Correlation between "oketsu" syndrome and autonomic nervous activity

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In order to clarify the correlation between "oketsu" syndrome and autonomic nervous activity, subjects were evaluated with laser Doppler flowmetry and spectral analyses of R-R intervals (RRs) and systolic blood pressure (SBP). According to the diagnostic criteria of "oketsu", the "oketsu" score (OS) was evaluated. In a sectional study, the results showed that a significant decrease in skin blood flow (SBF) was observed in proportion to the severity of the "oketsu" state, and the low-frequency component of SBP (SBP-LF) in the "oketsu" state was significantly larger than that in the non-"oketsu" state. In a diachronic study, 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 α-sympathetic nervous activity increased in the "oketsu" state, and this significant relationship was maintained even after change in the "oketsu" state.

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

Abbreviations BP, blood pressure; CVRR, 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-CVRR, quantity of change in CVRR; Δ-OS, quantity of change in OS; Δ-RR-HF, quantity of change in RR-HF; Δ-RR-LF, quantity of change in RR-LF; Δ-RR-L/H, quantity of change in power ratio of RR-LF to RR-HF; Δ-RRs, quantity of change in RRs; Δ-SBF, quantity of change in SBF; Δ-SBP, quantity of change in SBP; Δ-SBP-HF, quantity of change in SBP-HF; Δ-SBP-LF, quantity of change in SBP-LF; 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 pathophysiological concepts existing only in Kampo medicine. This pathological state refers to a state of insufficient blood circulation and blood stasis.[1)] For evaluation of the "oketsu" state, in this study we used the widely recognized diagnostic criteria ("oketsu" score) of Terasawa *et al.*[2)]

Previously, we reported that the "oketsu" syndrome is closely correlated with abnormalities of the microcirculation, based on observations of blood flow of the bulbar conjuctiva, and also such hemorheological abnormalities as the elevation of blood viscosity and erythrocyte aggregability, and the deterioration of erythrocyte deformability.[3~6)] However, it is known that blood flow is influenced 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, continuous measurement of skin blood flow (SBF) has become possible by simple manipulation of a laser Doppler flowmeter (LDF),[7~11)] and evaluations of the autonomic nervous activity based on spectral analysis of R-R intervals (RRs) and blood pressure (BP) have been reported.[12~16)]

The purpose of this study is to clarify the correlation between "oketsu" syndrome and autonomic nervous activity.

Subjects and Methods

Subjects. Forty-eight patients (24 males, 24 females) in a sectional study and twenty patients in a diachronic study, who visited the Department of Japanese Oriental (Kampo) Medicine, Toyama Medical and Pharmaceutical University Hospital, were examined in these studies. All subjects had no previous history of cerebrovascular disorder and hypertension. They were confirmed to be without autonomic neuropathy and cardiovascular disease by head-up tilting test and electrocardiogram. Before the experiment, a thorough explanation was given to each of the subjects, and their informed consent was obtained in written form. The protocols of these studies were approved by the Ethics Committee of Toyama Medical and Pharmaceutical University.

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Method. Evaluation of the "oketsu" state was performed according to the diagnostic criteria.[2] 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.[7] SBF was measured at 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 multi-channel 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. For a representative example, 400 successive RRs are shown in Fig.1.A, spectral analysis of the RRs performed by MEM is shown in Fig.1.C, SBP of the same example are shown in Fig.1.B, and the spectral analysis of SBP performed by MEM is shown in Fig.1.D.

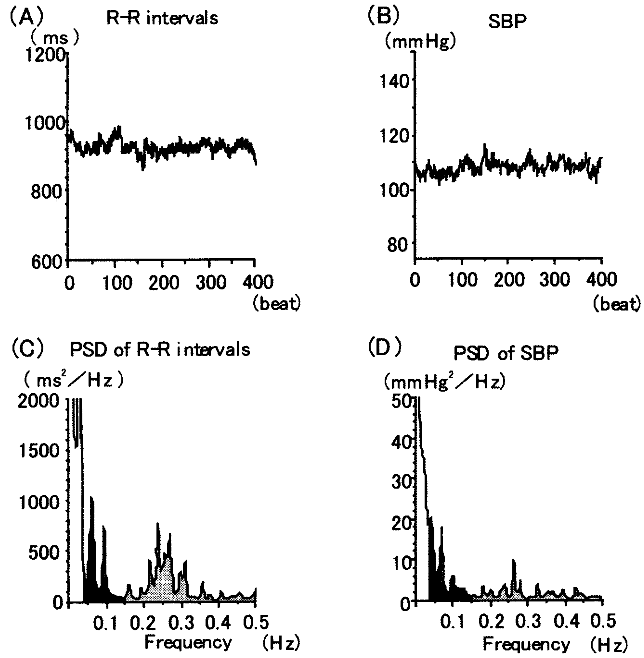

Fig. 1 Raw data and power spectral density.
The raw data of R-R intervals (RRs, A), power spectral density (PSD) curves of RRs (C), systolic blood pressure (SBP, B) and PSD curves of SBP (D). LF, power of low-frequency component of RRs or SBP, variability.

In the diachronic study, each subject underwent his own Kampo treatment based on the principles of traditional diagnosis after evaluation of OS and measurement of the parameters. Twelve weeks later, OS and the parameters were re-evaluated 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. The data were expressed as mean ±S.D. In the sectional study, differences among the three groups were determined by Kruskal-Wallis test, and $p<0.05$ was considered significant. Post-hoc tests were determined by the Mann-Whitney test, and $p<0.0167$ was considered significant. In the diachronic study, statistical analysis was performed using Spearman's rank correlation coefficient, and a level of $p<0.05$ was accepted as statistically significant.

Results

1. Sectional study

Subjects' characteristics among the groups. 48 patients were divided into three groups, a non-"oketsu" group (n=16, "oketsu" score was 20 points or less), a mildly affected group (n=16, "oketsu" score was 21 points or above, but less than 40 points), and a severely affected group (n=16, "oketsu" score was 40 points or above). There was no statistical significance in age, sex and clinical features among the three groups (Table 1).

Comparison of SBF, RRs and BP among the groups. SBF was 61.96±3.35 ml/min/100g in the non-"oketsu" group, 28.07± 2.47 in the mildly affected group, and

Table 1 Comparison of sex and age among the three groups in sectional study

Group	No.	Sex(M/F)	Age
Non-"oketsu" group	16	8/8	47.0±1.3
Mildly affected group	16	9/7	54.1±3.2
Severely affected group	16	7/9	49.5±2.2

18.18±1.75 in the severely affected group. Therefore, a significant decrease in SBF was observed in proportion to the severity of the "oketsu" state (Fig.2). RRs was 867.64±27.36 msec in the non-"oketsu" group, 917.30±31.85 in the mildly affected group, and 918.50±33.55 in the severely affected group. CV_{RR} was 3.64±0.29 % in the non-"oketsu" group, 3.94±0.35 in the mildly affected group, and 3.57±0.39 in the severely affected group. There were no significant differences in RRs, CV_{RR}, SBP, DBP, and MAP among the three groups.

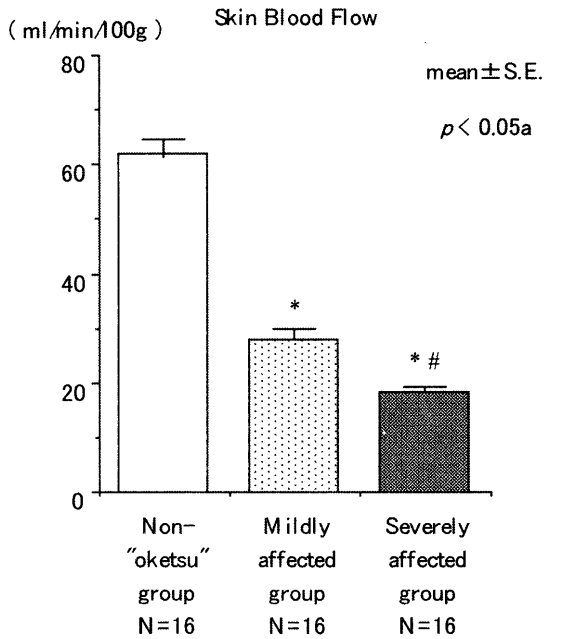

Fig. 2 Comparison of skin blood flow among the three groups.
The values are expressed as mean±S.E. Statistical analysis was done at Kruskal-Wallis test. $p<0.05$ a : significant difference at Kruskal-Wallis test. Post-hoc test was done by Mann-Whitney test. *$p<0.0167$: significant difference from non- "oketsu" group. #$p<0.0167$: significant difference from mildly affected group.

Spectral analyses of R-R interval and systolic blood pressure. The low-frequency component of R-R interval (RR-LF) was 57,994.6±7,629.1 msec^2 in the non-"oketsu" group, 87,796.3±8,533 in the mildly affected group, 162,201.3±18,851.5 in the severely affected group. RR-LF in the severely affected group was significantly larger than that in the non-"oketsu" group and the mildly affected group. No significant difference in RR-LF was observed between the non-"oketsu" group and the mildly affected group. The high-frequency component of R-R interval (RR-HF) was 157,569.6±31,248.2 msec^2 in the non-"oketsu" group, 125,425.7±19,307.4 in the mildly affected group, and 165,854.1±23,303.5 in the severely affected group, showing no significant differences. The power ratio (LHR) was 0.463±0.49 in the non-"oketsu" group, 0.813±0.61 in the mildly affected group, 1.060±0.65 in the severely affected group. LHR in the mildly affected and the severely affected groups was significantly larger than that in the non-"oketsu" group. No significant difference in LHR was observed between the mildly affected and the severely affected groups (Fig.3). The low-frequency component of SBP (SBP-LF) was 825.7±70.15 mmHg^2 in the non-"oketsu" group, 1,403.4±234.1 in the mildly affected group, 1,640.8±163.7 in the severely affected group. Therefore, there was significant difference in the SBP-LF among the groups classified in proportion to severity of the "oketsu" state. The high-frequency component of SBP (SBP-HF) was 1,175.6±146.9 mmHg^2 in the non-"oketsu" group, 1,212.5±181.7 in the mildly affected group, 1,219.5±139.3 in the severely affected group, and no significant differences were found (Fig. 4).

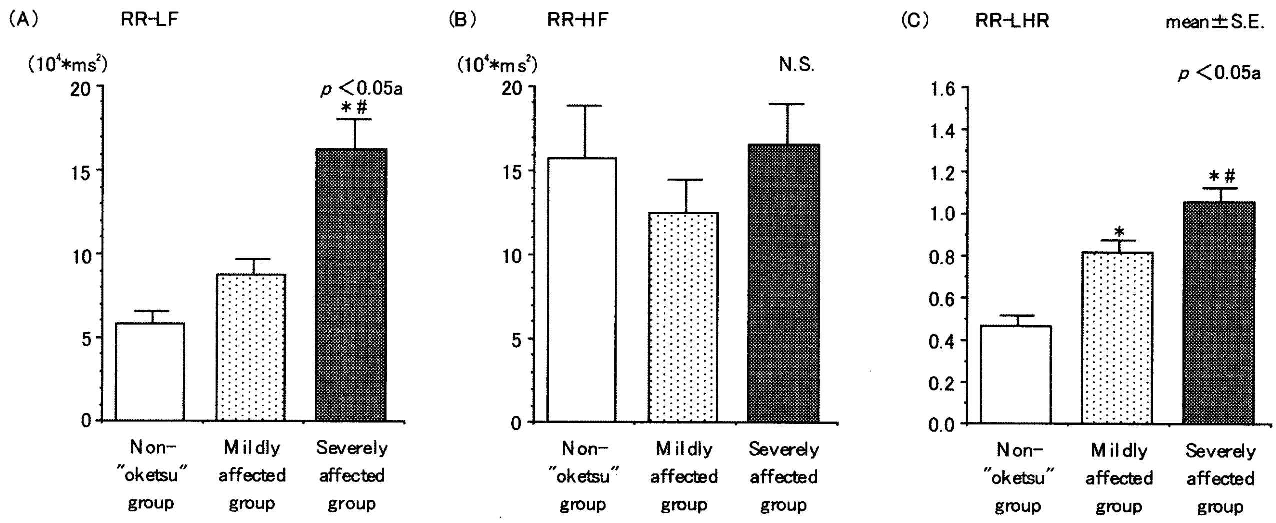

Fig. 3 Comparison of R-R interval variability-related parameters among the three group.
RR-LF, power of low-frequency componet at spectral analysis of R-R intervals (A) ; RR-HF, power of high-frequency component at spectral analysis of R-R intervals (B) ; RR-LHR, power ratio of LF to HF (C). The values are expressed as mean±S.E. Statistical analysis was done by Kruskal-Wallis test. $p<0.05$a : significant difference by Kruskal-Wallis test. N.S. : not significant. Post-hoc test was done by Mann-Whitney test. *$p<0.0167$: significant difference from non- "oketsu" group. #$p<0.0167$: significant difference from mildly affected group.

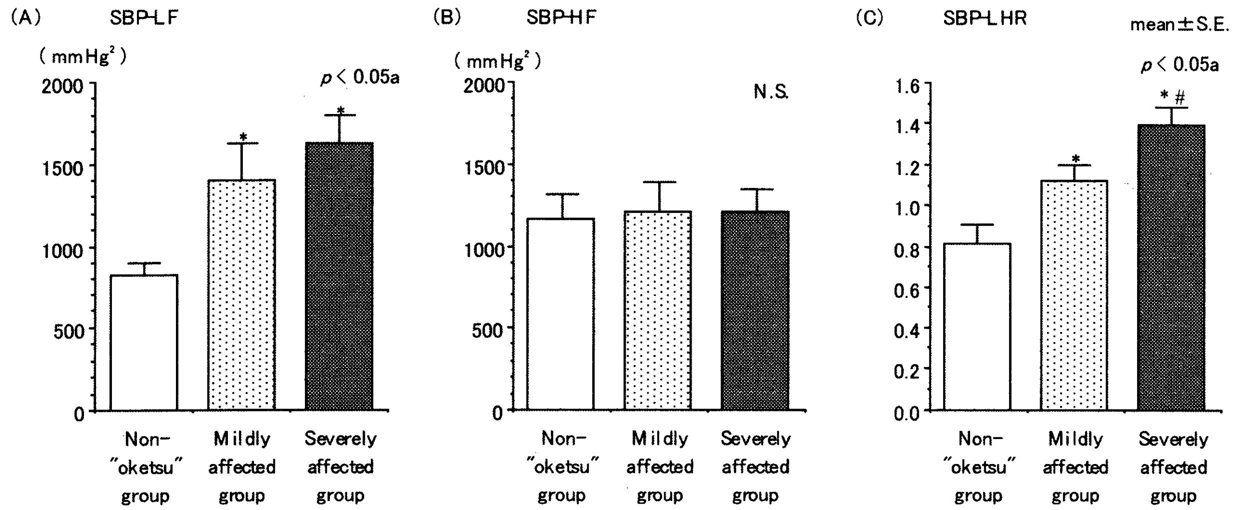

Fig. 4 Comparison of systolic blood pressure variability-related parameters among the three group.
SBP-LF, power of low-frequency componet at spectral analysis of sytolic blood pressure (A) ; SBP-HF, power of high-frequency component at spectral analysis of sytolic blood pressure (B) ; SBP-LHR, power ratio of LF to HF (C). The values are expressed as mean±S.E. Statistical analysis was done by Kruskal-Wallis test. p<0.05a : significant difference by Kruskal-Wallis test. N.S. : not significant. Post-hoc test was done by Mann-Whitney test. *p<0.0167 : significant difference from non- "oketsu" group. #p<0.0167 : significant difference from mildly affected group.

Table 2 Subject characteristics in diachronic study

No.	Sex	Age	Diagnasis	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 qastritis	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	44.0	Tokaku-joki-to

Table 3 Correlation between "oketsu" score and parameters in diachronic study

		Δ-OS	
		rho	p
Δ-SEF	(ml/min/100g)	-0.657	0.0042
Δ-RRs	(msec)	0.135	0.5561
Δ-SBP	(mmHg)	-0.034	0.8837
Δ-CV_{RR}	(%)	0.082	0.7251
Δ-RR-LF	($msec^2$)	0.336	0.1428
Δ-RR-HF	($msec^2$)	-0.203	0.3769
Δ-RR-L/H		0.687	0.0027
Δ-SBP-LF	($mmHg^2$)	0.722	0.0017
Δ-SBP-HF	($mmHg^2$)	-0.180	0.4331
Δ-SBP-L/H		0.471	0.0402

rho : Spearman's rank correlation coefficient

2. Sectional study

Subject characteristics. For this study, 20 subjects (9 males, 11 females, age 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 2. In 19 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 14 subjects. As for the parameters, all changed at 12 weeks later compared to those at week 0, although the degree of changes varied.

Correlation between the change in "oketsu" score and the changes in electrophysiological parameters. Table 3 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. 5A, 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. 5B, rho=0.722, p=0.0017), and Δ-SBP-L/H (rho=0.707, p

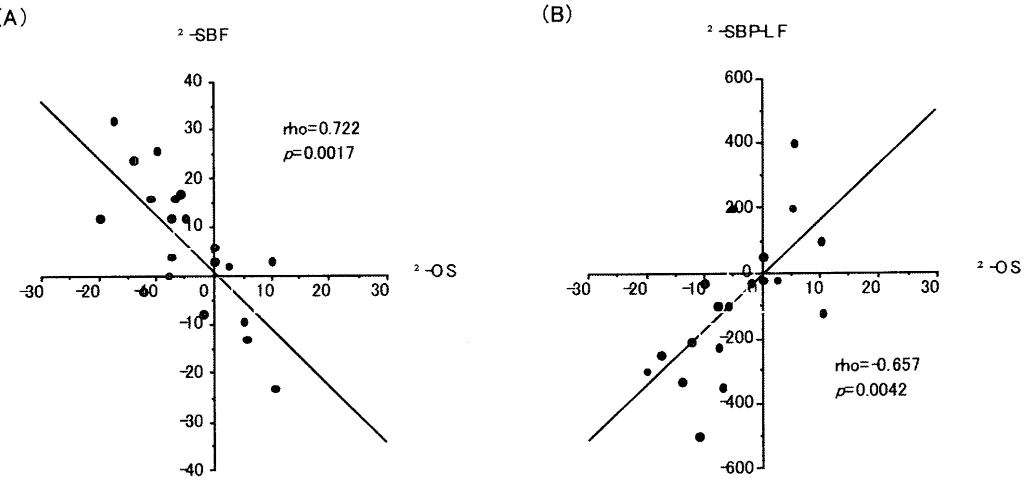

Fig. 5 The correlations between the quantity of change in "oketsu" score (Δ-OS) and each of the quantities of change in (A) the skin blood flow (Δ-SBF) and in (B) the low-frequency component of systolic blood pressure (Δ-SBP-LF).

=0.0021). There were no significant correlations between Δ-OS and Δ-RRs, Δ-SBP, Δ-CVRR, Δ-RR-LF, Δ-RR-HF or Δ-SBP-HF.

Discussion

SBF is influenced by diurnal variation of autonomic nervous activity, conscious state,[17] and emotional upsets.[18] In this study, the room was kept at a constant temperature, and all experiments were performed at the same time. SBF changes reflect sympathetic nervous activity because of abundant arterio-venous anastomoses with dense sympathetic innervation.[19,20] Data was collected for 8 min under stable conditions, and the average values of the data were used. A significant decrease in SBF was observed in relation to the severity of the "oketsu" state. Hagbarth *et al.* reported that skin sympathetic nerve activity consists of the vasoconstrictor and sudo-motor outflow, and SBF reduction depends on vasoconstrictor activity.[21] Therefore, the decrease of SBF in the "oketsu" state and significant negative correlation between Δ-SBF and Δ-OS are suggested to be due to the increase of skin sympathetic nervous activity.

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 and RR-L/H are regulated by both sympathetic and parasympathetic nervous activity.[12~16] On the other hand, using sympathetic blockade, SBP-LF was reported to reflect α-sympathetic nervous activity, although SBP-HF was considered not to be concerned with autonomic nervous activities.[13,16] CVRR is believed to be a marker of parasympathetic nervous activity. In the light of these observations, the present results suggest that "oketsu" state is associated with α-sympathetic nervous activity, although "oketsu" state is not correlated with cardiac parasympathetic nervous activity.

Conclusion

In this study, it was suggested that α-sympathetic nervous activity increased, and as a consequence SBF was reduced in the "oketsu" state.

Acknowledgements

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Japanese abstract

瘀血病態と自律神経活動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 間隔と収縮期血圧のスペクトル解析を用いて検討した。各対象者について瘀血診断基準により瘀血スコアを算出した。断面的検討では，皮膚血流量（SBF）は瘀血病態の重症化とともに減少し，収縮期血圧低周波数成分（SBP－LF）は軽度及び重度瘀血群が非瘀血群に比較して有意に高値を示した。経時的検討では，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）の変化量は瘀血スコアと正の相関を示した。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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