Correlation between "oketsu" syndrome and autonomic nervous activity - a diachronic study on the same subjects -

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Abstract

In order to confirm that autonomic nervous activity changes with the change in the "oketsu" state using a diachronic study with the same subjects, 20 patients were evaluated by laser Doppler flowmetry and spectral analyses of the R-R intervals (RRs) and systolic blood pressure (SBP). According to the diagnostic criteria of "oketsu", the "oketsu" score (OS) was evaluated. After evaluation of OS and measurement of the parameters, each subject underwent his own Kampo treatment. Twelve weeks later, OS and the parameters were re-evaluated for each subject. The changes in OS and the parameters between week 0 and 12 weeks later were investigated, with the quantity of each change being calculated as Δ-. Δ-SBF showed a significant negative correlation with Δ-OS, and Δ-RR-L/H, Δ-SBP-LF and Δ-SBP-L/H revealed significant positive correlations with Δ-OS. It is known that SBF changes with sympathetic nervous activity, and SBP-LF and SBP-L/H reflect α-sympathetic nervous activity. These results suggest that the significant relationship between OS and sympathetic nervous activity was maintained even after change in the "oketsu" state in the same subjects.

Key words "oketsu" syndrome, autonomic nervous activity, skin blood flow, spectral analysis.

Abbreviations BP, blood pressure; CV_{RR}, coefficients of variation of the R-R interval; ECG, electrocardiogram; OS, "oketsu" score; RRs, R-R intervals; RR-HF, high-frequency component of R-R interval; RR-LF, low-frequency component of R-R interval; RR-L/H, power ratio of RR-LF to RR-HF; SBF, skin blood flow; SBP, systolic blood pressure; SBP-HF, high-frequency component of systolic blood pressure; SBP-LF, low-frequency component of systolic blood pressure; SBP-L/H, power ratio of SBP-LF to SBP-HF; Δ-CV_{RR}, quantity of change in CV_{RR}; Δ-OS, quantity of change in OS; Δ-SBF, quantity of change in SBF; Δ-RR-LF, quantity of change in RR-LF; Δ-RR-HF, quantity of change in RR-HF; Δ-RR-L/H, quantity of change in power ratio of RR-LF to RR-HF; Δ-RRs, quantity of change in RRs; Δ-SBP, quantity of change in SBP; Δ-SBP-LF, quantity of change in SBP-LF; Δ-SBP-HF, quantity of change in SBP-HF; Δ-SBP-L/H, quantity of change in power ratio of SBP-LF to SBP-HF.

Introduction

"Oketsu", blood stasis or stagnant syndrome, is one of the pathological concepts of the system of Kampo medicine. This pathological state refers to a state of insufficient blood circulation and blood stasis.[1] Previously, we reported that the "oketsu" state is closely correlated with abnormalities of microcirculation, based on observations of blood flow of bulbar conjuctiva, and also with hemorheological abnormalities such as an elevation of blood viscosity, acceleration of erythrocyte aggregability, and a deterioration of erythrocyte deformability.[2)~5)]

However, it is known that blood flow is influenced

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not only by blood properties but also by functions of the heart and blood vessels, and functions of those are controlled by the autonomic nervous system. Some symptoms accompanying "oketsu" syndrome such as paroxysmal facial flush, hyperhidrosis, chilly constitution, stiff shoulder and thirst originate from abnormalities of the autonomic nervous system. Therefore, it is important to clarify the relation between "oketsu" syndrome and the autonomic nervous system. Recently, we reported that the severity of the "oketsu" state correlated significantly with skin blood flow of the palm side of the right forefinger-tip, and that α-sympathetic nervous activity increased in the "oketsu" state.[6] However, it had not been clarified whether or not the significant relationship between the "oketsu" state and the autonomic nervous activity was maintained even after changes in the "oketsu" state in the same subjects.

The purpose of this study is to confirm whether the autonomic nervous activity changes with changes in the "oketsu" state by a diachronic study on the same subjects.

Materials and Methods

Subjects: Twenty patients who visited our hospital between April 1999 and July 2001 were enrolled in this study. Exclusion criteria were a history of cerebrovascular disorder, cardiovascular disease, autonomic disorder or receiving anti-hypertensive medication. Before the experiment, a thorough explanation was given to each of the subjects, and their informed consent was obtained in written form. The protocol of this study was approved by the Ethics Committee of Toyama Medical and Pharmaceutical University.

Method: Evaluation of the "oketsu" state was performed according to the diagnostic criteria.[1] The "oketsu" score (OS) was determined by two specialists in Kampo medicine before evaluation of autonomic nervous activity.

Electrophysiological parameters such as skin blood flow (SBF), R-R intervals (RRs), systolic blood pressure (SBP), coefficients of variation of RRs (CVRR), low frequency component of R-R interval (RR-LF), high frequency component of R-R interval (RR-HF), power ratio of RR-LF to RR-HF (RR-L/H), low frequency component of systolic blood pressure (SBP-LF), high frequency component of systolic blood pressure (SBP-HF) and power ratio of SBP-LF to SBP-HF (SBP-L/H) were employed for the evaluation of autonomic nervous activity. These parameters were measured by a method similar to that of the previous study.[6] SBF was measured on the palm side of the right forefinger-tip by laser Doppler flowmeter (LASERFLO BPM403A, TSI, USA). The electrocardiogram (ECG, lead II) signal and respiratory movement wave were obtained with a cardioscope (OMP-7201, Nihon Kohden, Japan). Blood pressure (BP) was measured at the radial artery of the right wrist by a tonometric BP monitoring system (JENTOW-7700, Nippon Colin, Japan). The electric signals of SBF, ECG and BP were recorded on a magnetic tape using a multichannel Digital-Audio-Tape data recorder (RD-130 TE, TEAC, Japan).

The recorded ECG signals were converted to time intervals (RRs) between respective R waves with a pulse counter (98counter(9), Interface, Japan) and a personal computer (PC9801DA, NEC, Japan). The analog data of SBF and BP were input via an A/D converter (98AD12(16/8)-H, Interface, Japan) into the computer at a sampling time of 1ms (1MHz). Data of SBF and SBP were averaged for each RRs by numerical integration. CVRR were calculated from 100 electrocardiographically recorded RRs. Spectral analysis of RRs and SBP recorded over a 400-beat period was performed by maximum entropy method using analytical software developed in our laboratory. The areas of the two frequency components of RRs and SBP were measured by integrating a low frequency component, from 0.04 to 0.15 Hz, and a high frequency component, from 0.15 to 0.50 Hz. The power ratio of LF to HF as LF/HF was calculated.

After evaluation of OS and measurement of the parameters, each subject underwent his own Kampo treatment based on the principles of traditional diagnosis. Twelve weeks later, OS and the parameters were reevaluated again in each subject.

The changes in OS and the parameters between week 0 and at 12 weeks were investigated, and the quantity of each change was calculated as Δ-OS, Δ-SBF, Δ-RRs, Δ-SBP, Δ-CVRR, Δ-RR-LF, Δ-RR-HF, Δ-RR-L/H, Δ-SBP-LF, Δ-SBP-HF and Δ-SBP-L/H.

Statistical analysis: Statistical analysis was performed using Spearman's rank correlation coefficient, and a level of $p<0.05$ was accepted as statistically significant.

Results

Subject characteristics

For this study, 20 subjects (9 males, 11 females, range 36-68 yrs, 51.2±9.6 yrs) were employed. The diagnoses by western medicine and the Kampo medicines used are listed in Table I. All subjects showed normal ranges of blood cell count (red blood cells, white blood cells, platelets), concentrations of serum electrolytes (sodium, potassium, chlorine), liver function (glutamic oxalacetic transaminase and glutamic pyruvic transaminase) and renal function (blood urea nitrogen, creatinine).

In 18 of the 20 subjects, OS at 12 weeks was changed as compared to that at week 0. OS had increased in 5 subjects and decreased in 13 subjects. As for the parameters, all changed at 12 weeks later compared to those at week 0, although the degree of changes varied.

Table I Subject characteristics

No.	Sex	Age	Diagnosis	Pre-OS	Post-OS	Kampo prescription Used
1	F	43	Irritable Bowel Syndrome	5.0	10.0	Shinbu-to
2	M	56	Irritable Bowel Syndrome	7.0	5.0	Keishi-ka-shakuyaku-to
3	F	39	Headache	11.0	11.0	Goshuyu-to
4	F	44	Menopausal syndrome	15.0	7.5	Kami-shoyo-san
5	M	47	Chronic gastritis	17.0	27.5	Rikkunshi-to
6	F	52	Chronic urticaria	19.5	25.0	Shishi-hakuhi-to
7	M	58	Lumbago	22.0	22.0	Hachimi-jio-gan
8	F	37	Hyperlipidemia	25.0	17.5	Keishi-bukuryo-gan
9	M	41	Lumbago	30.0	19.0	Keishi-bukuryo-gan
10	F	64	Lumbago	32.0	42.0	Shakuyaku-kanzo-to
11	M	62	Osteoarthritis	35.0	25.0	Bofu-tsusho-san
12	M	61	Lumbago	37.0	32.0	Hachimi-jio-gan
13	F	58	Osteoarthritis	37.5	40.0	Toki-shakuyaku-san
14	M	52	Hyperlipidemia	43.0	37.0	Hachimi-jio-gan
15	M	45	Hyperlipidemia	45.0	27.5	Keishi-bukuryo-gan
16	F	59	Diabetes mellitus	45.0	38.0	Toki-shakuyaku-san
17	M	46	Diabetes mellitus	48.0	40.0	Keishi-bukuryo-gan
18	F	68	Osteoarthritis	52.0	38.0	Sokei-kakketsu-to
19	F	36	Hyperlipidemia	52.0	32.0	Keishi-bukuryo-gan
20	F	56	Constipation	56.5	40.0	Tokaku-joki-to

Table II-1 Subject parameters (SBF, RRs, SBP)

	SBF (ml/min/100g)			RRs (msec)			SBP (mmHg)		
No.	Pre	Post	Δ-	Pre	Post	Δ-	Pre	Post	Δ-
1	75.3	66.5	-8.8	792.4	803.0	10.6	122.2	127.4	5.2
2	47.0	39.1	-7.9	835.0	828.0	-7.0	128.3	131.1	2.8
3	49.1	51.6	2.5	760.7	766.1	5.4	96.4	98.1	1.7
4	54.2	58.7	4.5	1057.6	1004.1	-53.5	98.9	103.2	4.3
5	74.1	51.4	-22.7	824.0	819.5	-4.5	114.8	108.0	-6.8
6	60.5	47.3	-13.2	790.2	809.6	19.4	96.1	98.9	2.8
7	28.7	34.8	6.1	919.8	934.0	14.2	81.4	104.6	23.2
8	24.6	36.6	12.0	1009.2	984.3	-24.9	111.1	120.7	9.6
9	23.8	40.2	16.4	1043.6	1056.1	12.5	116.1	101.4	-14.7
10	29.2	32.1	2.9	865.5	882.8	17.3	146.0	134.2	-11.8
11	21.7	47.9	26.2	969.5	953.0	-16.5	110.7	120.4	9.7
12	23.1	35.4	12.3	678.7	732.5	53.8	134.6	125.2	-9.4
13	17.6	19.6	2.0	896.7	875.9	-20.8	97.8	98.7	0.9
14	17.4	34.4	17.0	942.5	862.3	-80.2	99.2	101.4	2.2
15	13.1	45.4	32.3	810.0	848.3	38.3	145.3	139.0	-6.3
16	8.1	23.9	15.8	882.8	858.6	-24.2	130.4	132.0	1.6
17	12.9	13.0	0.1	747.3	808.7	61.4	119.3	124.8	5.5
18	11.5	35.2	23.7	964.9	918.3	-46.6	106.7	132.6	25.9
19	5.8	17.8	12.0	973.7	922.7	-51.0	105.8	105.5	-0.3
20	11.4	8.4	-3.0	693.9	812.0	118.1	143.9	123.0	-20.9

Correlation between the change in "oketsu" score and the changes in electrophysiological parameters

The parameters of each subject were shown in Table II-1, 2, 3, and Table III depicts the relationship between Δ-OS and each of the parameters as calculated by Spearman's rank correlation coefficient. A significant negative correlation was observed between Δ-SBF and Δ-OS (Fig. 1A, rho=-0.657, p=0.0042). Δ-RR-L/H was positively correlated significantly with Δ-OS (rho=0.687, p=0.0027). Further, significant positive correlations were observed between Δ-OS and Δ-SBP-LF (Fig. 1B, rho=0.722, p=0.0017), and Δ-SBP-L/H (rho=-0.4710, p=0.0402). There were no significant correlations between Δ-OS and Δ-RRs, Δ-SBP, Δ-CV_{RR}, Δ-RR-LF, Δ-RR-HF or Δ-SBP-HF.

Table II-2 Subject parameters (CV_{RR}, RR-HF, RR-LF, RR-L/H)

	CV_{RR} (%)			RR-HF (msec^2)			RR-LF (msec^2)			RR-L/H		
No.	Pre	Post	Δ-	Pre	Post	Δ-	Pre	Post	Δ-	Pre	Post	Δ-
1	3.07	3.29	0.22	189054	159166	-29888	60305	75732	15427	0.32	0.48	0.16
2	3.12	2.99	-0.13	35420	45149	9729	26953	23945	-3008	0.76	0.53	-0.23
3	3.30	3.47	0.17	106012	95398	-10614	55145	44806	-10339	0.52	0.47	-0.05
4	3.85	3.67	-0.18	414293	397474	-16819	66093	48281	-17812	0.16	0.12	-0.04
5	5.89	4.91	-0.98	159350	129930	-29420	87883	98556	10673	0.55	0.76	0.21
6	3.93	4.11	0.18	159630	188435	28805	57702	59156	1454	0.36	0.31	-0.05
7	2.19	3.21	1.02	56316	53794	-2522	39551	40688	1137	0.70	0.76	0.06
8	4.47	4.23	-0.24	156394	205752	49358	132473	92316	-40157	0.85	0.45	-0.40
9	3.93	3.76	-0.17	115192	105816	-9376	100582	94476	-6106	0.87	0.89	0.02
10	3.73	4.21	0.48	44214	34025	-10189	50109	52011	1902	1.13	1.53	0.40
11	2.66	3.20	0.54	183504	144303	-39201	104609	76791	-27818	0.57	0.53	-0.04
12	2.33	3.36	1.03	65104	75659	10555	83613	64112	-19501	1.28	0.85	-0.43
13	1.28	2.45	1.17	84054	65020	-19034	78661	80567	1906	0.94	1.24	0.30
14	4.85	4.47	-0.38	309764	277191	-32573	226468	209313	-17155	0.73	0.76	0.03
15	3.42	4.05	0.63	77250	158029	80779	83595	95419	11824	1.08	0.60	-0.48
16	4.71	4.59	-0.12	204051	184250	-19801	202455	141525	-60930	0.99	0.77	-0.22
17	4.83	4.67	-0.16	115097	135326	20229	164557	186067	21510	1.43	1.37	-0.06
18	3.11	4.05	0.94	18891	38582	19691	24402	34230	9828	1.29	0.89	-0.40
19	6.56	5.31	-1.25	130099	100271	-29828	176820	107416	-69404	1.36	1.07	-0.29
20	1.03	1.88	0.85	67102	86633	19531	89540	62244	-27296	1.33	0.72	-0.61

Table II-3 Subject parameters (BP-HF, BP-LF, BP-L/H)

	BP-HF(mmHg^2)			BP-LF (mmHg^2)			BP-L/H		
No.	Pre	Post	Δ-	Pre	Post	Δ-	Pre	Post	Δ-
1	2345.4	2445.8	100.4	1123.0	1333.3	210.3	0.48	0.55	0.07
2	2500.4	2387.4	-113.0	666.3	640.4	-25.9	0.27	0.27	0.00
3	799.2	912.6	113.4	458.7	512.0	53.3	0.57	0.56	-0.01
4	1201.6	1415.9	214.3	1232.3	1012.5	-219.8	1.03	0.72	-0.31
5	1678.1	1433.2	-244.9	1131.3	1008.6	-122.7	0.67	0.70	0.03
6	958.9	1078.9	120.0	1168.0	1564.8	396.8	1.22	1.45	0.23
7	467.8	389.0	-78.8	428.9	412.7	-16.2	0.92	1.06	0.14
8	1111.9	973.2	-138.7	887.0	784.6	-102.4	0.80	0.81	0.01
9	1182.7	1294.7	112.0	1775.0	1284.2	-490.8	1.50	0.99	-0.51
10	1818.0	2017.0	199.0	1921.0	2002.4	81.4	1.06	0.99	-0.07
11	434.7	506.2	71.5	329.8	302.6	-27.2	0.76	0.60	-0.16
12	1977.2	1716.9	-260.3	3391.0	3615.5	224.5	1.72	2.11	0.39
13	225.7	308.5	82.8	244.6	224.5	-20.1	1.08	0.73	-0.35
14	600.3	429.6	-170.7	1504.4	1401.7	-102.7	2.51	3.26	0.75
15	1876.1	1993.1	117.0	2303.0	2054.3	-248.7	1.23	1.03	-0.20
16	975.7	1016.9	41.2	1595.0	1236.4	-358.6	1.63	1.22	-0.41
17	1382.5	1196.5	-186.0	1920.8	1830.4	-90.4	1.39	1.53	0.14
18	1835.2	2018.6	183.4	2062.5	1731.7	-330.8	1.12	0.86	-0.26
19	1127.7	1423.9	296.2	1343.5	1048.2	-295.3	1.19	0.74	-0.45
20	579.3	415.8	-163.5	724.1	514.0	-210.1	1.25	1.24	-0.01

Table III Correlation between "oketsu" score and parameters

		Δ-OS	
		rho	*p*
Δ-SBF	(ml/min/100g)	-0.6570	0.0042
Δ-RRs	(msec)	0.1350	0.5561
Δ-SBP	(mmHg)	-0.0340	0.8837
Δ-CV_{RR}	(%)	0.0820	0.7251
Δ-RR-LF	($msec^2$)	0.3360	0.1428
Δ-RR-HF	($msec^2$)	-0.2030	0.3769
Δ-RR-L/H		0.6870	0.0027
Δ-SBP-LF	($mmHg^2$)	0.7220	0.0017
Δ-SBP-HF	($mmHg^2$)	-0.1800	0.4331
Δ-SBP-L/H		-0.4710	0.0402

rho : Spearman's rank correlation coefficient

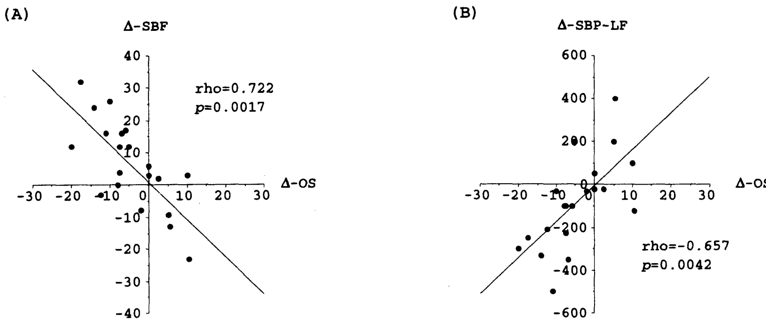

Fig. 1 The correlations between the quantity of change in "oketsu" score (Δ-OS) and each of the quantities of change in (A) the skin blood flow (Δ-SBF) and in (B) the low-frequency component of systolic blood pressure (Δ-SBP-LF).

Discussion

In this study, Δ-RRs and Δ-SBP did not exhibit significant correlation with Δ-OS. Although there are no reports about the direct relationship between "oketsu" syndrome and macrohemodynamics, it was reported that Keishi-bukuryo-gan, one of the Kampo prescriptions for improving the "oketsu" state, has no consequential influence on either cardiac function or large vessels.[7] This suggests that OS has no direct association with macrohemodynamics.

Concerning the relationship between OS and autonomic nervous activities, Δ-RR-L/H, Δ-SBP-LF and Δ-SBP-L/H were positively correlated with Δ-OS to a significant degree in this study, whereas Δ-CV_{RR}, Δ-RR-LF, Δ-RR-HF and Δ-SBP-HF showed no correlation with Δ-OS. Spectral analysis can be used to break down the stochastic process into its sinusoidal components. Power spectral analysis of the R-R interval and systolic arterial pressure variability is a widely accepted, useful and noninvasive method for indirect evaluation of autonomic nervous activity. From studies with sympathetic and/or parasympathetic blockade, it is considered that RR-HF (0.15-0.50 Hz) reflects parasympathetic nervous (vagal) activity, and RR-LF (0.04-0.15 Hz) and RR-L/H (LF/HF) are regulated by both sympathetic and parasympathetic nervous activity.[8)~11)] On the other hand, using sympathetic blockade, SBP-LF (0.04-0.15 Hz) was reported to reflect α-sympathetic nervous activity, although SBP-HF (0.15-0.50 Hz) was considered not to be concerned with autonomic nervous activities.[9),11)] CV_{RR} is believed to be a marker of parasympathetic nervous activity. In the light of these observations, the present results of the correlation between OS and various parameters suggest that OS is associated with α-sympathetic nervous activity, although OS is not correlated with cardiac parasympathetic nervous activity.

Δ-SBF displayed a negative correlation with Δ-OS in this study. SBF changes reflect sympathetic nervous activity because of abundant arterio-venous anastomoses with dense sympathetic innervation.[12)] It was reported that skin sympathetic nerve activity consists of vasoconstrictor and sudomotor outflow, and SBF reduction depends on vasoconstrictor activity.[13)] Therefore, the change in SBF indicates a change in sympathetic nervous activity, and thus the correlation between Δ-SBF and Δ-OS strongly suggests that OS is involved with sympathetic nervous activity. This result is in agreement with that of the power spectral analysis of the R-R interval and systolic arterial pressure variability.

It had not been clarified whether or not the significant relationship between the "Oketsu" state and autonomic nervous activity was maintained even after a change in the "oketsu" state in the same subjects after all. Nevertheless, this study did confirm that the significant relationship between OS and sympathetic nervous activity was maintained in spite of changes in the "oketsu" state in the same subjects.

Conclusion

In this study, it was confirmed that sympathetic nervous activity had a positive correlation with the "oketsu" score, and this significant correlation was maintained even after alterations in the "oketsu" state.

和文抄録

瘀血病態の経時的変化と自律神経活動の変化との関連性を明らかとするために，レーザードプラ血流計，R-R間隔および収縮期血圧のスペクトル解析を用いて検討した。患者20名を対象とし，瘀血スコアの変化と自律神経活動の変化との関連について統計学的に解析した。結果として，皮膚血流量（SBF）の変化量は瘀血スコアと負の相関を示し，R-R間隔成分比（RR-L/H）・収縮期血圧低周波成分（SBP-LF）・収縮期血圧成分比（SBP-L/H）は瘀血スコアと正の相関を示した。CV_{RR},・R-R間隔高周波成分（RR-HF）・収縮期血圧高周波成分（SBP-HF）については瘀血スコアとの間に有意な相関を認めなかった。SBFは交感神経活動にともない変化し，SBP-LFはα作動性交感神経活動と関連するとされている。今回の結果は，瘀血病態がα作動性交感神経活動と密接に関連していることを示唆するものである。

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References

1) Terasawa, K., Shinoda, H., Imadaya, A., Tosa, H., Bandoh, M., Sato, N.: The presentation of diagnostic criteria for "Yu-xie" (stagnated blood) conformation. *Int. J. Oriental Medicine* **14**, 194-213, 1989.
2) Terasawa, K., Itoh, T., Morimoto, Y., Hiyama, Y. and Tosa, H.: The characteristics of the microcirculation of bulbar conjunctiva in "Oketsu" syndrome. *J. Med. Pharm. Soc. WAKAN-YAKU* **5**, 200-205, 1988.
3) Terasawa, K., Toriizuka, K., Tosa, H., Ueno, M., Hayashi, T. and Shimizu, M.: Rheological studies on "Oketsu" syndrome I. The blood viscosity and diagnostic criteria. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 98-104, 1986.
4) Hikiami, H., Kohta, K., Sekiya, N., Shimada, Y., Itoh, T. and Terasawa, K.: Erythrocyte deformability in "Oketsu" syndrome and its relation to erythrocyte viscoelasticity. *J. Trad. Med.* **13**, 156-164, 1996.
5) Kohta, K., Hiyama, Y., Terasawa, K., Hamazaki, T., Itoh, T. and Tosa, H.: Hemorheological studies of "Oketsu" syndrome - Erythrocyte aggregation in "Oketsu" syndrome -. *J. Med. Pharm. Soc. WAKAN-YAKU* **9**, 221-228, 1992.
6) Kikuchi, K., Shibahara, N., Shimada, Y., Kita, T., Ito, T. and Terasawa, K.: Correlation between "Oketsu" syndrome and autonomic nervous activity. *J. Trad. Med.* **15**, 127-134, 1998.
7) Kuribayashi, H., Ito, T., Tosa, H., Hiyama, Y., Morimoto, Y. and Terasawa, K.: The effects of Keishi-bukuryo-gan on the hemodynamics in human subjects. *J. Med. Pharm. Soc. WAKAN-YAKU* **7**, 108-115, 1990.
8) Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., DellÅCOrto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S. and Malliani, A.: Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ. Res.* **59**, 178-193, 1986.
9) Japundzic, N., Grichois, M.L., Zitoun, P., Laude, D., and Elghozi, J.L.: Spectral analysis of blood pressure and heart rate in conscious rats: Effects of autonomic blockers. *J. Auton. Nerv. Syst.* **30**, 91-100, 1990.
10) Pomeranz, B., Macaulay, R.J.B., Caudill, M.A., Kutz, I., Adam, D., Gordon, D., Kilborn, K.M., Barger, A.C., Shannon, D.C., Cohen, R.J. and Benson, H.: Assessment of autonomic function in humans by heart rate spectral analysis. *Am. J. Physiol.* **248**, H151-153, 1985.
11) Oka, H., Mochio, S., Sato, K., Nohara, T., Numata, A., Isogai, Y.: Evaluation of diabetic autonomic neuropathy using spectral analyses of R-R interval and systolic blood pressure. *J. Auton. Nerv. Syst.* **29**, 585-591, 1992 (in Japanese).
12) Khan, F., Spence, V.A., Wilson, S.B.: Quantification of sympathetic vascular responses in skin by laser Doppler flowmetry. *Int. J Microcirc. Clin. Exp.* **10**, 145-153, 1991.
13) Hagbarth, K.E., Hallin, R.G., Hongel, A., Torebjork, H.E. and Wallin, B.G.: General characteristics of sympathetic activity in human skin nerves. *Acta Physiol. Scand.* **84**, 164-176, 1972.