

Effect of Keishi-bukuryo-gan on autonomic nervous activity

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Abstract

In order to confirm any effects of Keishi-bukuryo-gan (KBG) on the autonomic nervous system, 8 healthy volunteers were evaluated with laser Doppler flowmetry and spectral analysis of the R-R intervals (RR) and systolic blood pressure (SBP). After evaluation of the "oketsu" score and measurement of the electrophysiological parameters (PRE), each subject was administered KBG or hot water. The same parameters were re-measured at 15, 30, 45, 60 and 90 minutes after their administration to each subject. Changes in the parameters after the administration of KBG or hot water were investigated compared with PRE. In the experiment with KBG, skin blood flow (SBF) was increased at 90 min, although it had been significantly decreased at 15 min. By spectral analysis, SBP- low frequency (LF) and SBP- low to high frequency ratio (L/H) were initially increased at 15 min, and then were significantly decreased at 60 and 90 min. As for hot water, there were no significant changes in any of the parameters. It is known that SBF changes with sympathetic nervous activity, and SBP-LF and SBP-L/H reflect sympathetic nervous activity. These results suggest that KBG has certain effects on sympathetic nervous activity.

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

Abbreviations BP, Blood pressure; ECG, electrocardiogram; KBG, Keishi-bukuryo-gan; OS, oketsu score; RR, time intervals between respective R waves; RR-HF, high frequency component of R-R interval; RR-L/H, power ratio of low frequency component of R-R interval to high frequency component of R-R interval; RR-LF, low frequency component of R-R interval; SBF, skin blood flow; SBP, systolic blood pressure; SBP-HF, high frequency component of systolic blood pressure; SBP-L/H, power ratio of low frequency component of systolic blood pressure to high frequency component of systolic blood pressure; SBP-LF, low frequency component of systolic blood pressure.

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 the microcirculation, based on observations of blood flow of bulbar conjunctiva, and also with hemorheological abnormalities such as an elevation

of blood viscosity, acceleration of erythrocyte aggregability, and a deterioration of erythrocyte deformability.²⁻⁵⁾ In addition, we recently reported that the "oketsu" state is intimately concerned with autonomic nervous activity.^{6,7)}

Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan, KBG) is one of the most important Kampo prescriptions, and has been used clinically for "oketsu" (the blood stasis syndrome). KBG exerts an improving effect on the microcirculation of bulbar conjunctiva in humans,⁸⁾ an improving effect on hemorheology in humans,⁴⁾ an inhibitory effect on arteriosclerosis in the rabbit,⁹⁾ and a

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protective effect against vascular endothelial disorder in the spontaneously hypertensive rat.¹⁰⁾ However, an effect of KBG on the autonomic nervous system has not been confirmed.

In this study, KBG decoction was administered to healthy volunteers, and electrophysiological parameters were measured to clarify the effects of KBG on autonomic nervous activity.

Materials and Methods

Substances: KBG, consisting of five medicinal plants: Cinnamomi Cortex 4.0 g, Paeoniae Radix 4.0 g, Persicae Semen 4.0 g, Hoelen 4.0 g, Moutan Cortex 4.0 g, was prepared as a 100-ml decoction (37°C) just before each experiment. As a non-active control, 100 ml of hot water (37°C) was used.

Subjects: Eight healthy male volunteers aged 20-24 years (mean 21.9 years), with no previous history of neurological and/or cardiovascular diseases, were the subjects of our study. They were recruited from the student population of our university. None of them was a habitual smoker or coffee drinker, and they were instructed to avoid these products on the day of the study. Written informed consent was obtained, and this study complied with the Declaration of Helsinki.

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.

The electrophysiological parameters of skin blood flow (SBF), R-R intervals (RR), systolic blood pressure (SBP), high frequency component of R-R interval (RR-HF), power ratio of low frequency component to high frequency component of R-R interval (RR-L/H) and low frequency component of systolic blood pressure (SBP-LF) were employed for the evaluation of autonomic nervous activity. These parameters were measured by a method similar to that of the previous study.^{7,8)} 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 converted to time intervals between respective R waves (RR) with a pulse counter (98 counter (9), Interface, Japan) and a personal computer (PC9801DA, NEC, Japan). Data of SBF and SBP were averaged for each RR by numerical integration. Spectral analysis of RR 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 RR 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.

Medication Protocol: KBG or hot water was given to each individual subject on separate days at an interval of more than one week, and all experiments were performed between 9 am and 11 am. Subjects were allowed to have a light meal more than 2 hours before the study. Evaluation of OS and measurement of the parameters were done before administration of KBG or hot water (PRE), and each subject was administered KBG or hot water. The same electrophysiological parameters were re-measured at 15, 30, 45, 60 and 90 minutes after administration of KBG or hot water in each subject.

Statistical analysis: To measure quantitatively the responses of each parameter, the respective results of the parameters at each time was expressed as a percentage to PRE, with each result of the parameters in PRE being expressed as 100%. Data were presented as mean $\pm$ S.D. The responses were statistically tested using ANOVA followed by Bonferroni's least significant difference test.

Results

Subject characteristics

For this study, 8 male subjects (range 20-24 yrs, 21.9 ± 1.6 yrs) were employed. The characteristics of each subject are listed in Table I. In all subjects, OS did not change with the experiment of KBG or hot water.

Effects of Keishi-bukuryo-gan and hot water on parameters

The actual values of the parameters at each time are shown in Table II-1, 2, and the time course of the percentage against PRE for each parameter is shown in

Table I Subject characteristics

Subject No.	Age (years)	Body Height (cm)	Body Weight (kg)	"Oketsu" Score with Keishi-bukuryo-gan	"Oketsu" Score with Hot water
1	20	173.5	63.5	2.5	2.5
2	23	176.5	74.5	2.5	2.5
3	20	168.0	62.0	11.0	11.0
4	21	171.5	68.0	17.0	17.0
5	24	165.5	59.5	25.0	25.0
6	22	178.0	75.5	32.0	32.0
7	24	172.0	72.0	48.0	48.0
8	21	175.5	84.5	53.5	53.5

Table II-1 Time course of subject parameters by Keishi-bukuryo-gan or hot water (RR, SBP, SBF)

Parameter	Subject No.	Keishi-bukuryo-gan						Hot Water					
		PRE	15min	30min	45min	60min	90min	PRE	15min	30min	45min	60min	90min
RR (msec)	1	992.6	967.3	963.6	965.1	996.1	996.0	978.9	936.4	1001.2	935.1	1006.8	932.0
	2	769.8	779.8	771.7	776.3	774.6	773.3	767.6	790.6	740.1	734.4	737.1	784.8
	3	890.6	906.0	861.0	891.6	896.3	895.0	884.8	906.9	893.3	899.0	897.2	886.4
	4	839.5	851.5	812.7	844.5	841.0	812.1	824.0	782.9	838.7	836.4	786.3	836.0
	5	1012.1	1021.1	1029.1	1023.3	1019.2	1022.4	1009.2	1025.9	1031.9	1019.9	971.7	978.5
	6	954.3	964.7	970.3	958.0	972.9	967.2	945.7	913.5	966.9	953.4	971.1	915.8
	7	727.5	708.6	708.4	738.8	706.2	735.9	747.3	716.9	764.7	755.7	747.7	766.4
	8	999.1	1017.5	999.2	1017.2	1009.6	967.6	1023.4	986.2	1023.6	1053.3	986.8	980.0
SBP (mmHg)	1	113.5	113.7	113.7	113.9	110.3	113.9	116.4	112.7	112.0	112.9	112.6	111.4
	2	142.4	144.6	144.6	138.7	144.2	138.5	141.6	136.3	136.1	135.8	134.9	144.2
	3	102.9	100.8	99.9	99.6	100.7	100.2	101.8	98.1	102.0	98.2	103.0	103.1
	4	116.7	113.7	114.1	117.3	117.2	114.2	114.8	110.0	115.1	116.6	117.0	110.0
	5	108.5	105.7	105.2	108.9	110.3	109.2	111.1	112.3	107.7	114.1	112.9	112.2
	6	120.7	118.0	118.1	122.5	118.0	117.7	124.6	125.4	120.6	126.7	120.7	118.7
	7	115.3	111.9	112.9	112.6	111.9	115.7	119.3	119.6	114.9	115.5	115.4	122.7
	8	104.7	102.4	105.5	105.6	101.7	102.2	103.4	105.6	105.0	98.6	104.2	106.3
SBF (ml/min/100g)	1	60.0	60.7	58.5	60.1	60.5	58.2	61.9	56.4	63.0	60.0	63.0	66.4
	2	48.6	47.1	49.3	47.3	47.0	48.9	48.0	44.0	49.4	48.9	48.9	52.5
	3	56.4	57.1	55.1	54.8	56.8	56.6	55.8	52.9	53.4	54.1	57.1	56.2
	4	75.5	76.5	75.9	76.1	76.6	76.5	74.1	66.8	75.3	71.5	75.3	79.5
	5	24.1	24.3	24.2	23.4	23.6	24.2	24.6	24.4	24.6	23.4	25.2	26.9
	6	37.1	37.6	36.2	37.3	36.0	36.4	38.0	35.4	39.1	38.6	39.2	41.7
	7	12.6	12.8	12.6	12.3	12.8	12.3	13.0	11.9	13.2	12.4	13.1	13.5
	8	23.2	23.3	22.5	22.4	23.6	23.5	23.9	23.1	24.1	22.8	24.2	25.2

PRE, before administration of Keishi-bukuryo-gan or hot water; RR, time intervals between respective R waves; SBP, systolic blood pressure; SBF, skin blood flow.

Fig. 1.

In the experiment with KBG, SBF was increased at 90 min, although at 15 min it was decreased significantly compared with PRE. There were no significant changes in RR and SBP. However, spectral analysis of these parameters revealed that SBP-LF was initially increased at 15 min, and then decreased significantly at 60 and 90 min in comparison with PRE. As for hot water, there were no significant changes in any of the parameters.

Discussion

RR and SBP did not change by KBG in this study, in line with the report that KBG had no consequential

influence on either cardiac function or large vessels.¹¹⁾ This suggests that KBG has no direct effect on macrohemodynamics.

SBF was decreased at 15 min, and increased significantly at 90 min compared with PRE in this study. This result suggests that KBG has an effect on the microcirculation of the periphery of extremities. 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, a change in SBF indicates a change in sympathetic nervous activity, and thus

Table II-2 Time course of subject parameters by Keishi-bukuryo-gan or hot water (RR-HF, RR-L/H, SBP-LF)

Parameter	Subject No.	Keishi-bukuryo-gan						Hot Water					
		PRE	15min	30min	45min	60min	90min	PRE	15min	30min	45min	60min	90min
RR-HF (msec ²)	1	115999	113498	112614	117901	112631	116057	103182	105390	104202	105608	105294	103504
	2	53505	52142	52242	53907	54555	54536	41091	39838	42271	39150	41195	41799
	3	112682	109491	113646	109121	113328	114818	97243	92907	100045	98663	93065	93872
	4	156042	152912	150980	151076	157941	151604	180765	184789	172653	182145	183786	172137
	5	152204	148537	153234	147434	154019	153819	123041	125197	118030	126169	117995	125873
	6	290430	293765	281780	293402	281571	283718	348279	332690	336477	336173	357824	350149
	7	112332	109143	112635	113644	109555	109249	85267	82490	81158	85713	81376	86226
	8	287453	280148	278764	289466	288473	289174	197082	202640	200375	202084	202953	198339
RR-L/H (msec ²)	1	0.23	0.22	0.22	0.23	0.23	0.22	0.22	0.23	0.22	0.22	0.22	0.23
	2	0.28	0.27	0.28	0.28	0.27	0.28	0.28	0.30	0.26	0.29	0.27	0.27
	3	0.62	0.63	0.62	0.63	0.62	0.63	0.61	0.61	0.59	0.58	0.65	0.65
	4	0.55	0.53	0.55	0.56	0.56	0.55	0.55	0.55	0.59	0.55	0.55	0.55
	5	0.85	0.82	0.82	0.82	0.85	0.83	0.85	0.80	0.90	0.79	0.90	0.80
	6	0.56	0.57	0.54	0.56	0.56	0.55	0.55	0.55	0.57	0.57	0.55	0.56
	7	1.45	1.42	1.47	1.42	1.41	1.46	1.43	1.42	1.45	1.37	1.44	1.43
	8	0.80	0.78	0.77	0.78	0.81	0.81	0.79	0.78	0.79	0.74	0.74	0.76
SBP-LF (mmHg ²)	1	623	624	624	604	631	607	575	588	589	587	568	551
	2	714	728	719	698	698	694	555	582	568	556	543	548
	3	962	935	973	935	936	938	894	955	858	850	853	850
	4	1095	1104	1112	1104	1103	1103	1424	1550	1433	1466	1374	1303
	5	889	892	869	893	870	896	744	782	714	712	720	688
	6	861	863	877	875	865	838	1118	1151	1124	1079	1053	1040
	7	1947	1964	1982	1962	1900	1963	1492	1558	1520	1534	1441	1389
	8	1156	1156	1131	1166	1158	1129	792	845	806	802	733	788

PRE, before administration of Keishi-bukuryo-gan or hot water; RR-HF, high frequency component of R-R interval; RR-L/H, power ratio of low frequency component to high frequency component of R-R interval; SBP-LF, low frequency component of systolic blood pressure.

the changes in SBF after KBG administration suggest that KBG possesses an effect concerned with sympathetic nervous activity.

In regard to autonomic nervous activities, SBP-LF after the administration of KBG was significantly changed compared with PRE, whereas there were no significant changes in RR-HF and RR-L/H. Power spectral analysis of RR and SBP variability is a widely accepted, useful and a noninvasive method for indirect evaluation of autonomic nervous activity. It is considered that RR-HF reflects parasympathetic nervous activity, and the low frequency component of the R-R interval and RR-L/H are regulated by both sympathetic and parasympathetic nervous activity.¹⁴⁻¹⁷⁾ On the other hand, SBP-LF was reported to reflect α -sympathetic nervous activity, although the high frequency component of systolic blood pressure was considered not to be concerned with autonomic nervous activities.^{15,17)} In light of these observations, the present results suggest that KBG has an effect on α -sympathetic nervous activity, although it does not have an effect on cardiac parasympathetic nervous activity. This result is in agreement with the findings regarding SBF.

SBF was increased at 90 min after the administra-

tion of KBG, and SBP-LF was decreased at 60 and 90 min post KBG compared with PRE. In our previous report, it was clarified that sympathetic nervous activity had a positive correlation with OS, and this significant correlation was maintained even after alterations in the "oketsu" state.^{6,7)} On the basis of this observation, Kampo prescriptions for "oketsu" can be expected to have an inhibiting effect on sympathetic nervous activity.

However, the results at 15 min after KBG administration, a decrease in SBF and increase in SBP-LF, suggest quite the opposite, namely, that KBG has an enhancing effect on sympathetic nervous activity. The taste of KBG itself might possibly be related to this enhancing effect, because some subjects had in fact immediately complained about the terrible taste of KBG after its administration. But the complete details are unclear, and there remain various problems to be solved, inclusive of the evaluation of the mode of action of KBG on sympathetic nervous activity.

It had not been clarified whether or not KBG has an effect on the autonomic nervous system. Nevertheless, this study did confirm that KBG has an effect on sympathetic nervous activity.

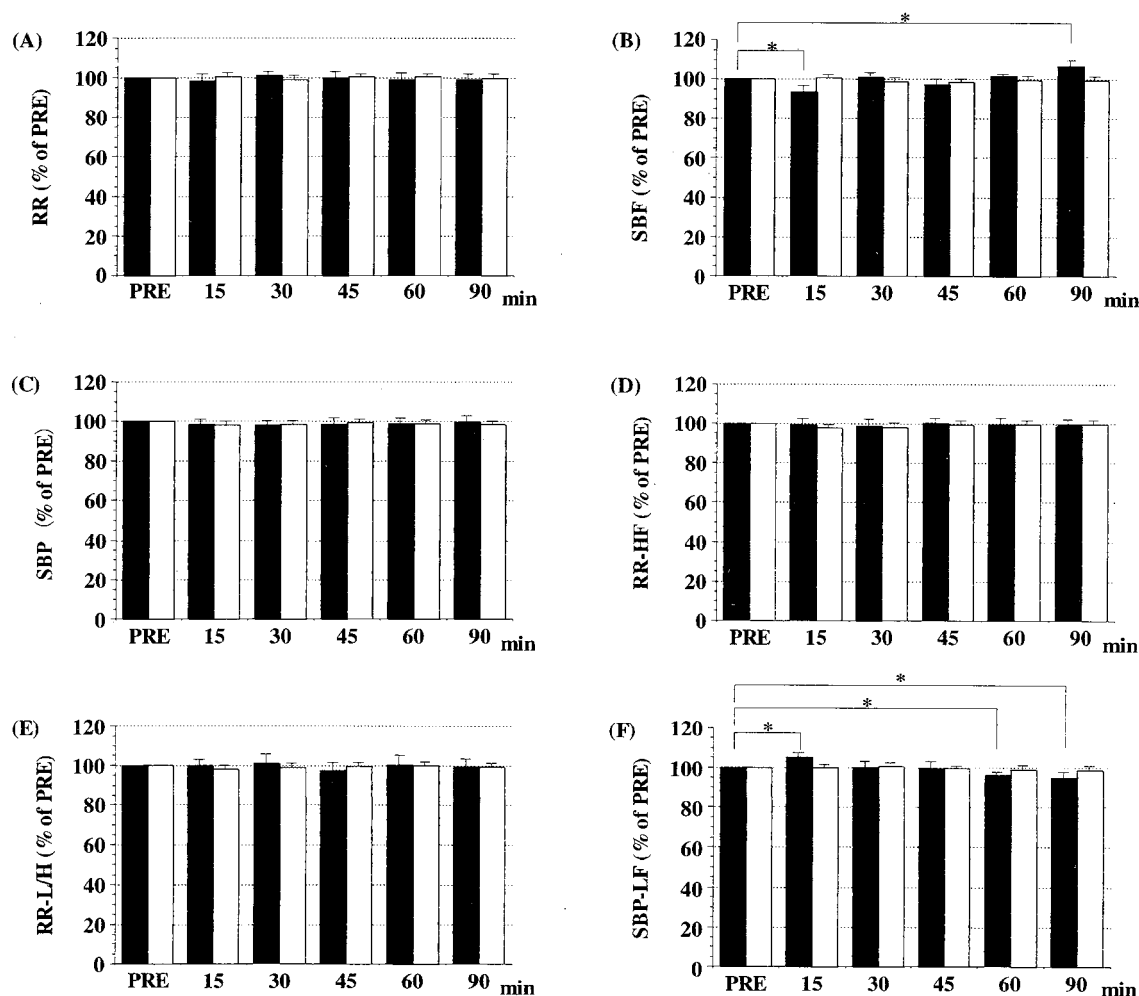


Fig. 1 Time course of parameters by Keishi-bukuryo-gan and hot water in normal subjects. (A)~(G) show the time courses of RR (A), SBF (B), SBP (C), RR-HF (D), RR-L/H (E), SBP-LF (F) on Keishi-bukuryo-gan (closed columns) and hot water (open columns). (* $p < 0.007$ versus PRE)

■ Keishi-bukuryo-gan
□ Hot Water

Conclusion

By using the power spectral analysis of RR and SBP variability, it was confirmed that KBG has an effect on the sympathetic nervous activity.

和文抄録

桂枝茯苓丸の自律神経活動に対する効果を明らかにするために、レーザー Doppler 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。健康者 8 名を対象とし、自律神経活動の変化を桂枝茯苓丸料と微温湯において統計学的に解析した。桂枝茯苓丸により、皮膚血流量 (SBF) は前値に比較して一旦 15 分後に減少し、

90 分後に有意に増加した。収縮期血圧低周波成分 (SBP-LF)・収縮期血圧成分比 (SBP-L/H) は前値に比較して一旦 15 分後に増加し、60 及び 90 分後に有意に減少した。微温湯では有意な変化はみられなかった。SBF は交感神経活動にともない変化し、SBP-LF 及び SBP-L/H は交感神経活動に関連するとされている。今回の結果は、桂枝茯苓丸が交感神経活動に対する作用を有していることを示唆するものである。

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