Physiological Background of the Loss of Fractal Heart Rate Dynamics

Mikko P. Tulppo, PhD; Antti M. Kiviniemi, MSc; Arto J. Hautala, PhD; Mika Kallio, MD; Tapio Seppänen, PhD; Timo H. Mäkikallio, MD; Heikki V. Huikuri, MD

Background—Altered fractal heart rate (HR) dynamics occur during various disease states, but the physiological background of abnormal fractal HR behavior is not well known. We tested the hypothesis that the fractal organization of human HR dynamics is determined by the balance between sympathetic and vagal outflow.

Methods and Results—A short-term fractal scaling exponent ($\alpha_t$) of HR dynamics, analyzed by the detrended fluctuation analysis (DFA) method, and the high-frequency (HF) and low-frequency (LF) spectral components of R-R intervals (0.15 to 0.4 Hz; $n=13$), along with muscle sympathetic nervous activity (MSNA) from the peroneus nerve ($n=11$), were assessed at rest and during cold face and cold hand immersion in healthy subjects. During cold face immersion, HF power increased (from 6.9±1.3 to 7.6±1.2 ln ms${^2}$, $P<0.01$), as did MSNA (from 32±17 to 44±14 bursts/100 heartbeats, $P<0.001$), and LF/HF ratio decreased ($P<0.01$). Cold hand immersion resulted in a similar increase in MSNA (from 34±17 to 52±19 bursts/100 heartbeats, $P<0.001$) but a decrease in HF spectral power (from 7.0±1.3 to 6.5±1.1 ln ms${^2}$, $P<0.05$) and an increase in the LF/HF ratio ($P<0.05$). The fractal scaling index $\alpha_t$ decreased in all subjects (from 0.85±0.27 to 0.67±0.30, $P<0.0001$) during cold face immersion but increased during cold hand immersion (from 0.77±0.22 to 0.97±0.20, $P<0.01$).

Conclusions—The fractal organization of human HR dynamics is determined by a delicate interplay between sympathetic and vagal outflow, with the breakdown of fractal HR behavior toward more random dynamics occurring during coactivation of sympathetic and vagal outflow. (Circulation. 2005;112:314-319.)

Key Words: dynamics ■ heart rate ■ nervous system, autonomic ■ physiology

Heart rate (HR) variability methods based on nonlinear system theory have been developed to evaluate cardiac regulation and to characterize the features of HR dynamics that may not be easily detectable by traditional analysis methods. Analysis of fractal scaling exponents by detrended fluctuation analysis (DFA) is one such method; it describes the fractal correlation properties of R-R interval data. Breakdown of short-term fractal organization in human HR dynamics, derived from DFA and expressed as a reduced scaling exponent ($\alpha_t$), has been observed in various disease states, such as in heart failure and before the onset of atrial fibrillation, and it indicates an increased risk of mortality and life-threatening arrhythmias in patients with and without structural heart disease.

We have previously shown that “normal” physiological changes in autonomic regulation, defined as withdrawal of vagal outflow at the time of increased sympathetic activity, caused by dynamic exercise and a passive head-up tilt test increase the fractal correlation of HR dynamics in healthy subjects. However, the physiological or pathophysiological background of reduced fractal correlation has not been well elucidated. The present research was designed to study HR dynamics by measuring the fractal scaling exponent $\alpha_t$, along with the time- and frequency-domain HR variability indices and muscle sympathetic nervous activity (MSNA) from the peroneus nerve, at baseline and during cold hand and cold face immersions in healthy males. We hypothesized that the breakdown of fractal organization in human HR dynamics is associated with concomitant sympathetic and vagal activation caused by cold face immersion in healthy subjects.

Methods

Subjects and Study Protocol
All subjects were healthy male volunteers ($n=13$, age 25±5 years, weight 79±10 kg, height 179±6 cm, [mean±SD]). The protocol was approved by the ethics committee of the Merikoski Rehabilitation and Research Center, and all subjects gave written informed consent. The subjects were not allowed to eat or drink coffee for 3 hours before the tests. Vigorous exercise and alcohol were also forbidden for 48 hours before the testing day. The subjects lay in a supine position in a quiet room for at least 15 minutes before data collection and became accustomed to breathing at a constant metronome-guided rate of 0.25 Hz for the duration of the experiments. The cold hand and cold face tests were performed in a randomized order. The cold hand test was performed by immersing...
the subject’s hand into ice water (0°C to 1°C) for 2 minutes. In the cold face test, cold compresses (0°C to 1°C) were applied bilaterally to the forehead and the maxillary region for 2 minutes. 15 The recovery between the interventions was 15 minutes. HR variability measurements and analysis were performed for all subjects, and MSNA was recorded and analyzed successfully for 11 subjects.

Measurements
ECG was recorded by standard methods (Nihon Kohden TEC-7700). Blood pressure was recorded on a beat-by-beat basis from a finger not exposed to the cold water (Finapres, Ohmeda). Blood pressure was also measured with an automatic blood pressure recorder at every 1 to 2 minutes throughout the protocol (Ohmeda). Respiration was measured with a disposable screen flow transducer (Medikro Oy). Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted into the peroneal nerve. A reference electrode was placed subcutaneously at 2 to 3 cm from the recording electrode. The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified, according to previously established criteria. 16 The nerve signal was amplified (50 000 times), passed through a band-pass filter with a bandwidth of 700 to 2000 Hz, and integrated with a time constant of 0.1 s. The nerve signal was also routed to an oscilloscope and a loudspeaker for monitoring throughout the study. Analog signals for ECG were sampled at 1000 Hz and signals for MSNA, blood pressure, and respiration at 512 Hz.

Analysis of MSNA
Burst frequency was analyzed as bursts/min and as bursts/100 heartbeats, and the average amplitude of bursts was analyzed in arbitrary units (AU) as described previously. 17,18

Time- and Frequency-Domain Analysis
The mean HR and SD of R-R intervals (SDNN) were used as time-domain measures of HR variability. An autoregressive model was used to estimate the power-spectrum densities of HR variability. 19,20 The power spectra were quantified by measuring the area under 2 frequency bands: low-frequency power (LF), from 0.04 to 0.15 Hz, and high-frequency power (HF), from 0.15 to 0.4 Hz. A logarithmic transformation to the natural base was performed on both spectral components of HR variability. The spectral component values are presented in absolute (ms²) and normalized units, which were obtained by dividing the power of each component by total variance, from which the very-low-frequency component had been subtracted, and multiplying this value by 100. 21,22

Analysis of Fractal HR Dynamics
HR time series in healthy subjects are fractal, because they display self-similar (scale-invariant) fluctuations over a wide range of time scales. 1,2 Fractal analysis methods differ from the traditional measures of HR variability because they do not measure the magnitude of variability but rather the qualitative characteristics and correlation features of HR behavior. Briefly, a scaling exponent obtained by the DFA method quantifies the relations of HR fluctuation at different scales. Low-exponent values correspond to dynamics where the magnitude of beat-to-beat HR variability is close to the magnitude of long-term variability. Conversely, high-exponent values correspond to dynamics where the magnitude of long-term variability is substantially higher than the beat-to-beat variability.

In the DFA method, the root-mean-square fluctuations of integrated and detrended data are measured in observation windows of different sizes and then plotted against the size of the window on a log-log scale (Figure 1). The scaling exponent α represents the slope of this line, which relates (log)fluctuation to (log)window size. The short-term (from 4 to 11 beats) scaling exponent (αs) was calculated on the basis of previous experiments. 2,13 Details of detrended fluctuation analysis have been described previously elsewhere. 1

Statistical Analysis
Standard statistical methods were used for the calculation of means and SDs. Normal gaussian distribution of the data was verified by the Kolmogorov-Smirnov goodness-of-fit test (z value > 1.0). A paired t test (2-tailed) was used to compare the changes in HR, blood pressure, MSNA, and HR variability parameters during the different protocols (SPSS 12.0.1 for Windows).

Results
Effect of Interventions on Fractal Scaling Exponent α1
Representative examples of R-R interval time series, power spectra, fractal characteristics of R-R intervals, and sympathetic activity (MSNA) at baseline and during cold face and cold hand immersion are shown in Figures 1 and 2. There was a marked increase in the HF power of R-R intervals that was concomitant with increased sympathetic activity, measured by MSNA, during cold face immersion. Conversely, HF power decreased parallel to augmented sympathetic activity during cold hand immersion. These opposite changes in vagal activity (based on HR and HF power changes) but similar changes in sympathetic activity (based on MSNA measurements) resulted in divergent changes in the short-term fractal scaling of R-R intervals analyzed by the DFA method. The fractal scaling exponent α1 decreased in all subjects during the cold face test (P < 0.0001) and increased during the cold hand intervention (P < 0.01; Figure 3).

Effect of Interventions on Spectral Measures of HR Variability
The changes in HR and the spectral measures of HR variability caused by cold face and cold hand immersion are shown in the Table. HR decreased (P < 0.05) and HF power increased (P < 0.01) as evidences of increased vagal activation during cold face immersion. HR increased (P < 0.001) and HF power decreased (P < 0.05), which suggests withdrawal of vagal activity, during the cold hand test. LF/HF ratio and LF power in normalized units decreased.
during cold face immersion \((P<0.01)\) and increased during cold hand immersion \((P<0.05)\).

Effect of Interventions on Sympathetic Activity
The changes in MSNA and blood pressure caused by cold face and cold hand immersion are shown in Figure 4. The number of MSNA bursts, expressed as bursts/min or bursts/100 heartbeats, and mean blood pressure increased during both interventions, which indicates an increase of sympathetic activity \((P<0.001\) for all). The amplitude of the bursts did not change during cold face immersion \((147\pm75\) to \(164\pm83\) AU, \(P=\text{NS}\)) but increased during the cold hand test \((146\pm74\) to \(172\pm74\) AU, \(P<0.001\)).

Discussion
The main finding of the present study is that the breakdown of the fractal organization of short-term HR dynamics occurs during the coactivation of vagal and sympathetic outflow in healthy subjects. The changes in sympathetic outflow were documented by the “gold standard” method from the \textit{peroneus} nerve and the altered vagal activity by the vagally mediated HF spectral component of R-R intervals. We used physiological stress here to activate the autonomic nervous system without pharmacological autonomic modulation aimed at mimicking real cardiovascular conditions in vivo.

Interpretation of the Analysis of Fractal HR Dynamics
The DFA technique is a modified root-mean-square analysis of random walk, and it quantifies the presence or absence of fractal correlation properties in the time series. In this method, a fractal signal results in an exponent value of \(1\), a random signal results in a value of \(0.5\), and strongly correlated signal behavior results in an exponent value of \(1.5\).\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) The increased short-term fractal exponent values \((\alpha_i)\) observed during cold hand immersion in the present study revealed stronger correlation of short-term HR dynamics during the intervention compared with the baseline conditions. The reduction in the short-term fractal scaling exponent \((\alpha_i)\) revealed the loss of the short-term fractal correlation properties of HR dynamics toward more random HR dynamics during the cold face immersion.

Effects of Interventions on Autonomic Regulation
The interplay between the sympathetic and vagal regulation of HR is usually organized in a reciprocal fashion, ie, increased activity in one system is accompanied by decreased activity in the other.\(^2\(^1\)\(^,\)\(^2\(^2\)\)\) Such reciprocal changes in sympathetic and vagal activity occurred during the cold hand test in the present study. The HF power of R-R intervals decreased as evidence of withdrawal of vagal activity; LF/HF ratio and MSNA increased as direct evidences of enhanced sympathetic outflow during cold hand immersion. These reciprocal changes in autonomic regulation resulted in stronger short-term fractal correlation expressed as an increased \(\alpha_i\) value. Similar behavior in \(\alpha_i\) values caused by reciprocal changes in autonomic regulation have been observed and reported in numerous previous studies, including the passive head-up tilt test,\(^1\(^4\)\) light-intensity exercise,\(^1\(^4\)\(^,\)\(^2\(^3\)\) and vagal blockade by atropine or glycopyrrolate.\(^1\(^4\)\(^,\)\(^2\(^4\)\(^,\)\(^2\(^5\)\)

The autonomic reflex caused by cold face immersion is composed of an afferent arm that consists of facial cutaneous receptors subserved by the sensory division of the trigeminal nerve and an efferent arm that consists of vagal fibers to the
The cold face test is a unique noninvasive maneuver to challenge the autonomic nervous system that simultaneously increases sympathetic activity and central vagal outflow. The present study, too, increased vagal activity was observed during the cold face test, measured as decreased HR and increased vagally mediated HF power of R-R intervals. Furthermore, direct measurements of sympathetic activity from the peroneus nerve indicated that sympathetic outflow is increased in all subjects during a cold face intervention. The novel finding of the present study was that sympathetic activation in the presence of enhanced vagal outflow resulted in a loss or breakdown of the short-term fractal organization of HR, expressed as a decreased LF/HF ratio. Reduced sympathetic activity and enhanced vagal outflow resulted in a loss or breakdown of the present study was that sympathetic activation in the presence of enhanced vagal outflow resulted in a loss or breakdown of the short-term fractal organization of HR, expressed as a decreased αi value. Similar changes in αi have been observed during infusion of physiologic doses of norepinephrine in healthy subjects. During norepinephrine infusion, too, the HF power of R-R intervals increased and HR decreased, which suggests increased vagal activity and simultaneous high levels of circulating sympathetic transmitter. Conversely, a pure enhanced vagal outflow did not change αi values, because R-R interval fluctuation increased in all analyzed window sizes (from 4 to 11 beats). The present study confirms the association between accentuated sympathovagal interaction and reduced short-term fractal organization of HR in healthy humans without pharmacological manipulation of autonomic regulation.

The LF/HF ratio behaved in a similar way as fractal HR dynamics, ie, LF/HF ratio increased during cold hand immersion and decreased during cold face immersion. Previous studies have also shown that there is a relatively good mutual correlation between the LF/HF ratio and the fractal scaling index αi in controlled laboratory conditions. However, there are fewer data on acute interventions, in which the LF/HF ratio decreases owing to reduced sympathetic activity and enhanced vagal outflow. Furthermore, during 24-hour ambulatory conditions, the correlation between these indexes becomes less evident, and they may not be more, during 24-hour ambulatory conditions, the correlation between the LF/HF ratio and the fractal scaling index also shown that there is a relatively good mutual correlation between the LF/HF ratio and the fractal scaling index. The reduction of the short-term fractal properties of HR, reduced LF/HF ratio, and adverse clinical outcome. For example, conditions that result in increased sympathetic activation and accompanying vagal activation may well increase vulnerability to arrhythmogenesis. Sympathetic activation changes the cardiac electrophysiological properties and increases the risk for both atrial and ventricular arrhythmias and augmented sinus pauses caused by vagal activation may increase the heterogeneity of repolarization and thereby facilitate the onset of sustained arrhythmias. The causal relationships between concomitant activation of both autonomic limbs, altered HR dynamics, and vulnerability to arrhythmias must be proven in future studies, however. Diving is the only reported physiological condition in which face immersion, resulting in coactivation of sympathetic and vagal activity, occurs and that has been documented to increase the vulnerability to life-threatening arrhythmias among patients with ion channelopathies and precipitate premature ventricular contractions.

### Effects of Cold Face and Cold Hand Immersion on HR Variability

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cold Face Immersion</th>
<th>P</th>
<th>Baseline</th>
<th>Cold Hand Immersion</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>58±6</td>
<td>55±5</td>
<td>0.039</td>
<td>57±6</td>
<td>64±9</td>
<td>0.001</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>68±41</td>
<td>89±39</td>
<td>0.077</td>
<td>63±37</td>
<td>76±41</td>
<td>0.412</td>
</tr>
<tr>
<td>HF, ln ms²</td>
<td>6.9±1.3</td>
<td>7.6±1.2</td>
<td>0.001</td>
<td>7.0±1.3</td>
<td>6.5±1.1</td>
<td>0.042</td>
</tr>
<tr>
<td>HF, NU</td>
<td>56±20</td>
<td>67±21</td>
<td>0.008</td>
<td>59±17</td>
<td>51±21</td>
<td>0.046</td>
</tr>
<tr>
<td>LF, ln ms²</td>
<td>6.6±0.9</td>
<td>6.8±0.9</td>
<td>0.323</td>
<td>6.4±1.0</td>
<td>6.3±0.7</td>
<td>0.651</td>
</tr>
<tr>
<td>LF, NU</td>
<td>44±20</td>
<td>33±21</td>
<td>0.008</td>
<td>41±17</td>
<td>49±21</td>
<td>0.046</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.99±0.84</td>
<td>0.74±0.86</td>
<td>0.007</td>
<td>0.85±0.65</td>
<td>1.21±1.17</td>
<td>0.048</td>
</tr>
<tr>
<td>Breathing frequency, Hz</td>
<td>0.25±0.01</td>
<td>0.25±0.01</td>
<td>0.542</td>
<td>0.25±0.01</td>
<td>0.25±0.02</td>
<td>0.347</td>
</tr>
</tbody>
</table>

NU indicates normalized units. Values are mean±SD.

### Implications

The reduction of the short-term fractal properties of HR and reduced LF/HF ratio have been shown to be associated with the occurrence of various adverse clinical events. The reduced short-term fractal scaling properties of HR can be used as a predictor of sudden cardiac death among elderly subjects and patients after an acute myocardial infarction. Altered beat-to-beat and fractal HR dynamics have also been observed to precede the onset of life-threatening ventricular tachyarrhythmias and atrial fibrillation. All of these observations suggest an adverse clinical outcome in subjects during conditions that result in a loss of normal fractal dynamics toward more random dynamics of HR behavior or loss of normal sympathovagal balance.

The present observations provide one plausible pathophysiological explanation for the association between the loss of fractal HR dynamics, reduced LF/HF ratio, and adverse clinical outcome. For example, conditions that result in increased sympathetic activation with concomitant vagal activation may well increase vulnerability to arrhythmogenesis. Sympathetic activation changes the cardiac electrophysiological properties and increases the risk for both atrial and ventricular arrhythmias, and augmented sinus pauses caused by vagal activation may increase the heterogeneity of repolarization and thereby facilitate the onset of sustained arrhythmias. The causal relationships between concomitant activation of both autonomic limbs, altered HR dynamics, and vulnerability to arrhythmias must be proven in future studies, however. Diving is the only reported physiological condition in which face immersion, resulting in coactivation of sympathetic and vagal activity, occurs and that has been documented to increase the vulnerability to life-threatening arrhythmias among patients with ion channelopathies and precipitate premature ventricular contractions.
The changes in fractal HR dynamics, HF power of R-R intervals, and MSNA during cold face immersion were consistent and well in line with our hypothesis in all subjects. The result was significant even in this limited-size population, which indicates its strong statistical power.

Conclusions

By using a fractal analysis method of HR variability, it was observed that coactivation of vagal and sympathetic outflow results in a change in HR dynamics from fractal toward more random HR organization and reduced LF/HF ratio in spectral analysis of HR variability. In contrast, “physiological” changes in autonomic regulation, eg, decreased vagal outflow at the time of increased sympathetic activity, resulted in a change of HR dynamics toward stronger short-term fractal correlation properties and increased LF/HF ratio in spectral analysis. These observations provide novel information on the mechanisms that determine the fractal organization and spectral characteristics of human HR behavior.

Acknowledgments

This research was funded by grants from the Medical Council of the Academy of Finland (Helsinki, Finland) and the Ministry of Education (Helsinki, Finland). Special thanks to Paavo Pietarila from the Department of Physical Sciences, University of Oulu (Oulu, Finland) for assisting in software development.

References

Sympathetic activation has electrophysiological effects that increase the heterogeneity of repolarization, which facilitates initiation of atrial fibrillation and ventricular arrhythmias and mortality in patients with heart disease. However, the pathophysiological link between atrial fibrillation and ventricular arrhythmias and mortality in patients with heart disease. However, the pathophysiological link between atrial fibrillation and ventricular arrhythmias and mortality in patients with heart disease.

These observations provide novel information about influences on HR dynamics in humans and suggest an interesting pathological mechanism to explain the association of altered HR dynamics with initiation of cardiac arrhythmias.
Physiological Background of the Loss of Fractal Heart Rate Dynamics
Mikko P. Tulppo, Antti M. Kiviniemi, Arto J. Hautala, Mika Kallio, Tapio Seppänen, Timo H. Mäkikallio and Heikki V. Huikuri

Circulation. 2005;112:314-319; originally published online July 11, 2005;
doi: 10.1161/CIRCULATIONAHA.104.523712

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/112/3/314

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/