Circadian Rhythms of Blood Pressure and Heart Rate in Patients with Human T-Lymphototropic Virus Type-I-Associated Myelopathy

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Noninvasive ambulatory blood pressure and heart rate monitoring were used to investigate cardiovascular dysfunction in patients with human T-lymphotropic virus type-I (HTLV-I)-associated myelopathy (HAM). The subjects were 23 patients with HAM, and 23 sex- and age-matched normotensive healthy volunteers (controls). Circadian rhythms of blood pressure and heart rate were present in both the HAM patients and controls. Amplitudes and the 24-hr mean systolic and diastolic blood pressures were significantly lower in the patients than in the controls. The 24 hr mean heart rate was significantly higher in the patients, the difference being particularly marked during the night. Differences in the acrophases of the systolic and diastolic blood pressures and heart rate between patients and controls were small but still significant. These results suggest that subclinical cardiovascular autonomic dysfunction is present in HAM patients.

Human T-lymphotropic virus type I-(HTLV-I)-associated myelopathy (HAM) is a chronic progressive myelopathy characterized by symmetrical upper
motor neuron disorder with bladder dysfunction, mild sensory disturbance, or both, as well as by high titers of antibody to HTLV-I in the serum and cerebrospinal fluid (Osame et al. 1986, 1987). Disturbed micturition is a common symptom in HAM patients that may be due to autonomic dysfunction (Osame et al. 1987; Matsuo et al. 1989). Recently, we noted that casual blood pressure is usually low in HAM patients. Cardiovascular dysfunction of HAM patients, however, has not been reported. To determine whether or not cardiovascular dysfunction (including autonomic function) is present we monitored blood pressure and heart rate of HAM patients noninvasively for 24 hr and measured the responses of blood pressure, heart rate and plasma norepinephrine to postural change.

**Subjects and Methods**

Twenty-three patients with HAM (6 men and 17 women), aged 40 to 71 years (51 ± 9; mean ± S.D.) were studied. All were outpatients and fulfilled the diagnostic criteria proposed by Osame et al. (1986, 1987). Their casual blood pressures varied from 84/46 to 122/74 (group average; 103 ± 9/59 ± 6) mmHg. All the electrocardiograms were normal. Fifteen had spastic gait, 8 needed wheelchairs, and 20 complained of disturbed micturition. Four of the patients had been treated with prednisolone (10 to 20 mg every other day) for about 2 years; the others had undergone only physical rehabilitation. None was bedridden. As the controls, 23 sex- and age-matched normotensive healthy volunteers (6 men and 17 women) aged 40 to 71 (52 ± 6) were studied. Their casual blood pressures varied from 102/50 to 134/82 (group average; 116 ± 10/69 ± 8) mmHg. None were taking medication, and none showed signs of cardiovascular disease. The purpose of the study was explained to each subject and informed consent was received from both the patients and controls.

**Twenty-four-hour ambulatory blood pressure and heart rate monitoring**

We used a portable noninvasive blood pressure monitor ABPM 630 (Nippon Colin, Nagoya) which can measure blood pressure and heart rate by either auscultation or oscillometry. The reliability and accuracy of the ABPM 630 had been confirmed (White et al. 1989; Imai et al. 1990). All subjects were fitted with the recorder in the afternoon and were asked to spend usual life and to record their activities on diary sheets. The diary sheets showed that patients and controls had similar daily activities: They went to bed about 11 p.m. and got up about 7 a.m. Systolic and diastolic blood pressures and heart rate were measured automatically every 30 min for 24 hr. The data was obtained by oscillometry.

**Blood pressure and heart rate response to postural change**

Because 8 patients were unable to stand, we conducted the test by shifting all of the patients from the supine to the sitting position. After a 30 min rest in supine position, the patients were asked to sit up as quickly as possible and to remain sitting for 10 min. During this period, blood pressure and heart rate were monitored once a minute with the ABPM 630.

**Plasma norepinephrine response to postural change**

This test was done between 10:00 a.m. and noon on 12 patients with HAM and 12 sex- and age-matched controls. Blood samples were taken from the forearm vein after 30 min in supine position and after 15 min in sitting position. The samples were collected in chilled tubes containing EDTA-2Na and promptly centrifuged at 4°C. Norepinephrine
Circadian Rhythms of BP and HR in HAM

levels were determined by high performance liquid chromatography (Goldstein et al. 1981).

Statistical procedures

We used Tong's model (1976) to analyze the data for the 24-hr blood pressure and heart rate. The general form of this model is

$$Y_t = \beta_0 + \beta_1 \cos\left(\frac{2\pi t}{T}\right) + \beta_2 \sin\left(\frac{2\pi t}{T}\right) + \epsilon_t$$

where $Y_t$ is the value for systolic or diastolic blood pressure or heart rate measured at time $t$, and $T$ the period. $\epsilon_t$ is a random error assumed to be independently and normally distributed with a mean of 0 and a variance of $\sigma^2$. $\beta_0$, $\beta_1$, $\beta_2$ and $\sigma^2$ are unknown parameters to be estimated. The period, $T$, was set at 24 hr and the time, zero, at 9:00 a.m., then the model was fitted to the data using the 1R program of BMDP. The parameters $\beta_0$, $\lambda$ and $\tau$ are the 24-hr mean level, amplitude and acrophase, respectively. We used the Wald statistic to test the difference of these parameters between the two groups.

The following expression of model (1) explains the results succinctly:

$$Y_t = \beta_0 + \lambda \cos\left(\frac{2\pi (t - \tau)}{T}\right) + \epsilon_t$$

where $\lambda = (\beta_1^2 + \beta_2^2)^{1/2}$ and $\tau = (T/2\pi)\tan^{-1}(\beta_2/\beta_1)$. In this model, the existence of circadian rhythm means that $\lambda$ is not zero.

We used the Wilcoxon signed-rank sum test to analyze the data for the blood pressure and heart rate responses to postural change, and the Wilcoxon rank sum test to analyze the data for the plasma norepinephrine response to postural change.

RESULTS

Circadian rhythms of blood pressure and heart rate were observed in both the HAM patients ($n=23$) and controls ($n=23$). Systolic and diastolic blood pressures in HAM patients were lower than in the controls during the 24-hr period. Heart rate similarly varied in the patients and controls, and a marked difference was seen in the two groups during the night (Fig. 1). Table 1 shows the circadian rhythms in the systolic and diastolic blood pressures and in heart rate in the patients and controls. The amplitudes and 24-hr means of the systolic and diastolic blood pressures of the patients were, however, significantly lower than those of the controls. Differences in the acrophases of the systolic and diastolic blood pressures of the patients and controls (approximately 13:00 vs. 15:00) were small but still significant. The 24-hr mean of the heart rate was significantly higher in the patients; whereas, the amplitude of the heart rate was significantly lower. The differences in the acrophases of the heart rates of the patients and controls (approximately 14:20 vs. 15:00) was very small but still significant.

With regard to the cardiovascular response to postural change in HAM patients, diastolic blood pressure and heart rate increased significantly 2 min after sitting up, and systolic blood pressure 5 min after (Table 2). There was no marked decrease in blood pressure in any patient taking the sitting position. No significant difference in the plasma norepinephrine level between the supine and sitting positions was found for the patients and controls. Postural change from the supine to sitting position induced an increase in plasma norepinephrine in both groups, but the ratio of the sitting position to the supine position was
DISCUSSION

One of the most important parameters obtained by monitoring ambulatory blood pressure is the 24-hr mean blood pressure (Pickering et al. 1985; Schmieder et al. 1987; Lavie et al. 1988). In our study, four HAM patients were being significantly lower for the patients (Table 3).

Fig. 1. Means and standard errors, and the predicted systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) over a 24-hr period in patients with HAM (n=23) and in controls (n=23), as calculated with model (1). Circadian rhythms of blood pressure and heart rate are present in both groups. Blood pressures of the HAM patients are lower than those of the controls during the 24-hr period. Heart rate variations are similar in both groups, but an obvious difference exists during the night.
TABLE 1. *Estimates (± s.e.) of parameters in Tong’s model* \( ^a \) fitted to data from 24-hr SBP, DBP and HR monitoring

<table>
<thead>
<tr>
<th>Subjects (number)</th>
<th>Parameter</th>
<th>( \beta_0 )</th>
<th>( \lambda )</th>
<th>( \tau )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>Patients with HAM (23)</td>
<td>107.6±0.4</td>
<td>3.3±0.6</td>
<td>3.5±0.7</td>
</tr>
<tr>
<td></td>
<td>Normal controls (23)</td>
<td>118.0±0.4</td>
<td>7.6±0.6</td>
<td>6.0(^b)</td>
</tr>
<tr>
<td>DBP</td>
<td>Patients with HAM (23)</td>
<td>62.8±0.3</td>
<td>2.3±0.4</td>
<td>4.0±0.7</td>
</tr>
<tr>
<td></td>
<td>Normal controls (23)</td>
<td>70.5±0.3</td>
<td>5.4±0.5</td>
<td>6.0(^b)</td>
</tr>
<tr>
<td>HR</td>
<td>Patients with HAM (23)</td>
<td>73.4±0.4</td>
<td>6.8±0.5</td>
<td>5.3±0.3</td>
</tr>
<tr>
<td></td>
<td>Normal controls (23)</td>
<td>71.7±0.3</td>
<td>8.3±0.5</td>
<td>6.0(^b)</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

\(^a\) \( y(t) = \beta_0 + \lambda \cos(2\pi(t_0 - \tau)/T) + \epsilon \). See text for details.

\(^b\) \( \tau \) was set at 6 because the model without the cosine term in Equation (2) fitted best.

\(^* p < 0.05\), \(^** p < 0.01\). Wald statistic.

TABLE 2. *Means (± s.e.) of SBP, DBP and HR increases in response to postural change in HAM patients measured at two different times*

<table>
<thead>
<tr>
<th>Time of measurement (number)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>HR (b/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 min after sitting (23)</td>
<td>2.0±1.9</td>
<td>3.3±1.6(^*)</td>
<td>2.8±1.6(^*)</td>
</tr>
<tr>
<td>5 min after sitting (23)</td>
<td>4.0±2.0(^*)</td>
<td>2.4±1.6</td>
<td>2.2±2.2</td>
</tr>
<tr>
<td>Values for supine position (23)</td>
<td>108.4±2.4</td>
<td>63.7±1.9</td>
<td>70.9±2.4</td>
</tr>
</tbody>
</table>

\(^* p < 0.05\). Wilcoxon signed-rank sum test.

TABLE 3. *Means (± s.e.) of plasma norepinephrine (pg/ml) on postural change*

<table>
<thead>
<tr>
<th>Subjects (number)</th>
<th>Posture</th>
<th>Sitting</th>
<th>Sitting/Supine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Sitting</td>
<td></td>
</tr>
<tr>
<td>Patients with HAM (12)</td>
<td>190.8±27.7</td>
<td>240.8±31.9</td>
<td>1.28±0.05</td>
</tr>
<tr>
<td>Normal controls (12)</td>
<td>208.3±25.4</td>
<td>n.s.(^a)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

\(^a\) n.s., difference between the two groups not significant at the 5\% level.

\(^* p < 0.05\). Wilcoxon rank sum test.
treated with prednisolone which exerts a pressor effect (Treadwell et al. 1964; Whitworth et al. 1989). Moreover, the 24-hr means of systolic and diastolic blood pressure in our controls were lower than those previously reported (Drayer and Weber 1985; Zachariah et al. 1989). Nevertheless, the 24-hr means of blood pressure in the HAM patients were significantly lower than those in the controls. Littler (1979) and Baumgart et al. (1989) hypothesized that variation in blood pressure is governed mainly by physical activities and sleep. The physical activities of moderately or severely disabled HAM patients are usually decreased. To evaluate the effect of disability on blood pressure, we made a similar study of 3 severely disabled patients (one man and 2 women) with HTLV-I seronegative chronic progressive myelopathy (familial spastic paraparesis). Their parameters were $\beta_s = 118.1 \pm 1.3$, $\lambda = 15.6 \pm 1.9$ and $\tau = 6.0$ for systolic blood pressure and $\beta_s = 68.2 \pm 1.1$, $\lambda = 8.6 \pm 1.5$ and $\tau = 6.0$ for diastolic blood pressure. No significant difference was found between these patients and the controls with respect to the 24-hr means of the systolic and diastolic blood pressures. We consider, therefore, that low blood pressure both during the day and at night is a characteristic feature of HAM patients. This finding is interesting, because one of the suggested pathomechanisms (Izumo et al. 1989) of HAM is impairment of blood supply to the thoracic spinal cord.

Patients with autonomic dysfunction have unique ambulatory blood pressure profiles that include (1) a tendency to have hypotensive episodes, especially those preceded by postural change; (2) low blood pressure during waking hours; (3) supine hypertension, even while asleep; (4) abrupt and large reductions in blood pressure; and (5) little or no variation in heart rate in association with blood pressure decreases (Mann et al. 1983; The National High Blood Pressure Education Program Coordinating Committee 1990). In the study reported here, the patients showed low blood pressure during waking hours. The amplitude of the circadian rhythm of the blood pressure was significantly lower in the HAM patients than in the controls.

Plasma norepinephrine levels in both supine and sitting position were low in the patients, and the ratio of sitting up to supine was significantly lower in the patients than in the controls. Norepinephrine is a neurotransmitter released from the postganglionic synapses in the sympathetic nervous system and has a pressor effect. Plasma norepinephrine in normal subjects has a circadian rhythm featuring a high level during the day and a low level during the night (Linsell et al. 1985). This circadian rhythm of plasma norepinephrine appears to parallel that of blood pressure in the present study, suggesting that the sympathetic nervous system is involved in the circadian rhythm of blood pressure. Moreover, the increase of plasma norepinephrine is approximately twofold in normal subjects when posture is changed from the supine to standing position (Cryer et al. 1974). Autonomic dysfunction, on the other hand, induces low blood pressure during waking hours (The National High Blood Pressure Education Program Coordinat-
Circadian Rhythms of BP and HR in HAM

A small but significant difference in acrophases of blood pressure was found between the patients and controls. On the basis of diary sheets, patients and controls had similar daily activities and the modes of activity did not seem to affect the acrophase of circadian rhythm. Imai et al. (1989) reported that exogenous glucocorticoid eliminated or reversed the circadian rhythm of blood pressure. In this study, four patients had received a low dose of prednisolone. However, their acrophase of blood pressure was similar to that of controls (τ = 6.0, both). The fact that our results differed from those of the above authors may be attributable to differences in the dosage of prednisolone. It is not clear whether the difference in acrophases of blood pressure between the HAM patients and the controls reflects autonomic dysfunction in the HAM patients or only a small difference of daily activities between the two groups.

With regard to heart rate, circadian rhythms were essentially the same in the HAM patients and controls; but, the 24-hr mean was significantly higher in the patients, the difference being marked during the night. Clinically, heart rate variation is used to assess parasympathetic integrity. For example, diabetic patients with autonomic neuropathy have faster heart rates even during the night than age-matched normal subjects (Ewing et al. 1982; Ewing 1984). The faster heart rates recorded for the HAM patients, particularly during the night, suggest the presence of a parasympathetic dysfunction in the cardiovascular nervous system of these patients. We conclude that HAM patients have a subclinical cardiovascular autonomic dysfunction, both sympathetic and parasympathetic.

References


