer for analysis of HR variability. All R-R interval time series were first edited automatically, after which careful manual editing was performed by visual inspection of the R-R intervals. Each R-R interval time series was passed through a filter to eliminate premature beats and artifacts and to delete the filling gaps with the use of recently described methods.16–18 In the final analysis of HR variability, 24-hour measurements were divided into segments of 8000 R-R intervals, and only segments with >85% sinus beats were included. One segment in 2 patients and no segments in control subjects were deleted because of this criterion. The mean length of all R-R intervals and standard deviation of all R-R intervals (SDNN) were computed as time domain measures. The power spectra of HR variability (Figure 1) were quantified by measuring the area in 3 frequency bands: 0.005 to 0.04 Hz (very low frequency [VLF]), 0.04 to 0.15 Hz (low frequency [LF]), and 0.15 to 0.4 Hz (high frequency [HF]).

Thereafter, the magnitude of HR variability was assessed quantitatively with the use of Poincaré plot analysis.17 The Poincaré plot is a diagram in which each R-R interval of a tachogram is plotted as a function of the previous R-R interval for a predetermined segment length (Figure 2). The markings of the plot are gathered around a line of unitary slope passing through the origin. Quantitative analysis of

### TABLE 1. HR and Measures of HR Variability in Control Subjects and in Patients With Hemispheric, Medullary, and Pontine Brain Infarction in the Acute Phase After Stroke

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>Hemisphere</th>
<th>Medulla</th>
<th>Pons</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI, ms</td>
<td>870±112</td>
<td>921±113</td>
<td>803±110</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>161±34</td>
<td>109±38‡</td>
<td>100±29‡</td>
</tr>
<tr>
<td>VLF, ms×ms</td>
<td>2777±1262</td>
<td>1184±496‡</td>
<td>946±669†</td>
</tr>
<tr>
<td>LF, ms×ms</td>
<td>980±704</td>
<td>494±298‡</td>
<td>489±446*</td>
</tr>
<tr>
<td>HF, ms×ms</td>
<td>860±1624</td>
<td>330±337</td>
<td>331±369</td>
</tr>
<tr>
<td>SD1, ms</td>
<td>29±20</td>
<td>22±10</td>
<td>21±11</td>
</tr>
<tr>
<td>SD2, ms</td>
<td>133±34</td>
<td>107±31†</td>
<td>93±26†</td>
</tr>
<tr>
<td>ApEn</td>
<td>1.10±0.19</td>
<td>1.11±0.18</td>
<td>1.03±0.24</td>
</tr>
<tr>
<td>α1</td>
<td>1.23±0.19</td>
<td>1.20±0.19</td>
<td>1.16±0.18</td>
</tr>
<tr>
<td>α2</td>
<td>1.08±0.09</td>
<td>1.05±0.10</td>
<td>1.07±0.07</td>
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</tbody>
</table>

Values are mean±SD. RRI indicates R-R interval; SDNN, standard deviation of all RRIs; VLF, very low frequency; LF, low frequency; HF, high frequency; SD1, instantaneous beat-to-beat RRI variability; SD2, long-term continuous RRI variability; ApEn, approximate entropy; α1, short-term scaling exponent; and α2, long-term scaling exponent. *P<0.05, †P<0.01, ‡P<0.001 for comparison between patients and control subjects (Mann-Whitney 2-sample test).

### TABLE 2. HR and Measures of HR Variability in Control Subjects and in Patients With Hemispheric, Medullary, and Pontine Brain Infarction at 6 Months After Stroke

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>Hemisphere</th>
<th>Medulla</th>
<th>Pons</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI, ms</td>
<td>870±112</td>
<td>969±106‡</td>
<td>880±156</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>161±34</td>
<td>127±39‡</td>
<td>131±34</td>
</tr>
<tr>
<td>VLF, ms×ms</td>
<td>2777±1262</td>
<td>1358±756‡</td>
<td>2849±3661</td>
</tr>
<tr>
<td>LF, ms×ms</td>
<td>980±704</td>
<td>595±410*</td>
<td>1443±1851</td>
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<tr>
<td>HF, ms×ms</td>
<td>860±1624</td>
<td>436±530</td>
<td>439±604</td>
</tr>
<tr>
<td>SD1, ms</td>
<td>29±20</td>
<td>23±10</td>
<td>23±15</td>
</tr>
<tr>
<td>SD2, ms</td>
<td>133±34</td>
<td>125±46</td>
<td>125±50</td>
</tr>
<tr>
<td>ApEn</td>
<td>1.10±0.19</td>
<td>1.10±0.21</td>
<td>0.98±0.18</td>
</tr>
<tr>
<td>α1</td>
<td>1.23±0.19</td>
<td>1.16±0.16</td>
<td>1.33±0.17</td>
</tr>
<tr>
<td>α2</td>
<td>1.08±0.09</td>
<td>1.06±0.10</td>
<td>1.04±0.11</td>
</tr>
</tbody>
</table>

Values are mean±SD. For abbreviations, see Table 1. *P<0.05, †P<0.01, ‡P<0.001 for comparison between patients and control subjects (Mann-Whitney 2-sample test).
a plot entails fitting an ellipse to the plot, with its center coinciding with the center point of the markings. The line defined as axis 2 describes the slope of the longitudinal axis, while the other axis (axis 1) defines the transverse slope, which is perpendicular to axis 2. The length of axis 1 is defined as the SD of the plot data in the direction that describes the instantaneous beat-to-beat variability of the data, SD1. The length of axis 2 is defined as the SD of the plot data in the perpendicular direction, SD2. This measure describes the continuous, long-term variability of the data in a given segment.

ApEn, a complexity measure that quantifies the regularity of time series data, was calculated from 24-hour recordings.20–22 ApEn measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in the next incremental comparisons. A greater likelihood of remaining close (high regularity) produces smaller ApEn values, and, conversely, random data produce higher ApEn values.

To quantify fractal correlation properties of HR, the detrended fluctuation analysis technique, which is a modified root-mean-square analysis of random walk, was used.20–22 In this study, fractal properties were defined separately for short-term (<11 beats, α1) and for long-term (>11 beats, α2) correlations of R-R interval data (short- and long-term scaling exponents).20–22

Statistical analyses were performed with the use of the Kruskal-Wallis test and the Mann-Whitney 2-sample test to compare the values of the control subjects and those of the patients. Pearson’s correlation coefficients were used in analyzing correlations between the various measures of HR variability.

**Results**

Table 1 presents the mean values of the different measures of HR variability in control subjects and in patients with acute stroke. In the patients with hemispheric brain infarction, as well as in patients with medullary brain stem infarction, the values of the SDNN (P<0.001), VLF (hemispheric, P<0.001; medullary, P<0.01), LF (hemispheric, P<0.01; medullary, P<0.05), and SD2 (P<0.01) were lower than those of the control subjects. However, no differences were found between the measures of HR variability of the patients with pontine brain stem infarction and those of the control subjects. The mean values of the HF spectral component, Poincaré measure SD1, and the complexity and fractal measures of HR variability (ApEn, α1, α2) of the patients and those of the control subjects were similar.

At 6 months after stroke (Table 2), the values of the SDNN (P<0.001), VLF (P<0.01), and LF (P<0.05) of the patients with hemispheric brain infarction were still impaired in comparison with those of the controls, but no differences were found between the values of the patients with brain stem stroke and those of the control subjects.

Table 3 presents the correlations between the various traditional, complexity, and fractal measures of HR variability in patients with acute stroke. The conventional frequency domain measures of HR variability as well as the Poincaré measures showed strong correlations (r=0.68 to r=0.90) with each other but only weak correlations (r=0.09 to r=0.56) with the complexity and fractal measures of HR variability. ApEn correlated strongly with α1 (r=−0.70), but all the other correlations between the dynamic measures of HR variability were weak.

Despite infrequent ectopic beats, none of the patients had serious arrhythmias during the ECG recording in either the acute phase or at 6 months. All the patients also had a favorable cardiac outcome during the 6-month follow-up period. No arrhythmic events, cardiac failure, or any other cardiac events were found.

In 5 patients with increased intracranial pressure due to large hemispheric brain infarction, no relevant spectral components of HR variability could be found. The values of the Poincaré, complexity, and fractal measures of these patients, however, did not differ from those of the control subjects and of the other patients. Two of these patients died a few days after their recordings, and the remaining 3 had a decreased state of consciousness. However, none of the patients were mechanically ventilated during the ECG recording.

No difference of HR variability could be found between the patients with right-sided lesion and the patients with left-sided lesion.

**Discussion**

The results of the present 6-month prospective study show that cerebral infarction located particularly in the hemispheric level or in the medulla oblongata causes cardiovascular autonomic dysregulation manifesting itself as impaired HR variability. The present data show that not only the traditional time and frequency domain measures of HR variability but also the Poincaré measures of HR variability may be suppressed in stroke patients, emphasizing the usefulness of this
last method in quantifying abnormalities of cardiovascular autonomic dysfunction in stroke. However, various novel complexity and fractal measures of HR dynamics were not altered in the present stroke patients.

The suppression of HR variability has previously been described in both hemispheric and brain stem strokes with the use of provocative cardiovascular reflex tests,3,4,23 such as deep breathing and the Valsalva maneuver, as well as with the use of the time domain and frequency domain measures of HR variability from 24-hour ECG recordings.4–6,24 Moreover, all the spectral components of HR variability have been shown to be abolished or significantly decreased in brain-dead patients.25–27 However, there appears to be only one previous study27 focusing on dynamic HR behavior in diseases of the nervous system. Recently, Oppenheimer and colleagues28 investigated the effects of left insular lesion on ApEn and correlation dimension and found that acute left insular stroke may result in a decrease in randomness of HR variability, manifesting as suppressed correlation dimension. However, they could not find any significant changes in ApEn as a consequence of left insular lesion.

Recent data suggest that Poincaré plot analysis as well as novel complexity and fractal measures of HR dynamics are even more useful than the traditional methods in evaluating the prognosis of patients with various cardiac diseases. Poincaré plot analysis of R-R intervals provides prognostic information on patients with heart failure and on patients vulnerable to life-threatening arrhythmias.13,14 In systemic hypertension, HR variability has also shown to be decreased with the use of traditional spectral analysis technique.29 Similarly, an altered ApEn has been found to correlate with the presence of life-threatening ventricular arrhythmias in patients with myocardial infarction and postoperative complications resulting from cardiac surgery, as well as with the severity of sickness in neonates, such as fetal acidosis and risk of sudden infant death syndrome.10,19,30–32 Furthermore, abnormal fractal characteristics of HR variability have been described in several studies of heart diseases.12,21,33 In particular, increased randomness of short-term HR behavior is associated with heart failure and vulnerability to life-threatening arrhythmias. It is evident that neurohumoral activation related to impaired cardiac function results in altered fractal characteristics of HR behavior but does not seem to be related to ischemic stroke. Fractal-like characteristics in HR behavior remain normal in patients after stroke, suggesting that nonlinear, dynamic methods of HR variability are able to document abnormal cardiovascular neural regulation but not abnormal central autonomic regulation. Reduction in overall HR variability seems to be more typically related to ischemic stroke.

In the present patients, the conventional linear measures of HR variability and the Poincaré measures showed strong correlations with each other, but the complexity and fractal measures of HR variability were not strongly related to any other single measure of HR variability or to HR itself. Although the computation and analysis of the spectral and nonspectral (Poincaré) measures of HR variability are different, all these methods are fundamentally based on measurement of the magnitude of HR variability. Therefore, it is not surprising that the traditional nonspectral measures, including quantitative Poincaré plot analysis, and spectral measures have a relatively strong correlation with each other. Our results agree with previous studies performed with healthy subjects and post–myocardial infarction patients,20,21 in which only weak correlations between the recorded spectral and complexity and fractal measures of HR variability were found.

In conclusion, cerebral infarction located either at the hemispheric level of the brain or in the medulla oblongata seems to alter the regulation of HR dynamics. The traditional time and frequency domain measures of HR variability and the 2-dimensional vector analysis of Poincaré plots are sensitive to detect abnormalities of HR fluctuation, whereas information provided by the novel complexity and fractal measures only has a limited value.

Acknowledgments

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References


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