Blood pressure (BP) and heart rate (HR) often fluctuate extensively in stroke patients during the acute to subacute phase. In addition, cerebral blood flow is dependent on systemic BP during these phases because of the disturbance of autoregulation of cerebral blood flow. Therefore it is important to consider the risk of stroke relapse or progression caused by fluctuating BP, such as an increase or decrease of BP and BP variability (BPV). Some clinical studies have shown that an abnormal pattern of variability of diurnal BP, evaluated by 24-h ambulatory BP monitoring, is associated with target organ damage. Currently, the Holter ECG is used to monitor spontaneous heart rate variability (HRV) to assess the function of the cardiac autonomic nervous system in stroke patients. Singh et al reported that autonomic nervous system activity, monitored by HRV, was related to 24-h BPV. Clinical and experimental studies have examined how the localization of stroke affects autonomic function and prognosis. Stroke patients with a lesion in the thalamus or brain stem often show high BP and other cardiovascular dysfunction. We assumed that stroke patients with a thalamic lesion, using 24-h HRV and 24-h BPV. The relationship between HRV, as well as 24-h BPV, and the change in BP during exercise was also investigated.

**Methods**

The subjects were patients who were admitted to the Stroke Medical Center within 2 weeks of their first stroke. The stroke group (Table 1) consisted of 55 inpatients (males, 29; mean age, 58.8 years old; ischemic/hemorrhagic etiology, 30/25) who were admitted to the Stroke Center within 2 weeks of their first stroke. The control group consisted of 15 age-matched healthy volunteers. The 24-h heart rate (HR) variability (HRV) and BP variability (BPV) were examined, and then the increase and recovery of BP and HR were measured during bicycle ergometer exercise at 4 METs. Components of 24-h HRV (low-frequency power (LF), high-frequency power (HF), and asleep–awake ratio of LF/HF (LF/HF$_{a-w}$)) were lower (p<0.01) than in the control group. There was a negative correlation between BP change during exercise and LF/HF or LF/HF$_{a-w}$ (r=-0.43 or r=-0.58, p<0.01), and a greater increase in systolic BP (102±9.8 mmHg, n=7) during exercise was observed in stroke patients with lower LF/HF$_{a-w}$ (≤1.0).

**Conclusions**

Lower HRV in stroke patients may relate to an increase in BP during exercise. HRV is useful for estimating the risk during medical rehabilitation.

**Key Words:** Autonomic nervous function; Blood pressure variability; Heart rate variability; Medical rehabilitation; Stroke

**Table 1 Characteristics of the Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Stroke group (n=55)</th>
<th>Control group (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean±SD)</td>
<td>58.8±9.5</td>
<td>60.1±3.9</td>
</tr>
<tr>
<td>M/F</td>
<td>29:26</td>
<td>7:8</td>
</tr>
<tr>
<td>Ischemic: hemorrhagic</td>
<td>30:25</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive patients (%)</td>
<td>35 (62.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Taking medication (%)</td>
<td>31 (56.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Leg Brunnstrom stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ill</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>VI</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Nocturnal BP decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dipper (%)</td>
<td>28 (50.9%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Dippere (%)</td>
<td>12 (21.2%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Extrem-dipper (%)</td>
<td>15 (29.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Total FIM score (mean±SD)</td>
<td>98.0±11.9</td>
<td>Full score</td>
</tr>
</tbody>
</table>

Leg Brunnstrom stage was determined at 4 weeks after onset of stroke. FIM, Functional Independence Measure was evaluated at 4 weeks after onset of stroke and is an indicator of independent performance of activities of daily living (full score =126 points).
consecutive inpatients with a thalamic lesion (mean age 58.8±9.48 (SD) years old; 29 men; 26 women; 30 ischemic and 25 hemorrhagic strokes); 35 also suffered from hypertension and 31 of them were receiving antihypertensive medication (calcium antagonist or angiotensin-converting enzyme inhibitor). The localization of the stroke was diagnosed using magnetic resonance imaging (MRI) examination of the head on the day of admission to hospital (Fig 1). The Brunnstrome stage of the paretic leg and functional independence measure (FIM) were assessed at 1 month after the onset of stroke. FIM is an indicator of the ability to perform activities of daily living; the full score is 126 points. Mean total FIM score was 98.0±11.9 points. The inclusion criteria for the study were as follows: (1) physical therapy for more than 1 month after admission to the Stroke Medical Center, (2) Brunnstrome stage of the paretic leg was III or better at 1 month after the onset of stroke, and (3) able to walk or ambulate with a wheelchair independently at 1 month after the onset of stroke. The Brunnstrome classification assesses the motor function in hemiplegic patients and stage III indicates that the patient can voluntarily move the limb with synergistic patterns.

The exclusion criteria were as follows: (1) diabetic peripheral neuropathy, which impairs autonomic nervous function, (2) cardiac failure or arrhythmia, and (3) medication that affects autonomic nervous activity.

The control group consisted of 15 age-matched healthy volunteers (7 men, 8 women; mean age 60.1±3.9 (SD) years old).

All subjects were informed of the purpose of the study and gave written consent. The protocol of the study was approved by the Ethics Committee of the Yokohama Stroke Medical Center.

**Recording Procedures**

For analysis of 24-h HRV and BPV, Holter ECG (Holter Analis II; Suzuken Co Ltd, Japan) and 24-h BP measurements (Kenz BPM AM-200; Suzuken) were performed at 1 month after the onset of stroke. These examinations were performed on a day when the patients were able to relax all day. Within 1 week of these examinations, all subjects completed a sub-maximal exercise test (4 METs) on an electrically braked bicycle ergometer (AEROBIKE 75 XL2ME Combi Co Ltd, Japan) in an upright sitting position. Subjects in whom the paretic leg was estimated to be Brunnstrom stage III or better had their leg fixed to the pedal with a belt so that they could push the pedal. Patients gripped the handle of the bicycle ergometer with their non-paretic hand, and the paretic hand was kept in a relaxed position to maintain their balance. HR and BP were recorded at 3-min intervals by an automatic BP recorder (Nippon Colin BP-103N; Colin Co Ltd, Japan). During a submaximal exercise test, as well as during recovery. We decided that we would abandon the exercise test if the subject’s systolic BP increased beyond 240 mmHg. Only 1 subject stopped the exercise test. The control group performed the same exercise test, with 24-h HRV and BPV analysis.

**Analysis of HRV**

The Holter ECG data were digitally sampled and scanned into a personal computer for 2 types of analysis of HRV: time series of R-R interval and power spectral analysis. We used power spectral analysis because it is useful for studying the effect of sympathetic and parasympathetic autonomic nervous system activity on the cardiovascular system.

The digitized R-R intervals were recorded and stored, and the power spectral densities were computed using fast-Fourier transformation and complex demodulation transformation method (CDM). The power spectral densities were analyzed in 3 areas of concentration of spectral power by means of CDM. In these 2 areas, low-frequency power (LF: 0.03–0.15Hz) was analyzed as an index of sympa-
Table 2  24-h HRV and BP in the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Stroke group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (ms/Hz1/2)</td>
<td>15.6±4.3</td>
<td>19.4±3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HF (ms/Hz1/2)</td>
<td>14.8±4.1</td>
<td>16.8±2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF/HF (ratio)</td>
<td>1.13±0.4</td>
<td>1.4±0.38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LF/HFd-n (ratio)</td>
<td>1.56±0.5</td>
<td>2.01±0.6</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td><strong>BPV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>126±34</td>
<td>124±26</td>
<td>NS</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>68±14</td>
<td>65±11</td>
<td>NS</td>
</tr>
<tr>
<td>BPV (ratio)</td>
<td>1.13±0.31</td>
<td>0.80±0.24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value, stroke group vs control group (NS, not significant). HRV, heart rate variability; LF, 24-h mean of low-frequency power spectrum; HF, 24-h mean of high-frequency power spectrum; LF/HF, ratio of LF/HF; LF/HFd-n, ratio of awake to asleep LF/HF; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPV, short-term blood pressure variability.

HRV During Exercise in Stroke Patients

Table 2 shows the 24-h HRV and BP in the study subjects. The ratio of LF to HF (LF/HF), an indirect index of sympathetic nervous system activity, was calculated for each data set. The asleep value of LF/HF was defined as the mean LF/HF value from the time at which the patient went to bed until the time of awakening, and the awake value of LF/HF was defined as the mean LF/HF value during the remaining hours of the day. The awake to asleep ratio of LF/HF, an indirect index of the balance of sympathetic and parasympathetic nervous system activity, was calculated for each data set

The following 4 parameters of power spectral analysis were used: (1) HF (ms/Hz1/2): 24-h mean of HF, (2) LF (ms/Hz1/2): 24-h mean of LF, (3) LF/HF (ratio): 24-h mean of LF/HF, and (4) LF/HFd-n (ratio): awake to asleep ratio of LF/HF = (awake value of LF/HF)/(asleep value of LF/HF).

Analysis of BPV

Noninvasive ambulatory BP monitoring was carried out with a Kenz BPM monitor, which recorded BP every 30 min for 24 h. For individual data, the asleep BP was defined as the mean BP from the time at which the patient went to bed until the time of awakening, and the awake BP was defined as the mean BP during the remaining hours of the day. Mean BP, systolic BP (SBP), and diastolic BP (DBP) were calculated. Then, the nocturnal decline in SBP and BPV were estimated. The nocturnal SBP decline was calculated by the following formula:

Nocturnal SBP decline = (awake SBP–asleep SBP)/ (awake SBP) x 100 (%).

All patients were subclassified on the basis of the nocturnal SBP decline as follows (JNC-VI): (1) non-dipper: decline of nocturnal SBP less than 10%; (2) dipper: 10–20% decline; and (3) extreme-dipper: decline greater than 20%. Short-term BPV, which represents the variability of BP in response to physical stress during 24 h, was calculated using the formula of Tochikubo:

Statistical Analysis

All values are presented as mean and SD. Univariate comparisons were performed by t-test for continuous variables, and chi-squared test was used for categorical variables. A value of p<0.05 was considered statistically significant. Statistical analysis was performed using Statview-J5.0 software for Macintosh (Abacus Concepts Inc, Calabasas, CA, USA).

Results

Twenty-Four-Hour HRV and BPV

BVP = 1/N ∑[SBPn-SBPn+b]2/SBP^2

All 4 parameters of 24-h HRV (LF, HF, LF/HF, and LF/HFd-n) were significantly lower in the stroke group than in the control group (Table 2). BPV was significantly higher in the stroke group compared with the control group (p<0.001; Table 2), although mean SBP and DBP did not differ. The stroke group showed a significantly higher frequency of the non-dipper type compared with the control group (p<0.001; Table 1). The 24-h mean LF/HF was significantly correlated with 24-h BPV in the stroke group (r=-0.488, p<0.002; Fig 2), although other parameters of HRV did not correlate with BPV.

Changes in BP and HR During Exercise

The increase in BP during exercise was greater in the stroke group (ΔSBP=79±12.8 mmHg) than that in the control group (ΔSBP=50±8.4 mmHg, p<0.001; Table 3). There were no significant differences in the other parameters (increase of SBP, increase in HR, and recovery of HR),

Fig 2. The relationship between 24-h mean LF/HF (LF, low frequency; HF, high frequency) and 24-h short-term blood pressure variability (BPV) in stroke patients with thalamic lesion, modified, because the stroke patients were unable to pedal a bicycle ergometer at the same work rate (W/min). To assess the movement intensity, the ventilatory profile and alveolar gas exchange were monitored breath by breath (AE-280; Minato Co Ltd, Japan). The exercise period finished 3 min after the movement intensity reached 4 METs (CVO2: 14 ml·kg^-1·min^-1). All subjects had a recovery period for 5 min after exercise. The changes (maximum value−baseline values) in BP (mmHg) and HR (beats/min) were monitored during the exercise period.
Relation Between HRV and BPV During Exercise

Decreased 24-h mean LF/HF, which may be associated with lowering of sympathetic nervous activity, showed a tendency to be associated with a greater increase in SBP during exercise \((r=-0.43, \ p<0.005; \ \text{Fig} \ 3)\). In addition, decreased LF/HFn-d, which indicates an imbalance of sympathetic and parasympathetic nervous activity between being awake and asleep, showed a tendency to be associated with a greater increase in SBP during exercise \((r=-0.58, \ p<0.001; \ \text{Fig} \ 3)\). The \(\Delta\)SBP \((102\pm9.8 \ \text{mmHg}, \ n=7)\) in the lower 24-h LF/HFn-d group \((\text{LF/HFn-d} \leq 1)\) was greater than that in the higher group \((\text{LF/HFn-d} > 1)\). Other parameters of HRV (HF, LF) did not correlate with circulatory change during exercise.

Discussion

The purpose of the present study was to examine the relationship between HRV and BPV during medical rehabilitation of stroke patients. In recent studies, stroke patients with a lesion in the thalamus or brain stem showed high BP and other cardiovascular dysfunction, because these areas are the center of the autonomic nervous system. Tokgöz et al. reported that stroke patients with a lesion in the thalamus, especially on the right, have decreased HRV and an increased incidence of sudden death. Moreover, Phillips et al. studied HRV, BPV, and micro-neurographic recordings of muscle sympathetic nervous activity, and concluded that strokes in the brain stem might result in partial baroreflex dysfunction, imbalance of sympathetic activity, and neurogenic paroxysmal hypertension.

Our study showed that 4 parameters of 24-h HRV (LF, HF, LF/HF, and LF/HF d-n) were significantly lower and BPV was significantly higher in stroke patients with a thalamic lesion than in the control group. Thus, in the very early phase of stroke with a lesion in the thalamus or brain stem, physicians must be careful with a bedside evaluation of the timing of sitting and standing exercise in medical rehabilitation.

Kario et al. reported that the prevalence of multiple lacunar infarction detected by head MRI was higher with the non-dipper type than with extreme-dipper type, and LF/HF d-n was significantly lower with the extreme-dipper type. They reasoned that the lower limit of BP in the autoregulation of cerebral blood flow is shifted upward in hypertensive patients with brain damage. Our results suggest that the stroke group had a higher frequency of the non-dipper type and decreased HRV.

Tochikubo et al. reported that short-term BPV is significantly enhanced by baroreflex dysfunction and decreased HRV. Our results showed that short-term BPV was greater in the stroke patients and that might be related to dysfunction of baroreflex and autonomic nervous dysfunction. The baroreflex plays a role in buffering moment-to-moment variations of BP.

In the present study, a greater increase in BP during exercise was observed in the stroke patients with lower LF/HF and LF/HF d-n (especially in those with LF/HF d-n \(\leq 1\)), and sympathetic nervous function was decreased after stroke with a thalamic lesion. Moreover, stroke patients suffered from many risk factors, such as hypertension, atherosclerosis and aging, which would cause an increase in SBP during exercise and greater diurnal variability of BP.

Minamizawa and Tochikubo suggested that autonomic nervous function controlled the distribution of blood flow to various organs, through a change in HR, BP and arterial resistance. Stroke patients often exhibit hypertension, which is related to the occurrence of atherosclerosis, and therefore must be assessed and managed carefully during...
HRV During Exercise in Stroke Patients

physical rehabilitation.25

Frequent repetition of short-duration physical therapy is appropriate for stroke patients with a lesion of the thalamus or brain stem in order to avoid large fluctuations of BP. Evaluation of autonomic nervous dysfunction by HRV in stroke patients prior to medical rehabilitation may be useful for planning an exercise program.

Conclusions

BP increased markedly during exercise in the stroke patients with lower HRV (LF/HF and LF/HFδ−). Therefore, measurement of HRV is useful for estimating the risk of physical therapy during medical rehabilitation in the acute and chronic phases of stroke.

References