Spectral characteristics of ventricular response to atrial fibrillation

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Power spectral analysis has recently been used to characterize the nonharmonic fluctuation of heart rate variability in dynamic systems (4, 14) as well as to quantify its harmonic components that reflect the autonomic modulations of sinus node activity (19, 20). Power spectra of irregular or noisy signals observed in dynamic systems often show a linear downsloping pattern (called power law relationship) when plotted as log power against log frequency, and the absolute value of the slope of the spectrum (spectral exponent) provides an assessment of complexity of the systems (9, 17). The power spectrum of the nonharmonic component of heart rate variability during sinus rhythm (SR) has been reported to show a power law relationship with a spectral exponent of \(-1\) (23, 29), suggesting its origination from complex regulatory processes.

During atrial fibrillation (AF), the sinus node loses its ability to govern the ventricular response (VR) and the R-R intervals on electrocardiogram (ECG) show totally nonharmonic fluctuation (6). Nevertheless, the R-R intervals during AF and SR seem to have some physiological characteristics in common, such as shortening in the upright position (16) and during exercise (1, 6, 16) and circadian rhythm with a nocturnal increase (21). The changes in the R-R interval during AF have been thought to result mainly from autonomic neural modulations of the electrophysiological properties of the atria and atrioventricular (AV) node (25, 26). Therefore, power spectral analysis of the R-R interval fluctuation during AF may provide useful information about the dynamic properties of such regulatory processes. Thus we investigated the spectral characteristics of the 24-h R-R interval fluctuation during AF and compared them with those during SR.

METHODS

Subjects. We evaluated 24-h ambulatory ECGs in 45 patients with chronic AF (31 males, 14 females; mean age ± SD, 66 ± 12 yr, age range 42–84 yr). Data were excluded if the ambulatory ECG showed artifacts or noises during >5% of the total monitoring period, frequent ventricular ectopic beats accounting for >5% of total recorded beats, bundle-branch blocks, or atrial tachyarrhythmias other than AF. The duration of chronic AF ranged from 10 mo to >20 yr (Table 1). No patient had cardiomyopathy. All but 3 patients were receiving cardiovascular medications, and 32 of them were receiving AV node-blocking drugs (digoxin and calcium antagonists). No patients were receiving \(\beta\)-adrenergic blockers or class Ia, Ic, or III antiarrhythmic drugs. Sixteen patients had chronic heart failure (CHF) of New York Heart Association (NYHA) class II or III, although none of them was in NYHA class IV.

We also evaluated 24-h ambulatory ECGs in 30 healthy age-matched subjects (25 males, 5 females; mean age 65 ± 12 yr, age range 44–84 yr). None of them had a medical history of chronic diseases or was taking any medications for 2 wk before the study. The ambulatory ECG in all of the healthy subjects showed normal SR during >95% of the total monitoring period.

All subjects gave their written informed consent. The procedures of this study were performed in accordance with the Ethical Guidelines of Nagoya City University Medical School.

Data collection. Ambulatory ECGs were recorded with a portable tape recorder (DMC-3253, Nihon Koden, Tokyo, Japan) for at least 24 h during normal daily activities. In six AF patients, another ambulatory ECG was recorded 12–28 days [mean ± SD (27 ± SD 37 ± 25 days) after the first recording under similar clinical conditions (functional class and medications). The data in these six patients were used to evaluate the reproducibility of measurements.
The spectral exponent was considered as the value that satisfied the following equation:

$$\log P = \log C - \beta \cdot \log f$$

where $P$ is the PSD, $f$ is the frequency, $\beta$ is the spectral exponent, and $C$ is a proportionality constant. When the logarithms of both sides of the equation are derived, this equation can be rewritten as:

$$\frac{\log P}{\log f} = \beta$$

which shows that $\beta$ can be estimated by linear regression of $\log$ PSD on $\log$ frequency. We used the method of Saul et al. (23) to avoid the effects of uneven density of spectral data points along the $\log$ frequency axis. Briefly, the $\log$ frequency axis was divided into 60 equally spaced bins/decade, i.e., 307 bins $0.0167 \log(\text{Hz})$ wide. Log PSD was averaged for each bin; the values for bins without data points in the lower frequency range were obtained by interpolation. Linear regression analysis was performed for the averaged $\log$ PSD and $\log$ frequency data of the bins within the frequency bands of interest.

The properties of dynamic systems, when their fluctuations show a power law spectrum, can be analyzed by comparing the spectral exponents with those of various types of noise seen in known dynamic systems (9, 11, 17). White noise shows a flat power spectrum with a spectral exponent of 0. White noise is a sequence of independent, random values uncorrelated with each other, indicating that the process is not regulated. Brownian noise shows a steep downsloping power law spectrum with a spectral exponent of $\approx 2$. The spectral exponent is known as a random walk, in which the value at any given instance is the result of a random shift from the previous value and, hence, the successive differences are uncorrelated. Brownian noise is another form of noise generated by nonregulated processes. Another type of noise, called 1/f noise, shows a downsloping power law spectrum with a spectral exponent of $\approx -1$. This type of noise shows long-range negative correlations in the successive differences, which cannot be generated as an additive process of uncorrelated noise and, hence, is generally regarded as being regulated.

Statistical analysis. The Statistical Analysis System (SAS) program package (SAS Institute, Cary, NC) was used for analysis. Differences in mean values were evaluated by Student’s $t$-test. The relationships between spectral characteristics and clinical features of AF were evaluated by multiple-regression analysis by the SAS Regression procedure with the Stepwise selection option. Categorical variables were processed as binary data (yes = 1 and no = 0) and a $P$ value $<0.15$ was used as the criteria for entering and retaining independent variables in the regression models.

The reproducibility of the parameters of spectral characteristics was evaluated by the intraclass correlation coefficient for one-way random-effects analysis of variance defining subjects as the random factor (24) and by the coefficient of repeatability of Bland and Altman (5), which estimates the limit for a true change distinguishable from random errors between repeated measurements.

Data are presented as means $\pm$ SD. $P$ values $<0.05$ were considered statistically significant.

RESULTS

Power spectrum of R-R interval fluctuation during AF and SR. Compared with the trendgrams of R-R interval in the healthy subjects with SR, the trendgrams in the AF patients showed a greater variability, although both groups showed circadian variation with a nocturnal lengthening in R-R interval (Fig. 1). The
power spectra plotted in linear scales revealed that the R-R interval fluctuation during AF showed a flat pattern at frequencies <0.25 Hz with no peaks such as that observed for the power spectrum during SR. The spectra for both AF and SR, however, showed a large power at the lowest end of the frequency axis.

When plotted as log PSD against log frequency, striking differences in the power spectrum between AF and SR were observed more clearly (Fig. 2). In contrast to the spectrum during SR, which showed a monotonous linear downsloping pattern <10\(^{-1}\) Hz, the spectrum during AF showed an angular shape with a breakpoint by which the spectrum was separated into two different structures, i.e., a linear downsloping structure below the breakpoint and a flat horizontal structure above the breakpoint. These two parts of the spectrum during AF were referred to as the long-term and short-term components, respectively.

This feature of the power spectrum was common to all AF patients studied, and visual inspection identified the breakpoint between 10\(^{-3}\) and 10\(^{-2}\) Hz in all patients. To examine the spectral characteristics of the long-term and short-term components, log PSD was regressed against log frequency between 10\(^{-4}\) and 10\(^{-3}\) Hz and between 10\(^{-2}\) and 10\(^{-1}\) Hz, respectively. The breakpoint frequency was determined as the frequency at which the regression lines for the two components crossed. To compare between AF and SR, the same frequency bands of the power spectra, which were also referred to as the long-term and short-term components, were examined in the same way.

The breakpoint frequency of the AF spectra ranged from 0.002 to 0.008 Hz (mean 0.005 ± 0.002 Hz). The regression analysis for the long-term component revealed that the spectral characteristics (spectral exponent and intercept at 10\(^{-4}\) Hz) for AF were comparable to those for SR (Fig. 3), except for the explained variance of the regression that was smaller for AF than SR (0.83 ± 0.06 vs. 0.94 ± 0.02, \(P < 0.001\)). In contrast, the analysis for the short-term component revealed marked differences between AF and SR (Fig. 3); although the spectral exponent for SR was comparable to the value for its long-term component, the spectral

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**Fig. 1.** Trendgrams (top) of 24-h fluctuation of R-R interval in a representative patient with chronic atrial fibrillation (AF; A) and in a healthy man with normal sinus rhythm (SR; B) and their power spectra (bottom) plotted in linear scales for power spectral density (PSD) and frequency.

**Fig. 2.** Log PSD vs. log frequency plots of power spectra of 24-h R-R fluctuation in representative patients with AF (A) and a healthy man with SR (B). Vertical and horizontal axes are in logarithmic scale. Solid lines, linear regression lines of log PSD on log frequency between 10\(^{-4}\) and 10\(^{-3}\) Hz and between 10\(^{-2}\) and 10\(^{-1}\) Hz. Vertical dashed line in A represents estimated breakpoint frequency separating long-term (LT) and short-term (ST) components.
exponent for AF was almost zero, indicating that the PSD was frequency independent. The explained variance for the short-term component during AF was markedly smaller than that during SR (0.13 ± 0.10 and 0.75 ± 0.08, respectively; P < 0.001).

Relationships to clinical features of AF. In the AF patients, the spectral characteristics, except the spectral exponent of the short-term component, showed considerable interindividual variations (Fig. 3). To examine whether these variations are explained by differences in clinical features, multiple-regression analysis was performed (Table 2). The regression models showed that the spectral exponent of the long-term component was associated with age and body mass index, whereas its intercept was associated with heart failure and valvular heart disease. The intercept of the short-term component was associated with medication with diuretics and heart failure.

Reproducibility of measures. There was no significant difference in the mean values of the spectral characteristics measured at different times in the six AF patients (Table 3). The intraclass correlation coefficients and coefficients of repeatability showed excellent agreement between repeated measurements.

DISCUSSION

Major findings. We found that the power spectrum of the 24-h fluctuation of R-R intervals during AF showed a unique shape with a breakpoint at 0.005 ± 0.002 Hz, by which the spectrum was divided into short-term and long-term components with different spectral characteristics. The short-term component showed a white noise-like flat spectrum, and the long-term component showed a 1/f noise-like power law spectrum. These features were in marked contrast to those for the power spectrum during SR, which showed a monotonous, downsloping power law relationship with no breakpoint. Interestingly, however, quantitative analysis revealed that the spectral characteristics of the long-term component (Table 3).

Table 2. Regression analysis of spectral characteristics of R-R interval fluctuation in AF patients by clinical features

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Regression Coefficient</th>
<th>R²</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT spectral exponent</td>
<td>Regression model</td>
<td>0.23</td>
<td>6.11</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.012</td>
<td>0.09</td>
<td>7.39</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Body mass index</td>
<td>0.057</td>
<td>0.09</td>
<td>4.20</td>
<td>0.050</td>
</tr>
<tr>
<td>LT intercept at 10⁻⁴ Hz</td>
<td>Regression model</td>
<td>0.29</td>
<td>5.55</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart failure*</td>
<td>-0.38</td>
<td>0.19</td>
<td>9.33</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Valvular heart disease*</td>
<td>0.19</td>
<td>0.06</td>
<td>4.12</td>
<td>0.049</td>
</tr>
<tr>
<td>ST intercept at 10⁻² Hz</td>
<td>Regression model</td>
<td>0.34</td>
<td>10.38</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication of diuretics*</td>
<td>0.33</td>
<td>0.15</td>
<td>16.30</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Heart failure*</td>
<td>-0.33</td>
<td>0.19</td>
<td>11.43</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LT, long-term component; ST, short-term component. *Variable processed as binary data (yes = 1, no = 0).

Table 3. Reproducibility of spectral characteristics of ventricular response fluctuation in AF patients who underwent repeated measurements

<table>
<thead>
<tr>
<th>Breakpoint frequency</th>
<th>ICC</th>
<th>P</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1</td>
<td>Time 2</td>
<td>0.0039 ± 0.0017</td>
<td>0.0039 ± 0.0008</td>
</tr>
<tr>
<td>LT spectral exponent</td>
<td>1.41 ± 0.16</td>
<td>1.44 ± 0.09</td>
<td>0.762</td>
</tr>
<tr>
<td>LT intercept at 10⁻⁴ Hz, log(ms²/Hz)</td>
<td>7.2 ± 0.3</td>
<td>7.2 ± 0.3</td>
<td>0.986</td>
</tr>
<tr>
<td>ST spectral exponent</td>
<td>-0.01 ± 0.04</td>
<td>-0.00 ± 0.05</td>
<td>0.999</td>
</tr>
<tr>
<td>ST intercept at 10⁻² Hz, log(ms²/Hz)</td>
<td>4.9 ± 0.2</td>
<td>4.9 ± 0.2</td>
<td>0.954</td>
</tr>
</tbody>
</table>

Time 1, time 2 values are means ± SD. ICC, intraclass correlation coefficient; CR, coefficient of repeatability; LT, long-term component; ST, short-term component. *Significance of intraclass correlation coefficient (n = 6 patients).
During AF were indistinguishable from those during SR in the same frequency range. These observations indicate that the dynamics of the processes generating the R-R interval fluctuation during AF differ between the short-term and long-term components and that, as to the long-term component, the fluctuations in R-R interval during AF and SR may originate from similar dynamics of cardiovascular regulation.

Earlier studies on VR fluctuation during AF. Since the beginning of this century, absolute ventricular arrhythmia has been recognized as an important characteristic of AF (22), and the mechanism for the irregularity in VR to AF has been a focus of electrophysiological studies (13, 15, 28). In 1970, Bootsma et al. (6) found that the autocorrelation coefficient calculated from 2,000 consecutive R-R intervals showed a flat shape and concluded that the VR to AF is random. On the other hand, long-term observations have reported different features of VR to AF. An increase in mean VR rate has been observed during exercise and in the upright posture (1, 6, 16). Raeder (21) reported a significant circadian rhythm in the diurnal variations of average R-R interval during AF, and he also reported that the circadian rhythm parameters (amplitude and phase) and the two-harmonic regression coefficients were comparable to those in subjects with SR. These earlier observations seem to be in line with our present findings and are supportive of the differential properties between short-term and long-term fluctuations of VR to AF.

Earlier studies also reported different mechanisms for the irregularity of VR and the variations in mean VR rate. VR irregularity is believed to originate from irregularity in the atrial activity during AF (6). Although some controversy remains concerning the mechanisms for the transmission of the irregular atrial activity to VR (12, 27), much electrophysiological evidence supports the role of concealed conduction within the AV node (8, 13, 15, 28), i.e., an interaction between rapid and random inputs to the AV node from the adjacent atrial tissue leads to summation and cancellation of wave fronts, thereby creating a high level of disorganization of the penetrating impulses. The determinants of mean VR rate during AF have been a focus of clinical studies. Such studies reported an important role of AV nodal conductivity and refractoriness (1, 25) and/or atrial refractoriness, which reduces the atrial f wave frequency, thereby decreasing the degree of concealed conduction within the AV node (26).

Although the VR irregularity and the variations in mean VR rate were investigated separately in these earlier studies, the distinction between these two aspects of VR fluctuation seems unclear. Consequently, the ranges of components or frequencies of VR fluctuation that correspond to the reported properties and mechanisms have been undetermined.

Spectral characteristics of VR fluctuation during AF. Using 24-h power spectral analysis, we demonstrated that the R-R interval fluctuation during AF can be separated into short-term and long-term components with different spectral characteristics that seem to correspond to the properties of the two different aspects of VR fluctuation in the earlier studies. The white noise-like feature of the short-term component indicates that R-R intervals during AF are uncorrelated in this frequency range (0.005 ± 0.002 Hz) and that the mechanisms for VR irregularity, which may include irregular atrial activity and resultant concealed conduction in the AV node, have no frequency dependency at least within this frequency range. The power law spectrum with a spectral exponent of 1.26 ± 0.40 observed for the long-term component indicates that R-R intervals during AF show long-range negative correlation and suggests that the fluctuation may be generated by regulatory processes (9, 11, 17). The power law relationship that stretched close to the lowest end of frequency (a cycle length of nearly 1 day) suggests that the long-term component may include the diurnal variations in R-R interval, such as those related to circadian rhythm of body temperature, sleep-wake cycle, and physical and mental activities.

One might speculate that the breakpoint frequency may represent the upper frequency limit of the regulation of R-R interval during AF. This is unlikely, however, because Nagayoshi et al. (16) reported that the average R-R interval during AF showed rapid postural changes, with the shortest R-R interval occurring 15–20 s after active standing, and it also showed shortening during Valsalva strain and immediately after the beginning of handgrip. Thus it is more likely that above the breakpoint frequency, the irregularity in VR fluctuation dominates over its regulatory changes.

Relationships to R-R interval fluctuation during SR. Although the spectral characteristics for the short-term component differed strikingly between AF and SR, those for the long-term component were quite similar. This observation suggests that despite the different peripheral mechanisms determining R-R intervals between AF and SR, the dynamics of the regulatory process underlying the long-term component may be common. In an experiment with anesthetized dogs, O'Toole et al. (18) observed parallel chronotropic and dromotropic responses in the sinoatrial rate and antegrade AV conduction during the baroreflex modulation of the cardiac vagal outflow. They also observed that the dromotropic response of the AV conduction was independently regulated by the vagus when the chronotropic response was prevented with atrial pacing. The long-term VR fluctuation during AF is likely to be mediated through the modulations of electrophysiological properties in the atrium and the AV node by the autonomic nervous (16) and endocrine (3) systems; however, it may be speculated that the dynamics observed in the long-term component during both AF and SR may originate from the dynamics of the central nervous controls of these regulatory systems.

Relationships to clinical features. The regression models for the spectral characteristics also seem to provide insights into the underlying mechanisms. In the regression model for the intercept of the short-term component, medication with diuretics and heart failure showed positive and negative contributions, respectively. These might be attributable to shortening in
atrial refractory period by decreased serum potassium level with diuretics and to its lengthening by reduced vagal activity in heart failure (2, 10), because the shortening in atrial refractoriness increases fibrillatory activity, thereby increasing the irregularity of VR interval (2, 8, 12). Age of the patients seemed contributory to increase in the spectral exponent of the long-term component. This seems consistent with the finding of Lipsitz et al. (14), who reported an age-related increase in the spectral exponent of R-R interval fluctuation during SR, which may be attributable to the age-related loss of complexity in the cardiovascular regulatory systems (9, 17). Heart failure also contributed negatively to the intercept of the long-term component. This effect seems attributable to the decreased diurnal variations in neurohumoral activities in patients with heart failure (7, 30) as well as to their restricted daily activities.

Limitations. The patient population of this study was heterogeneous, and patients continued to receive medication. Thus the findings concerning the relationships between the spectral characteristics and clinical features are preliminary and need to be confirmed by more specifically designed studies. On the other hand, despite this heterogeneous population, the unique shape of the VR interval spectrum was commonly observed in all AF patients studied, suggesting that the spectral characteristics we observed may be fundamental features of chronic AF.

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REFERENCES