Correlation between "oketsu" syndrome and autonomic nervous activity

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Abstract

In order to clarify the correlation between "oketsu" syndrome and autonomic nervous activity, 48 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", 48 patients were classified into three groups : non- "oketsu", mildly affected, and severely affected with "oketsu" syndrome. Then the correlations between the "oketsu" state and the autonomic nervous activities were analyzed statistically. The results showed that a significant decrease in Skin Blood Flow (SBF) was observed in proportion to the severity of the "oketsu" state. There was no significant difference in CV_{R-R} and the high-frequency component of RRs among the three groups, but the low-frequency component of SBP (SBP-LF) in the "oketsu" state was significantly larger than that in the non-"oketsu" state. SBF changes with sympathetic nervous activity, and SBP-LF reflects α- sympathetic nervous activity. These results suggest that in the oketsu" state α-sympathetic nervous activity is increased, and consequently SBF is reduced.

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

Abbreviations SBF, skin blood flow ; LDF, laser Doppler flowmeter ; ECG, electrocardiogram ; RRs, R-R intervals ; BP, blood pressure ; SBP, systolic blood pressure ; DBP, diastolic blood pressure ; MAP, mean blood pressure ; CV_{R-R}, coefficients of variation of the R-R interval ; MEM, maximum entropy method ; LF, low-frequency component ; HF, high-frequency component ; LHR, power ratio of LF to HF ; RR-LF, low-frequency component of R-R intervals ; RR-HF, high-frequency component of R-R intervals ; SBP-LF, low-frequency component of systolic blood pressure ; SBP-HF, high-frequency component of systolic blood pressure.

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 conjunctiva, 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, as the hemorheological abnormalities, but also by the autonomic nervous system, including functions of the heart and blood vessels. In Kampo medicine, it is thought that "oketsu" syndrome

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includes some symptoms of autonomic nervous system, making it necessary to clarify the correlation between "oketsu" syndrome and autonomic nervous activity.

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.

Materials and Methods

Subjects : Forty-eight patients (24 males, 24 females), who visited the Department of Japanese Oriental (Kampo) Medicine, Toyama Medical and Pharmaceutical University Hospital, were examined in this study. 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. Written informed consent was obtained.

The evaluation of "oketsu" syndrome : According to the diagnostic criteria of Terasawa *et al.* ("oketsu" score),[2] the 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). The "oketsu" score was determined by two specialists in Kampo medicine before the measurement of SBF, arterial BP and recording an electrocardiogram (ECG).

Recording : SBF was measured with LDF (LASERFLO BPM403A, TSI, USA). The disk probe (ϕ8.0 mm) was attached to the palm side of the right forefinger-tip with a probe-holder. The ECG (lead II) signal and respiratory movement wave were obtained with a cardioscope (OMP-7201, Nihon Kohden, Japan). BP was measured with a continuous, noninvasive monitoring system (JENTOW-7700, Nippon Colin, Japan). The pulse wave was obtained using a sensor placed on the radial artery at the right wrist. Tonometric BP measurements were calculated using the amplitude of the pulse wave, while the feedback BP of the opposite side was measured by an oscillometric method for correcting the tonometric BP. 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).

Data analysis : The recorded ECG signals were converted to time intervals (RRs) between respective R waves with a pulse counter (98 counter (9), Interface, Japan) and a personal computer (PC 9801 DA, NEC, Japan). The analogue data of SBF and BP were input via an A/D converter (98 AD 12 (16/8)-H, Interface, Japan) into the computer at a sampling time of 1ms (1MHz). SBF, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MAP) data were averaged for each RR by numerical integration. The coefficients of variation of the R-R interval (CV_{R-R}) 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 (MEM) using analytical software developed in our laboratory. The areas of two frequency components of RRs and SBP were measured by integrating a low-frequency component (LF), from 0.04 to 0.15 Hz, and high-frequency component (HF), from 0.15 to 0.50 Hz. The power ratio of LF to HF as LF/HF (L/H Ratio, LHR) was measured. 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.

Procedures : In order to prevent any stress or anxiety, the schedule and procedures were explained to all subjects before beginning the tests. The test room was kept quiet and the temperature was maintained in a range of 25.0±1.0°C. All experiments were performed between 9 a.m. and 11 a.m. Subjects were stopped from taking drugs from the night of the day before the study, and were allowed to have a light meal more than 2 hours before the study. After urination, they stayed in the room for 15 min in a supine

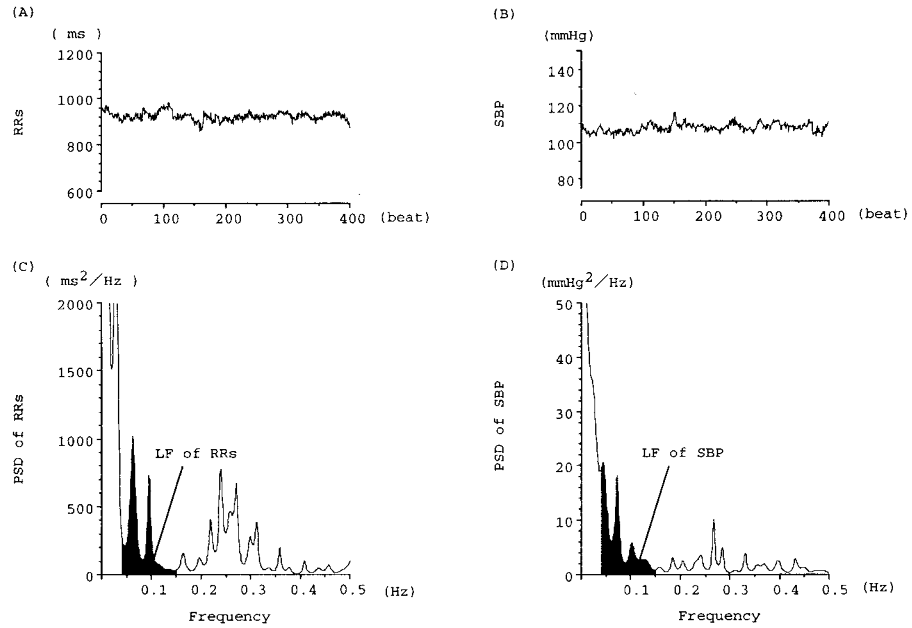

Fig. 1 Raw data and power spectral density.
The raw data of R-R intervals (RRs, A), power spectral density (PSD) curves of RRs (C), systolic blood pressure (SBP, B) and PSD curves of SBP (D). LF, power of low-frequency component of RRs or SBP, variability.

position, and then electrodes for ECG, sphygmomanometer and LDF were put in place. After resting for 5 min and SBF, heart rate, respiratory fluctuations and BP had stabilized, the study was begun. The data were collected for 8 min in the supine position. During the study, the subjects were requested to keep their eyes open to confirm their awake state, to refrain from deep breathing and coughing, and to breathe spontaneously at more than 10 breaths/min (or at 12 cycles/min = 0.2 Hz) if possible.

Statistical analysis : The data were expressed as mean ± S.E. Differences among the three groups were determined by Kruskal-Wallis test, and $p<0.05$ was considered significant. Post-hoc tests were determined by Mann-Whitney test, and $p<0.0167$ was considered significant.

Results

Subjects' characteristics among the groups

Subjects were classified into non-"oketsu" group (n=16), mildly affected group (n=16), and severely affected group (n=16). There was no statistical significance in age, sex and clinical features among the three groups (Table I). All subjects were in the normal range concerning number of blood cell count (Red

Table I Subjects' characteristics among the three groups.

	Non "oketsu" group (n=16)	Mildly affected group (n=16)	Severely affected group (n=16)
Sex (M/F)	8/8	9/7	7/9
Age	47.0±1.3	54.1±3.2	49.7±2.2
Hyperlipidemia	3 (18.8%)	5 (31.3%)	4 (25.0%)
Liver dysfunction	4 (25.0%)	2 (12.5%)	4 (25.0%)
Impaired glucose tolerance	1 (6.3%)	0 (0.0%)	2 (12.5%)

blood cell, white blood cell, platelet), a concentration of serum electrolytes (Sodium, Potassium, Chlorine) and renal function (Blood Urea Nitrogen, Creatinine). 12 patients had hyperlipidemia, and 10 patients had liver dysfunction. But there was no statistical significance in the concentration of serum total cholesterol, triglyceride, glutamic oxalacetic transaminase, and glutamic pyruvic transaminase among the three groups. 3 patients had impaired glucose tolerance (not diabetes mellitus), and their daily profiles of plasma glucose were controlled in the normal range by diet therapy. There was no statistical significance in the concentration of fasting plasma glucose among the three groups.

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 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_{R-R} 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 and CV_{R-R} among the three groups (Fig. 3).

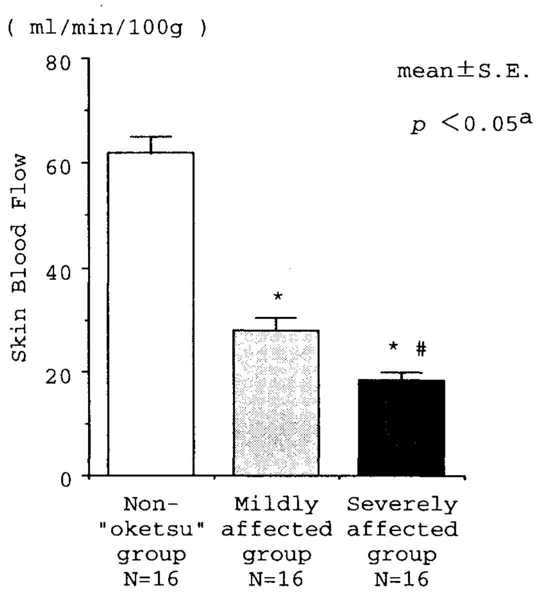

Fig. 2 Comparison of skin blood flow among the three groups.
The values are expressed as mean±S.E. Statistical analysis was done by Kruskal-Wallis test. $p<0.05^a$: significant difference by Kruskal-Wallis test. Post-hoc test was done by Mann-Whithey test. $^*p<0.0167$: significant difference from non-"oketsu"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

And there were also no significant differences in

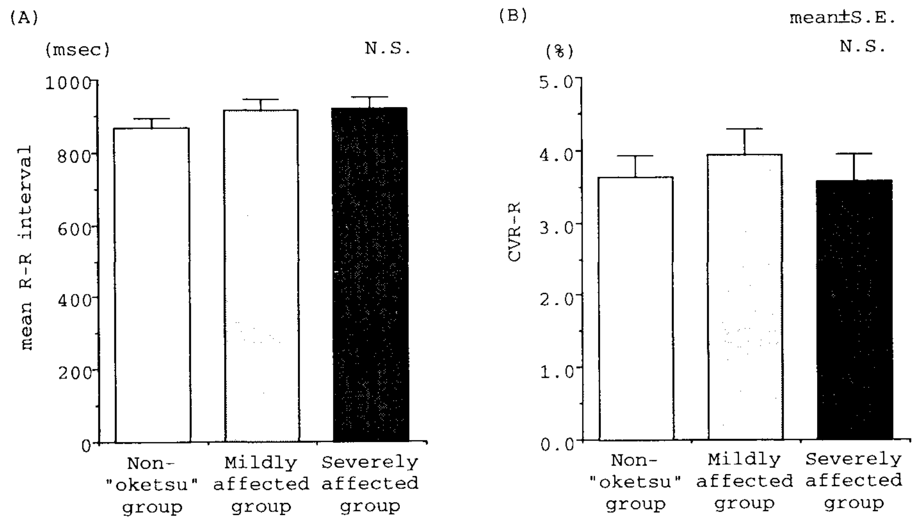

Fig. 3 Comparison of mean R-R intervals and CV_{R-R} among the groups.
(A) and (B) showed mean R-R intervals and CV_{R-R}. The values are expressed as mean±S.E. Statistical analysis was done by Kruskal-Wallis test. N. S. : not significantly different

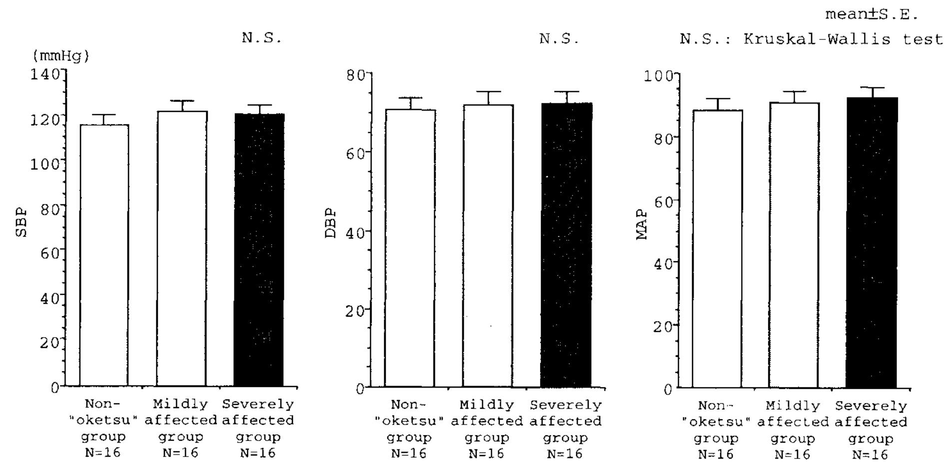

Fig. 4 Comparison of blood pressure among the groups.
The values are expressed as mean±S.E. Statistical analysis was done by Kruskal-Wallis test.
N.S.: no significant difference by Kruskal-Wallis test.

SBP, DBP, and MAP among the three groups (Fig. 4).

Spectral analyses of R-R interval and systolic blood pressure

The low-freguency component of R-R interval (RR-LF) was 57,994.6 ± 7,629.1 msec² 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 msec² 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

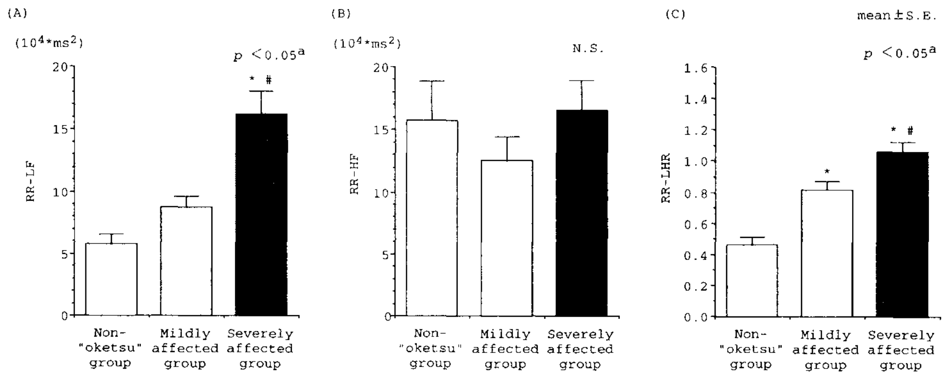

Fig. 5 Comparison of R-R interval variability-related parameters among the three groups.
RR-LF, power of low-frequency component at spectral analysis of R-R intervals (A) ; RR-HF, power of high-frequency component at spectral analysis of R-R intervals (B) ; RR-LHR, power ratio of LF to HF (C). The values 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. *$p<0.0167$: signficant difference from non-"oketsu" group. #$p<0.0167$: significant difference from mildly affected group.

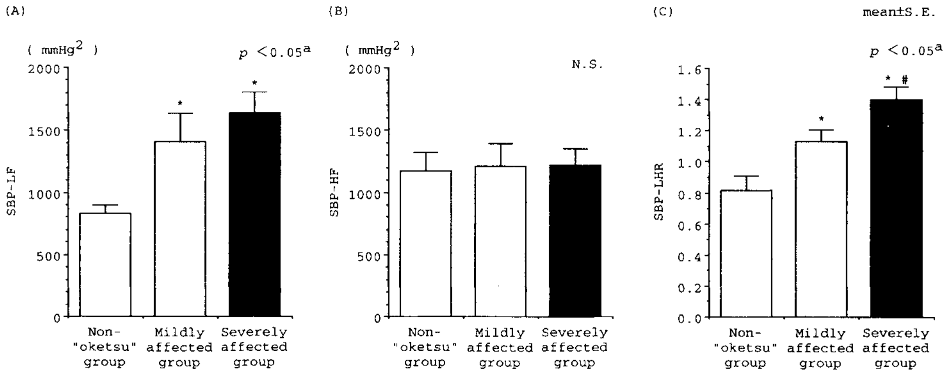

Fig. 6 Comparison of systolic blood pressure variability-related parameters among the three groups.
SBP-LF, power of low-frequency component at spectral analysis of systolic blood pressure (A); SBP-HF, power of high-frequency component at spectral analysis of systolic blood pressure (B) ; SBP-LHR, power ratio of LF to HF (C). The values are expressed as mean±S.E. Statistical analysis was done by Kruskal-Wallis test. $p<0.05^a$: 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.

the mildly affected and the severely affected groups (Fig. 5).

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. 6).

Discussion

Cutaneous microcirculations consist of capillary vessels which supply nutrition and arterio-venous anastomoses which regulate body temperature, and the blood flow of the latter far exceeds that of the former.[17] There are no muscles deep in the palm side of the finger-tip, and a high density of arterio-venous anastomoses richly innervated with sympathetic fibers exists in this area.[17,18] Furthermore, stable and clear flow responses can be obtained in this area for the evaluation of sympathetic vascular function.[17] Therefore, the LDF probe was attached to the palm side of the finger-tip with a probe-holder.

SBF is influenced by diurnal variation of autonomic nervous activity, conscious state,[19] and emotional upsets.[20] 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.[18,21] 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.[22] Therefore, the decrease of SBF in the "oketsu" state is suggested to be due to the increase of skin sympathetic nervous activity.

There was no significant difference in CV_{R-R}. It is known that CV_{R-R} is largely reduced by atropine (parasympathetic muscarinic blocker), and is thought to be a marker of parasympathetic nervous activity. This suggests that there is no influence of cardiac parasympathetic nervous activity in the "oketsu" state.

The results of the spectral analysis of RRs showed that LHR in the "oketsu" state was significantly larger than that of the non-"oketsu" state. Furthere, there was no significant difference in RR-LF between the mildly affected and non-"oketsu" groups, but that in the severely affected group was significantly larger than that in the non-"oketsu" group. There was no significant difference in RR-HF among the three groups. Pagani *et al.* showed that, while at rest, RR-LF decreased with chronic β-blockade. Furthermore, there was no increase during tilting of the supine position with either acute or chronic administration of β-blockade. RR-LF is therefore considered to be associated with sympathetic nervous system function.[18] Japundzic *et al.* reported that RR-LF was reduced by atropine at rest and that this response was mediated by parasympathetic, in addition to sympathetic nervous system function.[19] In addition, RR-HF is thought to be synchronized by respiration. It was reported that RR-HF was reduced by atropine but remained unchanged in response to propranolol, indicating that RR-HF is mediated not by sympathetic, but rather by parasympathetic nervous system function.[20] That is to say, these results indicate that RR-HF is modulated by parasympathetic nervous system function only, but RR-LF is associated with both sympathetic and parasympathetic nervous system function. There is still the question of whether RR-LH is a marker of sympathetic nervous system function. Our spectral analysis of RRs showed that parasympathetic nervous activity did not decrease or increase in the "oketsu" state. This result agrees with that of CV_{R-R}.

The spectral analysis of SBP demonstrated that SBP-LF in the "oketsu" state was significantly larger than that in the non-"oketsu" state. Japundzic *et al.* found that SBP-LF was unchanged by atropine or atenolol but reduced by prazosin, an α-blocker. These data suggested that SBP-LF was mediated by sympathetic nervous system activity, especially α-sympathetic nervous activity, while SBP-HF was independent of the autonomic nervous system.[19] Therefore, the significant increase of SBP-LF suggests that α-sympathetic nervous activity increases in the "oketsu" state.

Conclusion

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

和文抄録

瘀血病態と自律神経活動との関連性を明かとするために，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。患者 48 名を瘀血診断基準により非瘀血群，軽度瘀血群，重度瘀血群の 3 群に分類し，自律神経活動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）は瘀血病態の重症化とともに減少した。CV_{R-R}，R-R 間隔高周波数成分については 3 群間に有意差を認めなかったが，収縮期血圧低周波数成分（SBP-LF）で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。SBF は交感神経活動にともない変化し，また，SBP-LF は α-交感神経活動と関連するとされている。今回の結果は，瘀血病態では α-交感神経活動が亢進状態にあり，それにともない SBF が減少していることを示唆するものである。

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