Role of Autonomic Nervous Dysfunction in Electrocardiographic Abnormalities and Cardiac Injury in Patients With Acute Subarachnoid Hemorrhage

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Electrocardiographic abnormalities, cardiac injury, and autonomic nervous function were investigated in patients with acute-phase subarachnoid hemorrhage (SAH) (42 patients with SAH related to ruptured aneurysm and 42 control subjects). Electrocardiogram and Holter electrocardiogram for spectral analysis of heart rate variability (HRV) were recorded. Concentrations of cardiogenic enzymes (ie, creatine kinase-myocardial fraction [CK-MB], myosin light chain I, and troponin T), plasma concentrations of catecholamine (ie, noradrenaline, adrenaline, 3-methoxy-4-hydroxy-phenylethylene glycol [MHPG]) and HRV were compared in the acute and chronic phase of SAH, and with the values in the control subjects. As previously reported, patients with acute SAH exhibited electrocardiographic (ECG) abnormalities and increased concentrations of both cardiogenic enzymes and plasma catecholamines, suggesting that acceleration of sympathetic activity is involved. However, HRV analysis showed enhanced parasympathetic activity, probably associated with increased intracranial pressure after the onset of SAH, which may be explained by accentuated antagonism, negative feedback of noradrenaline to the center, and reduction of sympathetic activity after reaching a peak level. The results suggest that not only sympathetic activity but also vagal activity is enhanced during the acute phase of SAH, thus contributing to the ECG abnormalities and the onset of cardiac injury. (Circ J 2003; 67: 753–756)

Key Words: Acute subarachnoid hemorrhage; Autonomic nervous dysfunction; Cardiac injury; Electrocardiographic abnormalities; Heart rate variability

Previous studies have reported that electrocardiographic abnormalities, arrhythmia,1–4 cardiomyopathy5,6 and lung edema7,8 can concurrently develop in patients with acute subarachnoid hemorrhage (SAH). In addition, it has been indicated that abnormalities in autonomic nervous system function, especially excessive secretion of catecholamines, are etiologically involved in those associated disorders9,10. However, other studies have reported that there was no correlation between the concentrations of plasma catecholamines and ECG abnormalities3,10–12 and it has been suggested that there is an association between the enhanced parasympathetic nervous activity and electrocardiographic (ECG) abnormalities.13–15 Thus, the exact mechanism remains to be identified.

In the present study, we investigated the role of the autonomic nervous system in the production of ECG abnormalities and cardiac injury in the acute phase of SAH. For this purpose, we applied spectral analysis of heart rate variability (HRV) to serially recorded Holter ECGs, and measured the concentrations of both cardiogenic enzymes and plasma catecholamines during the acute and chronic phase of SAH.

Methods

Subjects
We studied 42 patients with SAH associated with ruptured aneurysms, within 24 h of onset, who were admitted to the Department of Neurosurgery, Nagasaki University Hospital and its affiliated institutions between December 1998 and November 2000 (11 males, 31 females, mean±SD age: 64±14 years) and 42 control inpatients with other diseases who were matched to the test group with respect to age and gender. Of the 47 patients with SAH, 5 were removed from the study because they died during follow-up and patients with arrhythmia, heart diseases, diabetes mellitus, neurological, renal, or lung diseases were also excluded.

Methods

On admission (day 1), the day after admission (day 2), and 30 days or more after admission (chronic phase), 12-lead ECGs were recorded and the concentrations of serum cardiogenic enzymes (ie, creatine kinase-myocardial fraction [CK-MB], myosin light chain I, and troponin T), and plasma catecholamines (ie, noradrenaline, adrenaline, and 3-methoxy-4-hydroxy-phenylethylene glycol [MHPG], a central noradrenaline metabolite) were measured. In addition, Holter electrocardiography was performed on admission and in the chronic phase (30 days or more after admission) for spectral analysis of HRV.

The QTc prolongation (QTc interval >450 ms), U wave (presence of negative U wave excluding aVR and positive U wave >0.2 mV), ST elevation (ST segment elevation...
>0.25 mV), ST depression (ST segment depression >0.1 mV), negative T wave (presence of negative T wave >0.25 mV), ST depression (ST segment depression >0.1 mV), U wave (presence of U wave >0.1 mV), negative T wave (presence of negative T wave >0.25 mV), ST depression (ST segment depression >0.1 mV), U wave (presence of U wave >0.1 mV), Q wave (presence of Q wave >0.1 mV), AV block (PQ interval >200 ms) were identified on the ECGs. Blood samples were collected while supine at rest and used for the measurement of the serum cardiogenic enzymes and plasma catecholamines.

For Holter electrocardiography, an FM-100 electrocardiograph (Fukuda Denshi, Tokyo) was used and the electrocardiograms were serially recorded for 24 h. Data were analyzed using an SCM-2000 device (Fukuda Denshi) with a sampling interval of 8 ms. Time-series data on the R-R intervals were prepared. Using HPS-RRA analytical software (Fukuda Denshi), spectral analysis of HRV was performed, as described below. The 24-h time-series data were divided into 60-min intervals. The initial head (512 s) of the time-series data on the R-R intervals were prepared. Using HPS-RRA analytical software (Fukuda Denshi), spectral analysis of HRV was performed, as described below. The 24-h time-series data were divided into 60-min intervals. The initial head (512 s) of the time-series data on the R-R intervals were prepared. Using HPS-RRA analytical software (Fukuda Denshi), spectral analysis of HRV was performed, as described below. The 24-h time-series data were divided into 60-min intervals. The initial head (512 s) was converted into data using Spline’s (tentative spelling) supplementation method. Using Hanning’s window, 0–0.5 Hz fast Fourier transform (FFT) spectra were prepared (analysis was possible at ≥0.002 Hz). For noise manipulation, data with R-R intervals ratio of 80% or less were excluded. The time of analysis initiation was divided into 150-s intervals, and 21 FFT spectra per 60 min were prepared. The mean of the added spectra was regarded as the representative value per 60 min. From the representative FFT spectrum, the low frequency (LF, 0.039–0.148 Hz: unit, ms2) and high frequency (HF, 0.148–0.398 Hz: unit ms2) components, and the LF/HF ratio were computed. The 24-h entire-interval mean values and mean nighttime sleep (23.00–05.00 h) values were compared between the acute and chronic phases, and with the control group.

### Results

**ECG Abnormalities**

Thirty-nine (93%) of the 42 patients with acute SAH showed ECG abnormalities (Table 1), especially prolongation of QTc, presence of U wave, and ST depression. In the chronic phase, 16 (38%) of the 42 patients had abnormalities (Table 1).

**Heart Rate, QTc Interval and Arrhythmia**

No significant differences were noted in heart rate on day 1 or 2, or in the chronic phase (Table 2). The QTc interval was significantly prolonged on days 1 and 2, compared with the chronic phase. However, there was no significant difference in this parameter between days 1 and 2. With regard to cardiac arrhythmias, the frequency of supraventricular/ventricular premature contractions in the acute phase was significantly higher than in the chronic phase.

### Table 1 Electrocardiographic Abnormalities in Patients With Acute Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>ECG abnormalities</th>
<th>Acute phase n (%)</th>
<th>Chronic phase n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTC prolonged</td>
<td>39/42 (93)</td>
<td>16/42 (38)</td>
</tr>
<tr>
<td>U wave</td>
<td>36 (86)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>ST depression</td>
<td>26 (62)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>ST elevation</td>
<td>29 (69)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>T inversion</td>
<td>6 (14)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Q wave</td>
<td>12 (29)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>8 (19)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>9 (21)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>AV block</td>
<td>2 (4)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>QTc prolonged</td>
<td>4 (10)</td>
<td>2 (13)</td>
</tr>
</tbody>
</table>

### Table 2 Comparison of Heart Rate, QTc Interval and Arrhythmia on Days 1, 2 and 30

<table>
<thead>
<tr>
<th></th>
<th>Day 1 (n=42)</th>
<th>Day 2 (n=42)</th>
<th>Day 30 (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>79±21</td>
<td>80±20</td>
<td>77±15</td>
<td>NS</td>
</tr>
<tr>
<td>QTc interval (s)</td>
<td>0.49±0.05</td>
<td>0.49±0.09</td>
<td>0.42±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>SVPC (per day)</td>
<td>2.54±3.85</td>
<td>NT</td>
<td>497±87</td>
<td>NT &lt;0.05</td>
</tr>
<tr>
<td>VPC (per day)</td>
<td>1.97±4.10</td>
<td>NT</td>
<td>315±69</td>
<td>NT &lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SD.

### Table 3 Comparison of Concentrations of Serum Cardiogenic Enzymes and Plasma Catecholamines on Days 1, 2 and 30

<table>
<thead>
<tr>
<th></th>
<th>Day 1 (n=42)</th>
<th>Day 2 (n=42)</th>
<th>Day 30 (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPK (mg/dl)</td>
<td>14±3.15</td>
<td>78±4.29</td>
<td>42±3.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>19.0±7.8</td>
<td>19.6±4.5</td>
<td>1.8±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Myosin light chain (ng/ml)</td>
<td>3.5±1.1</td>
<td>6.1±1.3</td>
<td>1.5±0.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Troponin T (ng/ml)</td>
<td>0.05±0.011</td>
<td>0.20±0.093</td>
<td>0.01±0.002</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Noradrenaline (ng/ml)</td>
<td>1.17±0.10</td>
<td>0.83±0.06</td>
<td>0.39±0.02</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adrenaline (ng/ml)</td>
<td>0.42±0.048</td>
<td>0.11±0.013</td>
<td>0.05±0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MHPG (ng/ml)</td>
<td>39.5±5.9</td>
<td>35.7±4.4</td>
<td>24.1±2.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Concentrations of Cardiogenic Enzymes and Plasma Catecholamines

The serum concentrations of cardiogenic enzymes, CK, CK-MB, myosin light chain I, and troponin T on day 2 were significantly higher than in the chronic phase (Table 3). Furthermore, the serum concentrations of CK, myosin light chain I, and troponin T were significantly higher on day 2 than on day 1. However, there were no significant differences between the values measured in the chronic phase and those on day 1.

Plasma catecholamine concentrations (ie, noradrenaline, adrenaline, MHPG) were significantly higher on days 1 and 2 than in the chronic phase. In addition, the values on day 1 were significantly higher than those on day 2.

Changes in LF

Both the 24-h entire-interval mean and the mean value during nighttime sleep were significantly higher in the chronic phase than in the acute phase, and in the control group (Fig 1). There were no significant differences in these parameters between the acute phase and the control group.
Changes in HF

Both the 24-h entire-interval mean and the mean value during nighttime sleep were significantly higher in the acute phase than in the chronic phase, and in the control group (Fig 2). Furthermore, these values were significantly higher in the chronic phase than in the control group.

Changes in LF/HF ratio

Both the 24-h entire-interval mean and the mean value during nighttime sleep were significantly lower in the acute phase than in the chronic phase, and in the control group (Fig 3). However, there were no significant differences in these parameters between the chronic phase and the control group.

Discussion

The present study identified various ECG abnormalities and increases in the concentrations of cardiogenic enzymes and plasma catecholamines in patients with acute SAH, as reported previously.1–6,9,10 Our results suggest that accelerated sympathetic activity is involved in the production of the abnormalities and cardiac injury. However, spectral analysis of HRV showed that the HF component was higher and the LF/HF ratio lower during the acute phase than during the chronic phase in SAH patients and the control group, suggesting enhanced vagal activity and reduced sympathetic activity. Thus, there was a paradox between the concentrations of the plasma catecholamines and the results of spectral analysis of HRV and we suggest that it involves accentuated antagonism,16 in which the acceleration of background sympatheticotonia increases the effects of the vagi and the latter then influence the sinus cycle more markedly than the sympathetic nerves and there is negative feedback to the cardiogenic center, in which increased noradrenaline concentrations decrease the LF, as reported by Breuer et al.15 In addition, the acceleration of sympathetic nervous activity occurred immediately after the onset of SAH, which, as an etiological factor, suggests that the peak occurred within a short period. In other words, sympathetic nervous activity was markedly accelerated at the onset of SAH, which coincided with an increase in blood catecholamine concentrations.

Immediately after the onset of SAH, spectral analysis of HRV showed an increase in the LF/HF ratio; however, there was a specific interval between onset and admission. The following hypothesis is assumed: the sympathetic nervous activity subsided from its peak level, and the high intracranial pressure associated with SAH augmented vagal activity. In this regard, spectral analysis of HRV showed augmentation of vagal activity, which more markedly influenced the sinus cycle, at the time when blood catecholamine concentrations were persistently high.

A number of investigators have argued against the concept of accentuated antagonism. For example, Hainsworth reported that the effects of sympathetic and parasympathetic nerves comprised a simple arithmetic sum when not heart rate but the cardiac cycle was investigated.17 However, even in that case, there is a specific interval between the onset of SAH and admission. The sympathetic activity had diminished from its peak level, suggesting that the high intracranial pressure-related enhancement of vagal activity is predominant.

Several studies have reported a lack of correlation between increases in catecholamines and ECG abnormalities3,10–12 and others have suggested an association between enhanced vagal activity and the abnormalities3,14,18. In addition, Sviegjel et al reported that the HF peak was detected at 4–5 days after the onset of SAH, augmenting vagal activity and decreasing the heart rate.19

In conclusion, we have demonstrated in the present study that the acute phase of SAH is characterized by augmentation of vagal activity, as indicated by an increase in the HF component, in addition to the acceleration of sympathetic nervous activity, as suggested by increases in plasma catecholamine concentrations. Our findings might assist in explaining the origin of the ECG abnormalities and cardiac injury seen in patients with SAH.

References