A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R–R interval

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Abstract

A new non-linear method of assessing cardiac autonomic function was examined in a pharmacological experiment in ten healthy volunteers. The R–R interval data obtained under a control condition and in autonomic blockade by atropine and by propranolol were analyzed by each of the new methods employing Lorenz plot, spectral analysis and the coefficient of variation. With our method we derived two measures, the cardiac vagal index and the cardiac sympathetic index, which indicate vagal and sympathetic function separately. These two indices were found to be more reliable than those obtained by the other two methods. We anticipate that the non-invasive assessment of short-term cardiac autonomic function will come to be performed more reliably and conveniently by this method.

Keywords: Cardiac autonomic function; R–R interval; Lorenz plot; Spectral analysis; Coefficient of variation

1. Introduction

Numerous methods of quantifying heart rate variability have been proposed. Among them, the standard deviation (SD), the coefficient of variation (SD/mean, CV) and several indices based on beat-to-beat variations calculated using simple statistics have been used for the assessment of cardiac autonomic function (CAF) in relation to age [29] and in diabetic neuropathy [4,13,18], parkinsonism [10,15] and psychiatric patients receiving antipsychotic medication [9,21,25,26]. It has not been ascertained, however, what these measures indicate in relation to autonomic nervous system (ANS) function. Spectral analysis of the fluctuation of the R–R interval (RR fluctuation) has been repeatedly performed, especially under experimental conditions, in both man [8,16,17,19,22] and animals [1,6,20]. It has provided relatively consistent results indicating that a low-frequency component of the spectral band reflects both vagal and sympathetic tone and a high-frequency component reflects exclusively vagal tone. This method, however, requires complicated mathematical processes that vary among investigations, such as the technique for calculating spectral density, interpolation and low-frequency filtering of the original data, although standards for the processing have recently been proposed [23]. Furthermore, the need for controlled respiration remains to be explored.

In our neuropsychiatric practice and research, we felt a need for a more convenient method of assessing short-term CAF to evaluate the cardiac autonomic changes in patients in a psychotic state, during epileptic discharges, or during short-term mental stress. For this purpose, we introduced a new method of analyzing the RR fluctuation from which we extracted two indices sensitive to the change in sympathetic and parasympathetic functions, respectively. Further, we compared these indices with the results derived by the two conventional methods of spectral analysis and the CV.

2. Subjects and experimental procedures

The subjects were ten healthy volunteers (five men and five women; aged 21 to 38) with no illness that would lead to an autonomic disturbance or would contra-indicate the autonomic blocking agents used in this study. No subject
was medicated and none was a smoker or a habitual drinker. Written informed consent was obtained from all of them after the experimental procedure had been fully explained.

The three phases of the experiment were performed on separate days in each subject. The subject received no medication for the control measurement on one day, received atropine sulfate (0.5 mg intramuscularly) at 1:30 p.m. on another day and propranolol hydrochloride on another day (10 mg orally twice, at 9 a.m. and at 12 a.m.). The order of phase presentation was randomized among the subjects. These doses and methods of administration were chosen to produce mild autonomic blockade during the measurement while preventing the central parasympathomimetic effect of atropine. When a subject complained of drowsiness, fever or symptoms indicating dehydration such as diarrhea and dryness of the mouth, any of which would modify cardiac rhythm, the experiment was postponed until the day when he or she was in a normal condition.

In each experiment, the R–R interval was measured in the subjects with their eyes open in each of the three postures of supine (at rest and doing mental serial subtraction), sitting and standing; this order was also randomized to exclude the 'effect of sequence'. The subjects were instructed to refrain from body movement, utterance and deep breathing during the measurement and they were continuously observed by an experimenter throughout the experiment. The experiment was started at 2 p.m., and the R–R interval was measured for 5 min in each condition with an inter-measurement interval of 2 min. The amplified electrocardiographic signal (band-width, 0.15 to 200 Hz) from standard lead II was fed through an analog-to-digital converter into a microcomputer at a sampling frequency of 2000 Hz and the R–R interval was measured with an accuracy of one ms triggered by the R wave. Consecutive 3 min R–R intervals without noise were analyzed. The data acquired during the first 3 min of the 5 min segment were used in all cases because the subjects tended to show transient tachycardia during the last 2 min, probably due to irritation, whereas premature beats were not observed in any subject. The same R–R interval data were analyzed by three methods: Lorenz plot, spectral analysis and the CV of the R–R interval.

3. Methods

3.1. Lorenz plot

The Lorenz plot, a new method which we introduce in this report, is a two-dimensional non-linear plot which was originally designed for application in meteorology [11] and has recently been applied in the field of electrophysiology [2,3,5,14]. When the sequence of the consecutive R–R interval is expressed by \( I_1, I_2, \ldots, I_n \), the Lorenz plot is constructed by plotting \( I_{k+1} \) against \( I_k \) \((k = 1, 2, \ldots, n-1)\). Fig. 1 shows the Lorenz plot for one of the subjects. In this plot, the RR fluctuation is transformed into the points distributed on a two-dimensional plane which usually form an ellipsoid configuration.

We calculated two components of the RR fluctuation from plots such as this one: the length of the transverse axis \((T)\) which is vertical to the line \( I_k = I_{k+1} \), and that of the longitudinal axis \((L)\) which is parallel with the line \( I_k = I_{k+1} \). When two adjacent intervals \( I_m \) and \( I_{m+1} \) in the sequence differ greatly (large beat-to-beat variation), the point \((I_m, I_{m+1})\) is plotted distant from the line \( I_k = I_{k+1} \) on the plane, resulting in large \( T \). On the other hand, when the fluctuation is great but continuous (large amplitude, but small beat-to-beat variation), the plotted points are distributed widely but along the line \( I_k = I_{k+1} \), resulting in large \( L \) and small \( T \). Thus the two components reflect different aspects of the RR fluctuation. Each component is calculated to four times the standard deviations of the fluctuation, and the CV of the sum of \( T \) and \( L \).

To obtain the autonomic indices, we examined the four measures of \( T, L, L \times T \), and \( L/T \) ratio.

![Fig. 1. The 3 min R–R interval tachogram in one of the subjects (upper) and the Lorenz plot of the same R–R interval data (lower) are illustrated. In the Lorenz plot, the fluctuation of the R–R interval in a healthy adult is usually transformed into an ellipsoid figure, as in this subject. The length of the transverse axis, \( T \), reflects beat-to-beat variation in the tachogram, while that of the longitudinal axis, \( L \), reflects overall amplitude of the fluctuation in the tachogram.](image-url)
3.2. Spectral analysis

In this analysis, the data for the 3 min were transformed into 1,024 equi-distant intervals (in ms) by linear interpolation. The mean interval was subtracted from the interpolated time series and a Hanning window was applied. Based on the resulting data, the low-frequency component (0.04–0.15 Hz, LH) and the high-frequency component (0.15–0.4 Hz, HF) were calculated from the spectral density (ms²/Hz) obtained by fast Fourier transform (FFT) [7].

3.3. CV

The CV was calculated for the original 3 min R–R intervals and the value was expressed as a percent.

All statistical comparisons were conducted using a paired t test (two-tailed) except that for spectral analysis. Since the results of spectral analysis were highly variable, they were regarded as non-parametric data and Wilcoxon’s signed-ranks test was employed in their statistical analysis.

4. Results

4.1. Lorenz plot

4.1.1. L and T

The mean ± standard error for L and T are shown in Table 1.

L was significantly decreased by atropine under all four conditions, whereas it was not changed by propranolol under any condition and T was also significantly decreased by atropine under three of the four conditions. It showed some increase due to propranolol under all four conditions and the increase was significant under two of them. Thus, while L was affected only by parasympathetic blockade, T was affected by both sympathetic and parasympathetic blockade under these limited conditions.

Table 1
The measured L and T of the Lorenz plot

<table>
<thead>
<tr>
<th></th>
<th>Supine (rest.)</th>
<th>Supine (arith.)</th>
<th>Sitting</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>L 117.0 ± 59.1</td>
<td>96.0 ± 25.5</td>
<td>106.6 ± 26.8</td>
<td>83.3 ± 19.4</td>
</tr>
<tr>
<td></td>
<td>T 81.5 ± 52.5</td>
<td>63.5 ± 25.8</td>
<td>68.6 ± 23.9</td>
<td>42.3 ± 16.2</td>
</tr>
<tr>
<td>Atropine</td>
<td>L 57.5 ± 30.0</td>
<td>62.7 ± 23.9</td>
<td>73.6 ± 28.3</td>
<td>65.5 ± 23.9</td>
</tr>
<tr>
<td></td>
<td>T 46.0 ± 20.0</td>
<td>38.1 ± 16.6</td>
<td>43.9 ± 15.9</td>
<td>35.5 ± 19.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>L 107.5 ± 46.9</td>
<td>98.6 ± 29.7</td>
<td>106.6 ± 39.8</td>
<td>72.6 ± 23.9</td>
</tr>
<tr>
<td></td>
<td>T 88.7 ± 46.3</td>
<td>81.9 ± 32.5</td>
<td>85.0 ± 27.5</td>
<td>44.3 ± 18.6</td>
</tr>
</tbody>
</table>

* p < 0.01 versus control.
** p < 0.05 versus control.
NS Not significant versus control.

Rest.: resting, arith.: mental arithmetic.
significant under three of the four conditions, being most prominent in standing posture. This indicates that the \( L/T \) ratio is an index of cardiac sympathetic function except in the resting supine condition, which is not affected by vagal activity. We termed this measure the ‘cardiac sympathetic index’ (CSI).

Thus, of the four measures tested, \( \log_{10}(L \times T) \) and \( L/T \) ratio were found to be the most sensitive and consistent indices of parasympathetic and sympathetic blockade, respectively.

When the results of the two indices are visually described, the area of the ellipse on the Lorenz plot becomes larger as the vagal activity is elevated and the configuration becomes longer and narrower as the sympathetic activity is elevated.

For both indices, all of the significant changes according to autonomic blockade were preserved when the comparison was performed based on solely those data for the first 100 R–R intervals of the original 3 min data set.

4.2. Spectral analysis

The power of each spectral band was expressed relative to the control value (%), and the mean ± standard error is shown in Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The results of the spectral analysis</th>
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<tr>
<td></td>
<td>Supine (rest.)</td>
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<tr>
<td>Atropine</td>
<td>HF</td>
</tr>
<tr>
<td></td>
<td>LF</td>
</tr>
<tr>
<td>Propranolol</td>
<td>HF</td>
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<td></td>
<td>LF</td>
</tr>
</tbody>
</table>

* \( p < 0.05 \) versus control.
NS Not significant versus control.
Rest.: resting, arith.: mental arithmetic.

Under three of the four conditions, the HF was decreased significantly by atropine, as was expected based on previous studies, but it failed to show significant decrease under the supine mental arithmetic condition. The HF was significantly increased by propranolol under the sitting and standing conditions.

While the LF was significantly decreased by atropine under two of the four conditions, it was not changed significantly by propranolol under any of the conditions and thus, the expected decrease in the LF by sympathetic blockade was not found.

When the data for one subject that produced the high variability of the results were excluded from the analysis, both the HF and the LF were significantly decreased by atropine under all conditions, though neither of them was significantly changed by propranolol under any condition.

4.3. CV

The mean ± standard error is shown in Table 3.

The CV was significantly decreased by atropine in the resting supine condition, but otherwise it did not show any significant change according to the autonomic blockade in our study.

5. Discussion

Of the three methods used in this study, the Lorenz plot yielded the most reliable indices, while the CV yielded the least reliable.

It has not been clarified what the CV indicates except that it shows a correlation with vagal activity [8]. Accord-
ing to our results, the CV discloses mild cardiac autonomic change only under a limited set of conditions (resting in the supine position after atropine administration).

Although spectral analysis has provided stable results, there exists a discrepancy between our results and those in previous studies. This may be partly due to the longer duration of the R–R interval used in previous studies, where intervals of more than 4 min were analyzed, to the lack of controlled respiration and the mild degree of autonomic blockade used in this study, or to some combination of these factors. The difference in the method of calculating the spectral band might be another reason for the discrepancy. We tried, in addition to FFT, ‘coarse-graining spectral analysis’ [24], in which the so-called 1/f noise component is removed for better assessment of short-term CAF. This method, however, yielded no more stable results than those in the results herein described. An alternative method of spectral analysis such as autoregressive method [27] or an alternative index like the LF/HF ratio [16,19] might yield more consistent results, though it is extremely doubtful whether these results would be more reliable than those obtained from our method.

In spite of the small sample and several factors that would have been disadvantageous to spectral analysis, the new indices derived from the Lorenz plot, CVI and CSI, yielded stable results. This suggests the shielding of our method against the physiological noise disturbing HF and LF.

The results for these two indices show that the level of significance varied according to the posture. The sympathetic blockade was most pronounced in standing subjects and the parasympathetic blockade during supine resting. It was reported that sympathetic activity becomes elevated as the posture shifted from supine to standing [16,19,28] and the generally accepted assumption that the vagal tone is maximal for supine resting was supported by some investigations [16,19]. If the autonomic blockade is most prominent under such conditions, our results seem consistent in regard to the postural change.

The advantages of our method are: (1) that mild changes of sympathetic and parasympathetic autonomic functions can be assessed simultaneously and independently under any of these conditions except in supine resting, (2) that controlled respiration or other manoeuvres are not required, (3) that only 100 R–R intervals (less than 2 min in most cases) are enough for the assessment and (4) that the autonomic change is noticeable visually on the Lorenz plot as presented in these results. These advantages may enable us to assess CAF more reliably and easily both in clinical practice and under experimental conditions.

We should, however, keep in mind that the results of this study were obtained in physiologically normal subjects under mild autonomic blockade and moreover that the change in the two indices suggests the shift in regulatory activity, not the degree of activity or tone, of the ANS, as in other measures of heart rate variability [12]. Therefore, when our method is applied to the elderly or subjects with autonomic activity at the extreme levels, the results should be interpreted with caution.

References


