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Sympathetic Skin Response and Cardiovascular Autonomic Function Tests in Parkinson's Disease

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Autonomic dysfunction commonly occurs in Parkinson's disease, but the pathogenesis of autonomic dysregulation remains uncertain. Autonomic functions regulating the cardiovascular system have been investigated in Parkinson's disease, but those involving the extremities has not been well demonstrated. To compare autonomic dysfunctions of the cardiovascular system with those of the extremities, we performed sympathetic skin response (SSR) and cardiovascular autonomic function tests (CAFT) - 30 : 15 ratio, E : I ratio, Valsalva ratio, isometric exercise test (IET) - in 37 patients with Parkinson's disease and 33 age- and sex-matched healthy controls. The patients were asked to stop antiparkinsonian medications for at least 12 hours prior to the tests. SSR was measured at the right hand and foot after electrical stimulation of the right median and posterior tibial nerves. Absent SSR at either one or both extremities and CAFT beyond normal ranges were regarded as abnormal. Abnormal SSR was observed in 59% of patients, while abnormal CAFT were found in the range of 32%~81%. Patients with abnormal SSR showed more frequent and severe CAFT abnormalities than did patients with normal SSR. Among the CAFT, IET was well correlated with the SSR. The results suggest that parkinsonian sympathetic dysfunction involving either the cardiovascular system or the extremities may have the same pathophysiology.

Key Words: Parkinson's disease, sympathetic skin response, cardiovascular autonomic function test, extremity

Disturbances of autonomic nervous system function are common in Parkinson's disease (PD), but the pathological lesions responsible for autonomic dysfunction have not been clearly found (Aminoff and Wilcox, 1971; Appenzeller and Gross, 1971; Goetz *et al.* 1986). Lewy bodies, the characteristic pathologic findings associated with neuronal loss in Parkinson's disease, are found in preganglionic structures of the sympathetic as well as the parasympathetic nervous system, such as the spinal intermediolateral horn, the sympathetic ganglia, the locus ceruleus, the raphe nuclei, the parabrachial area, the vagal dorsal motor nucleus, and the hypothalamus (Rajput and Rozdilsky, 1976; Sandyk *et al.* 1987; Gray, 1988). There is strong evidence that cardiovascular autonomic function may be impaired in PD (Appenzeller and Gross, 1971; Goetz *et al.* 1986; Ludin et al, 1987). However, the autonomic dysfunction involving the extremities has not been well documented because the methods of testing are more difficult and less objective.

Sympathetic skin response (SSR) is an easy meth-

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od for obtaining objective information on sympathetic autonomic function of the extremities. A variety of stimuli reflexively evoke a transient change in the electrical potential of the skin (Shahani *et al.* 1984; Montagna *et al.* 1985; Day *et al.* 1986; Uncini *et al.* 1988). The efferent arm of the reflex consists of sympathetic nerve fibers which innervate eccrine sweat glands in the skin. The response is abnormal in various diseases affecting sympathetic efferent nerve fibers, such as diabetic polyneuropathy (Soliven *et al.* 1987; Niakan and Harati, 1988), multiple sclerosis (Gutrecht *et al.* 1993; Elie and Louboutin, 1995), carpal tunnel syndrome (Caccia *et al.* 1993), amyotrophic lateral sclerosis (Dettmers *et al.* 1993), and cerebellar degeneration (Yokota *et al.* 1993).

In this study, we examined a group of 37 PD patients and compared them with age- and sex- matched controls to investigate the correlation between SSR and cardiovascular autonomic function tests.

MATERIALS AND METHODS

Subjects

Autonomic function was studied in 44 patients diagnosed as PD in Severance Hospital. Patients with cardiac arrhythmia (n=2), hypertension (systolic pressure over 180 mmHg or diastolic pressure over 90 mmHg, n=3) and patients taking medication (such as propranolol, n=2) known to influence autonomic nervous function were excluded. Owing to combinations of these factors, 7 patients were excluded; thus 37 PD patients were studied (14 men, 23 women). Mean age of PD was 65.3 (±1.3) years (men: 64.9 years, women: 65.6 years; range, 43~81 years). Mean duration of PD was 5 years 6 months, and mean height of patients was 162 (±1.3) cm. Clinical severity was scored according to the Hoehn and Yahr scale: 19 patients were at stage I, 12 at stage II, and 6 at stage III (Table 1). Patients answered a questionnaire and were asked to stop antiparkinsonian medications for at least 12 hours prior to tests.

Thirty three age- and sex-matched controls (13 men, 20 women) were selected from a database of healthy subjects and given the same battery of tests. Mean age of controls was 64.5 (±1.5) years (men: 64.7 years, women: 64.4 years; range, 46~81 years), and the age of controls did not differ from that of patients. Mean height of controls was 158 (±1.4) cm. PD patients were studied before, during, and after the period in which the controls were tested. All the subjects gave informed consent.

Sympathetic skin response

The patients and controls were asked to relax and breath regularly for a short time in a quiet room with a temperature between 22 and 24°C. The skin temperature was measured in the palm of the hand with a thermal probe. The skin underlying the recording sites was cleaned carefully with a dry cloth immediately prior to placing the surface electrodes, which were attached using sticking plaster. In the upper limbs, two active recording electrodes were placed at the palm of the hand. The reference electrodes were placed at the dorsum of the hand. In the lower limbs, the active recording electrode was placed at the sole of the foot and the reference electrode was placed at the dorsum of the foot. A conventional 4-channel EMG system served as recording unit. Electrical stimuli were delivered at the ankle in the lower limbs and at the wrist in the upper limbs. The technical characteristics for the recording were a band pass filter between 1 and 1000 Hz, a timed analysis of 5 sec and the appropriate gain to adequately measure the voltage of the response between 100 and 500 μV per division. Latencies were measured manually by setting cursors from the stimulus artifact of onset of potential, and amplitudes were measured from peak to peak. In order to avoid false results due to habituation, the

Table 1. Clinical characteristics in 37 patients with Parkinson's disease

Sex	No. (%)	Stage*		
		I	II	III
Male	14 (38%)	8	5	1
Female	23 (62%)	11	7	5
Total	37 (100%)	19	12	6

*: Hoehn and Yahr classification (1967)
Values are number of patients (% of values).

largest response evoked by any of the first 5 stimuli was analyzed.

Cardiovascular autonomic function test

Autonomic nervous function was investigated as previously described (Aminoff and Wilcox, 1971; Rabits, 1997).

30 : 15 ratio: The responses of the heart rate to changing from supine to standing position were checked during recording of ECG monitoring. The ratio of the R-R intervals corresponded to the thirtieth and fifteenth heart beats. A ratio of less than 1.04 was abnormal.

E : I ratio: It was determined by dividing the longest R-R interval during expiration by the shortest R-R interval during inspiration. A mean ratio was calculated from 10 consecutive respiratory cycles as previously described. Although an E : I ratio of <1.15 is often used as the cut-off point for normality, the ratio declines normally with age. Therefore for the purposes of this study, since the age range of patients was wide, an age-adjusted normal scale was used.

Valsalva ratio: The Valsalva ratio was defined as the ratio between the longest R-R interval in the 30s period at the end of the Valsalva maneuver and the shortest R-R interval in the 15s period at the beginning of the valsalva maneuver. During this maneuver, each subject maintained an air pressure of 40 mmHg by blowing into a mouthpiece connected to a sphygmomanometor. Each subject performed three tests, separated by a rest period of 2 minutes and the mean of the three ratios was calculated. Since the Valsalva ratio decreased with age, we used the normal values determined by Rabits (1997).

Isometric exercise test: There was an increase in arterial blood pressure during sustained isometric contraction of a group of muscles. An increase in diastolic pressure of less than 15 mmHg after 5 minutes of sustained handgrip at 30% of the maximum voluntary effort was abnormal.

Statistical analysis

Statistical analysis was done using the statistical package SPSS-PC. Bivariate comparisons were done by using Chi-square test, Independent-samples t-test, and ANOVA. The results were expressed as mean value and SD. The level of significance was set at $P<0.05$.

RESULTS

The autonomic symptoms of controls and PD patients with present and absent SSR are described in Table 2. Sweat dysfunction and salivation were more severe in patients with a loss of SSR.

Among the cardiovascular autonomic function tests (CAFT), the E : I ratio was abnormal in more

Table 2. Autonomic symptoms in 37 patients with Parkinson's disease and 33 controls

Autonomic symptom	Controls (n=33)	Sympathetic skin response	
		Absent (n=22)	Present (n=15)
Dizziness	6 (18%)	19 (86%)	12 (80%)
Urinary dysfunction	8 (24%)	18 (82%)	12 (80%)
Indigestion	2 (6%)	5 (23%)	1 (7%)
Constipation	4 (12%)	15 (68%)	9 (60%)
Sweat dysfunction	0 (0%)	11 (50%)	2 (13%)
Salivation	0 (0%)	12 (55%)	1 (7%)
Impotence*	0 (0%)	5 (71%)	2 (29%)
3 or more complaints	0 (0%)	20 (91%)	9 (60%)
No complaint	18 (55%)	0 (0%)	1 (7%)

*: Impotence only in male.
Values are number of subjects (% of values).

than 81% of patients. The abnormal values detected in the other autonomic function tests were that SSR was 59%, Valsalva ratio 58%, IET 51%, and 30 : 15 ratio 32%. In the controls, the abnormal values showed that the Valsalva ratio was 24%, E : I ratio 21%, IET 9%, and 30 : 15 ratio 3%. The E : I ratio showed that the abnormality was 21% even in the control group, but none of the 33 normal subjects recorded a loss of SSR (Table 3).

A loss of SSR of the hand was found in 22 persons (59%) and of the foot was found in 10 persons (27%). When we tested the right median nerve, the mean amplitude of the SSR recorded both from the hand and foot were 0.78±0.08 mV, and 0.34±0.04 mV respectively; in addition we tested the posterior tibial nerve, and they were 0.63±0.07 mV, and 0.33 ±0.04 mV respectively. Mean latencies of the SSR recorded in the hand and foot were 1.32±0.03 sec, and 1.81±0.03 sec respectively by stimulating right median nerve; 1.43±0.03 sec, and 1.96±0.04 sec respectively by stimulating posterior tibial nerve. Statistically significant difference of SSR amplitude and latency values between controls and PD patients, was not found (Table 4).

Table 3. Abnormal values of the autonomic function tests of the controls and patients

	Controls	Patients
30 : 15	1/33 (3%)	11/34 (32%)
E : I	7/33 (21%)	29/36 (81%)
Valsalva	8/33 (24%)	21/36 (58%)
IET	3/33 (9%)	19/37 (51%)
SSR	0 (0%)	22/37 (59%)

Values are number of subjects (% of abnormal).

Patients with absent SSR showed more frequent and severe cardiovascular autonomic function test abnormalities than did patients who presented with SSR (Fig. 1). In patients with a loss of SSR, the abnormal ratio of the cardiovascular autonomic function revealed that the E : I ratio was 86%, IET 77%, Valsalva ratio 62%, and 30 : 15 ratio 45%. However, in patients with normal SSR, the abnormal ratio was 73% of the E : I ratio, 53% of Valsalva ratio, 14% of 30 : 15 ratio, and 13% of IET. In the

Table 4. Sympathetic skin response in controls and patients with Parkinson's disease

	Controls	Patients	*p*
Result of sympathetic skin response			
SSR (−) in hand	0 (0%)	22 (59%)	
SSR (−) in foot	0 (0%)	10 (27%)	
SSR (+) in hand & foot	33 (100%)	15 (41%)	
Sympathetic skin response latency (sec)			
Median nerve stim.			
hand	1.32±0.03	1.37±0.04	*ns*
foot	1.81±0.03	1.83±0.04	*ns*
Post. tibial nerve stim.			
hand	1.43±0.03	1.46±0.04	*ns*
foot	1.96±0.04	1.91±0.04	*ns*
Sympathetic skin response amplitude (mV)			
Median nerve stim.			
hand	0.78±0.08	0.65±0.07	*ns*
foot	0.34±0.04	0.36±0.06	*ns*
Post. tibial nerve stim.			
hand	0.63±0.07	0.52±0.13	*ns*
foot	0.33±0.04	0.31±0.05	*ns*

Values are mean±standard error of mean.
ns: not significant
Analyzed by Independent-samples t test

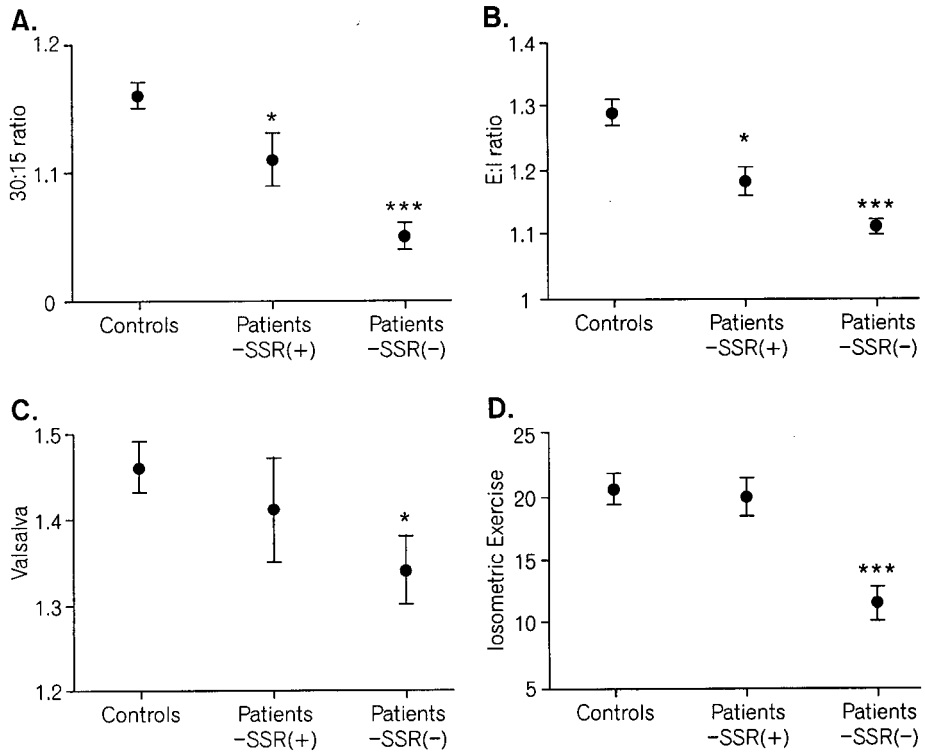

*Fig. 1. Comparison of cardiovascular autonomic function tests and sympathetic skin response. Patients with absent SSR showed more severe cardiovascular autonomic function test abnormalities. Values are mean ± standard error of mean, and analyzed by ANOVA. *: $p<0.05$, **: $p<0.005$, ***: $p<0.0005$*

CAFT, IET was correlated best with SSR (Table 5).

DISCUSSION

The loss of SSR was detected in 59% of 37 PD patients. This figure is higher than the previous ones, which ranges from 7.7% to 37.9% (Taly and Muthane, 1992; Wang *et al.* 1993; Bordet *et al.* 1996; Hirashima *et al.* 1996). Even though the age and symptom duration were similar, the autonomic nervous dysfunction was more severe than in previous studies. This possibility is supported by the fact that our patient group showed that the abnormality of the E : I ratio, and 30 : 15 ratio was 81%, and 32% respectively, whereas each was 27%, and 0%, in Bordet's study group (Bordet *et al.* 1996). In this study, the E : I ratio showed the highest abnormal rate of all the cardiovascular autonomic function tests (CAFT). This result was in accord with previous reports in which the rate was the highest in the tests on PD patients (Ludin *et al.* 1987;

Table 5. Cardiovascular autonomic function tests between patients with absent vs present SSR

	SSR		*p*
	Absent	Present	
30 : 15	9/20 (45%)	2/14 (14%)	*ns*
E : I	18/21 (86%)	11/15 (73%)	*ns*
Valsalva	13/21 (62%)	8/15 (53%)	*ns*
IET	17/22 (77%)	2/15 (13%)	$p<0.05$

Values are number of patient (% of values).
ns: not significant
Analyzed by Chi-Square test

Turkka *et al.* 1987; Wang *et al.* 1993). However, there was a low specificity, showing that the abnormality was 21% even in the control group. Compared with the E : I ratio, SSR had a very high specificity, such that SSR was normal in all cases of controls, like many previous reports in which none of the control group recorded a loss of SSR (Soliven *et al.* 1987; Shahani *et al.* 1990; Wang *et al.* 1993; Kim and Chun, 1994; Bordet *et al.* 1996; Hirashima *et al.* 1996).

Mean latencies and amplitudes of SSR showed no significant difference between the control group and the PD patient group. As SSR had a lot of variability due to many influencing factors, the loss of SSR had the only meaning as an abnormal finding. The amplitude and latency of SSR is not clinically well defined yet. It has often been asserted that amplitude is not a reliable factor because it is affected by many factors inside and outside the body, such as emotion and external environment (Day *et al.* 1986; Uncini *et al.* 1988). The latencies have not been clearly demonstrated to be a criteria because the periods of latencies tend to be constant, regardless of stimulated parts of the body and different stimulations (Tzeng *et al.* 1993). Therefore, as shown in this study, the presence of SSR is more meaningful and significant than the amplitudes and latencies themselves.

SSR in diabetic polyneuropathy showed the frequency of abnormality two times more than CAFT. These results show that SSR is a more sensitive test because diabetes is mainly developed in the peripheral nervous system (Soliven *et al.* 1987; Niakan and Harati, 1988; Shahani *et al.* 1990). Our study showed that a loss of SSR in PD was 59%, which was between 32~81%, the abnormal range of CAFT. This may suggest that the autonomic nervous system dysfunction in PD is the result of central and peripheral nervous system impairment.

SSR was a valuable and objective test of the autonomic nervous function in PD patients, like CAFT. Patients with abnormal SSR showed more frequent and severe CAFT abnormalities than did patients with normal SSR. This finding demonstrated that the autonomic dysfunction of extremities was closely related to the cardiovascular autonomic dysfunction. Among the CAFT, IET was well correlated with SSR since both tests examined the sympathetic efferent nerve function. Lewy bodies have been found in sympathetic ganglia as well as vagal dorsal motor nucleus, substancia nigra, and hypothalamus (Rajput and Rozdilsky, 1976; Sandyk *et al.* 1987; Gray, 1988). That the pathological lesions are responsible for autonomic dysfunction in PD patients remains uncertain. In this study, the results suggest that parkinsonian sympathetic dysfunction involving either the cardiovascular system or the extremities may have the same pathophysiology. In addition, we suggest that the autonomic dysfunction in PD may be caused not only by the central lesion such as the vagal dorsal motor nucleus, but also by the peripheral lesion such as the sympathetic ganglia.

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