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The effects of Keishi-bukuryo-gan on the hemodynamics in human subjects

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Abstract

The effect of Keishi-bukuryo-gan on hemodynamics was investigated in five patients with mild oketsu state and six healthy volunteers as control. By using the ear-oximeter dye-dilution procedure, the values of cardiac output were observed, and mean blood pressure, heart rate, and peripheral vascular resistance were also measured before and after the administration of Keishi-bukuryo-gan (6.0 g of pills with hot water, 200 ml). The results showed no significant difference in any of the parameters following the administration of Keishi-bukuryo-gan between the patient and control groups, indicating that Keishi-bukuryo-gan has no consequential influence on either cardiac function or large vessels. Taking this together with our previous data, Keishi-bukuryo-gan was demonstrated to improve the blood flow of the microcirculation without any changes in macrohemodynamics.

Key words Keishi-bukuryo-gan (Keisi-bukuryô-gan), hemodynamics, cardiac output, oketsu state, microcirculation.

Abbreviations CI, cardiac index ; CO, cardiac output ; HR, heart rate ; MBP, mean blood pressure ; oketsu (Yu-Xue), 瘀血 ; PVR, peripheral vascular resistance ; Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸.

Introduction

Recently some of the important concepts of pathophysiology in Kampo medicine have been viewed in the light of modern medicine.[1-4] One of these is the condition of illness which is commonly referred to as "Oketsu," the stagnation of blood, wherein blood in Kampo medicine has the meaning of a red coloured component of the fluid elements of the body. There have been several reports so far which revealed the beneficial effects of a series of Kampo formulas classified as "Ku-oketsu-zai" anti-blood stagnation agents on the microcirculation,[5,6] and especially concerning the popular formula Keishi-bukuryo-gan both in the oketsu state and non-oketsu state[7] in intact human subjects. These drugs are believed to exert their pharmacological effects on the microcirculation mainly through decreased blood viscosity,[8] increased blood flow rate or microvessel modulation,[7] hence by way of an increased regional blood supply. On the other hand, reports which discussed the effects of these drugs on hemodynamics such as cardiac output, peripheral vascular resistance, blood pressure and heart rate are very few, and none, seemingly, have appeared with sufficient detail. This dearth of more information must be at least partly due to the methodological difficulties involved in the measurement of cardiac output.

The present study was undertaken in an attempt to clarify the effects of Keishi-bukuryo-gan on hemodynamics by using the ear-oximeter dye-dilution method.[9]

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Subjects and Methods

Subjects : All participants gave their informed consent and were assessed in terms of oketsu grade according to the criteria of Oketsu Score[10] (Terasawa) in advance. Two groups of subjects were studied : The normal control group consisted of six normal healthy male volunteers, students of Toyama Medical and Pharmaceutical University, aged 20–23 years, with oketsu scores less than 20. The oketsu group consisted of five patients (two males, three females) who were hospitalized at the university hospital (Department of Japanese Oriental Medicine, Toyama Medical and Pharmaceutical University) during the study period. None of the patients suffered from apparent cardiovascular disorders, but their oketsu scores ranged from 21 to 32, the scores of a mildly affected oketsu state. All the characteristics of the subjects are listed in Table I.

Because of the peculiarity of the ear-oximeter dye-dilution method, which requires a suitably shaped ear auricle and smooth skin so that the ear detector can be attached firmly to the auricle, subjects whose three consecutive values of cardiac output varied larger than 500 ml and/or whose dye-dilution curves were different from normal were eliminated from this study.

Substances : Keishi-bukuryo-gan prepared by the hospital pharmacy of the Toyama Medical and Pharmaceutical University was used in this study. Six grams of Keishi-bukuryo-gan pills consisted of 3.0 g of honey (*Apis indica* RADOSZKOWSKI, China) and the following five medicinal plants : Cinnamomi Cortex (*Cinnamomum cassia* BLUME, China) 0.6 g, Poria (*Poria cocos* WOLF, North Korea) 0.6 g, Moutan Cortex (*Paeonia moutan* SIMS, China) 0.6 g, Persicae Semen (*Prunus persica* BATASCH, North Korea) 0.6 g and Paeoniae Radix (*Paeonia lactiflora* PALL., North Korea) 0.6 g.

Indocyanine-green (Diagnogreen, Daiichi Seiyaku Co., Ltd., Tokyo) was used as the indicating substance, which was resolved in the dilution liquid at a concentration of 5 mg/ml before use.

Measurement of hemodynamic parameters : For hemodynamic evaluation, heart rate (beats/min), blood pressure (mmHg) and cardiac output (l/min) were measured as basic parameters in the following ways. After overnight fasting, at 9 : 00 a.m. each subject lay down in a supine position, a tourniquet was applied to the right brachium for continuous monitoring of blood pressure with oscillation-based automatic blood pressure equipment (STBP-680, Nippon Colin Co., Ltd., Nagoya), the heart rate was monitored by electrocardiogram taken with leg leads and an intravenous line was established with an 18G plastic needle into the right antecubital vein for the injec-

Table I The characteristics of the subjects.

	Name	Sex	Age (years)	O-S	Ht (%)	Height (cm)	Weight (kg)	Diagnosis
1	NM	M	21	12	44	173	70	healthy
2	SH	M	20	14	43	175	71	healthy
3	YS	M	23	14	41	175	60	healthy
4	MY	M	20	16	48	168	55	healthy
5	OS	M	21	16	38	163	50	healthy
6	HY	M	22	20	46	165	58	healthy
7	FT	F	60	21	37	152	49	D.M.
8	KT	M	48	26	47	164	69	F.L.
9	MY	M	41	28	43	170	67	B.P.
10	IS	F	16	30	38	160	68	Obesity
11	OK	F	66	32	37	159	47	Neurosis

O-S, Oketsu Score ; Ht, hematocrit ; D.M., diabetes mellitus ; B.P., back pain ; F.L., fatty liver.
Cases 1–6 : control group (oketsu score less than 20).
Cases 7–11 : oketsu group (oketsu score more than 21).

tion of dye and flushing fluid. For the determination of cardiac output, an earpiece dye-dilution cardiac-output computer (Earpiece densitometer MLC-4100, Nihon-Kohden, Tokyo) was used. In prepearation for measurement, a small dose of bitter vasodilator ointment (Finalgon, Tanabe Seiyaku Co., Ltd., Osaka) for hyperemization was applied to the appropriate portion of the auricle and rubbed in for 10 min and then a slightly heated earpiece was attached there firmly but gently for continuous detection of the dye-dilution curve.

In this study, cardiac output was measured by the following technique : 1 ml of 0.5% indocyanine green test solution was infused intravenously and quickly flushed with 10 ml of 5% dextrose in water, and the dye-dilution curve was traced for 1 min thereafter. The output was then calculated by the computer in the instrument according to "Hamilton's method."[16] By the dye-dilution method, the average concentration of dye during the initial circulationis used to calculate the relationship between the quantity of dye injected and the volume of blood which flows through the heart, and hence the cardiac output. The equation given by Hamilton expressing this relation is : $CO=I/\int c(t)\,dt$, in which CO stands for cardiac output, I represents the amount of dye injected (mg), c (t) equals the average concentration of the dye (mg/ml) during the primary curve, and t equals the duration of the primary curve (sec) (Fig. 1). All the basic parameters, cardiac output, heart rate and blood pressure, were taken as average of three consecutive values which were determined successively at five minutes intervals throughout the whole study. Mean blood pressure (MBP, mmHg) was calculated as the sum of one-third the systolic plus two-thirds of the diastolic pressures. The standard formula used to calculate peripheral vascular resistance (PVR) was : $PVR=MBP/CO\times 80$ (dyne・sec/cm^{-5}). The cardiac index (CI, $l/min/m^2$) was calculated by dividing the CO value by the body area of the subject.

Medication protocol (1) Control study : After the baseline hemodynamic studies in the normal group, the subjects were each made to drink 200 ml of hot water (30℃). Thirty minutes later, the hemodynamic studies were again similarly repeated to identify any possible obscure side effects that may be induced by this measuring procedure itself.

(2) Medication studies : After the baseline hemodynamic studies, the subjects in the normal control group received 6.0 g of Keishi-bukuryo-gan with 200 ml of hot water (30℃). Thirty minutes after the ingestion of the test dose, the hemodynamic studies were repeated as previously. Then, for the patients in the oketsu group, the same protocol was applied.

Statistical method : The grouped data are presented as mean ± standard deviation. The variations in parameters between the values before and after the test dose ingestion were analyzed by the Student's t-test. The level of statistical significance was defined as $p<0.05$.

Results

One of the typical dye-dilution curves of a

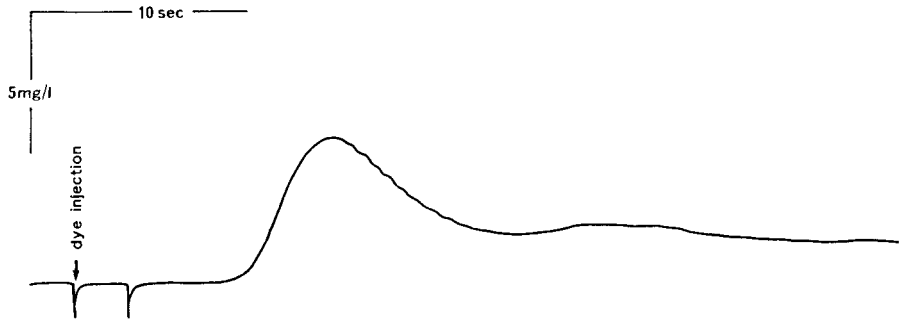

Fig. 1 A normal dye-dilution curve obtained by ear densitometer.

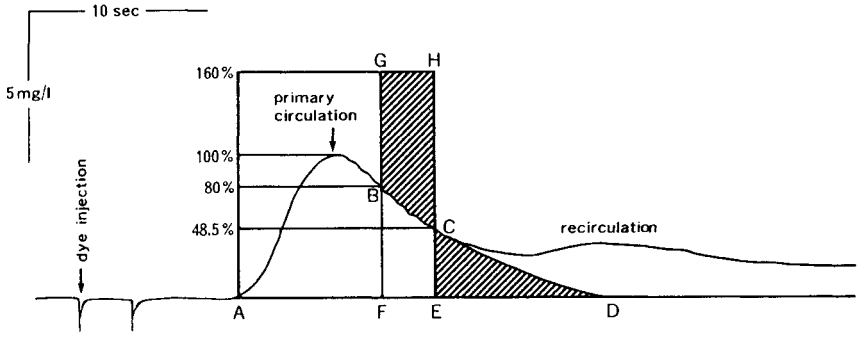

Fig. 2 Hamilton's method for the calculation of the average dye concentration.
The average concentration of the injected dye in the initial circulation is calculated according to Hamilton's method where the extrapolated latter part of the initial circulation which is mixed with the secondary circulation will be measured by counting the area BCHG that is equal to DEF.

normal pattern is illustrated in Fig. 1. The normal pattern has two plateaus, the first representing the initial circulation of the dye, the second recirculation. The average dye concentration in the primary circulation can be calculated by integrating the area in the first plataeu, the right margin of which is determined by crossing with the horizontal line of 48.5% in height of the plateau, so that the area of BCHG equals that of CED or the extrapolation of the initial plateau to zero concentration, as illustrated in Fig. 2.

Because of the initial elimination of such potential study subjects as those showing unstable and/or uncertain figures in terms of the determination of cardiac output, all the output studies examined showed the normal configuration.

Hemodynamic studies

1) *The results of the control trial in the normal group with hot water loading*

Heart rate (HR, beats/min) in the baseline was 66±10 (mean±s.d.), while the value obtained after the water load was 65±10, indicating no significant difference between the two (Fig. 3a ○). Mean blood pressure (MBP, mmHg) showed a slight increase, though not significant, as the baseline value was 86±7 compared to load value of 92±7 (Fig. 3b ○). Cardiac index (CI, l/min/m^2) was 4.3±0.7 before the load and 4.7±0.8 after, showing a slight but not significant increment (Fig. 3c ○). Peripheral vascular resistance (PVR, dyne·sec/cm^{-5}) showed a minor insignificant decrease between the values of 968.3±163.1 before and 955.3±129.1 after (Fig. 3d ○).

2) *The results of the medication trial in the normal group with administration of Keishi-bukuryo-gan*

Heart rate (HR) showed no change in the values between before and after the test drug administration, 66±7 and 66±6 respectively (Fig. 3a ●). Mean blood pressure (MBP) values before and after were 86±9 and 87±9, respectively, with no remarkable changes (Fig. 3b ●). Cardiac index (CI) was 4.1±0.7 both before and after (Fig. 3c ●). Peripheral vascular resistance (PVR) was 1059.2±243.0 before and 1017.2±176.4 after, a slight but not significant decrease (Fig. 3d ●).

3) *The results of the medication trial in the oketsu group with administration of Keishi-bukuryo-gan*

Heart rate (HR) changed little with values before and after, 67±8 and 66±8, respectively (Fig. 4a ●). Mean blood pressure (MBP) before was 87±13, and after 88±13, showing very little change (Fig. 4b ●). Cardiac index (CI) was 3.8±1.1 before and 3.9±0.9 after, revealing no significant difference (Fig. 4c ●). Peripheral vascular resistance (PVR) values before and after were 1223.8±129.9 and 1235.0±184.7, without significant variance (Fig. 4d ●).

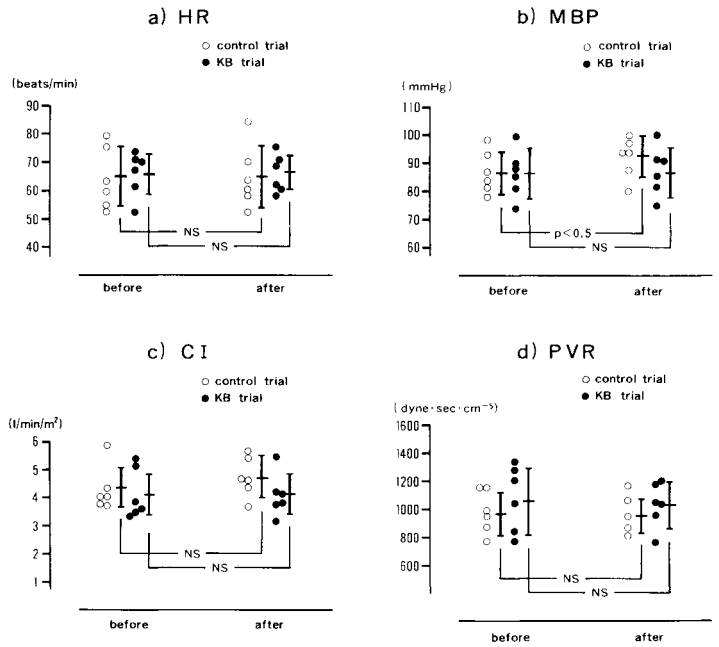

Fig. 3 Hemodynamic changes in the non-oketsu group.
The results of the hemodynamic parameters in the normal group are expressed in a), b), c) and d) showing the results of HR, MBP, CI and PVR respectively. Open circles express the average values of each subject in the non-oketsu group before and after the hot water load as a control test. Closed circles show the average values of each subject in the oketsu group before and after the Keishi-bukuryo-gan administration as a medication trial.

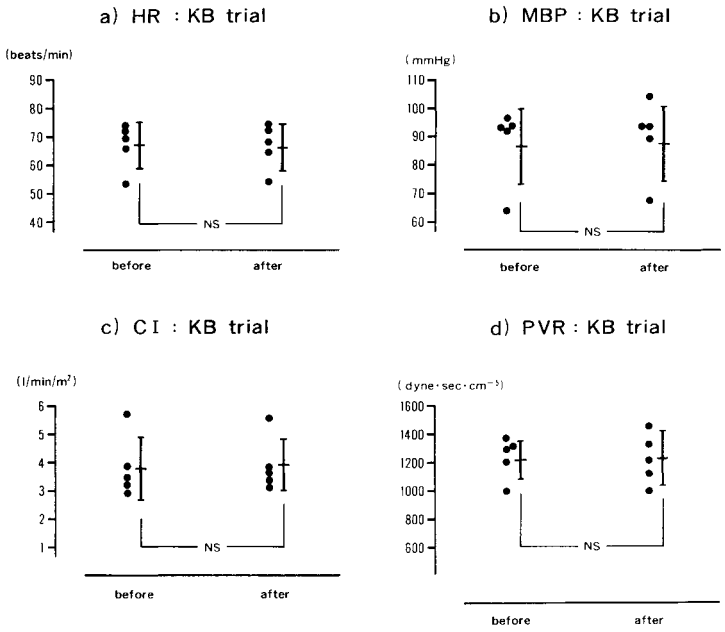

Fig. 4 Hemodynamic changes in the oketsu group.
The hemodynamic changes, HR, MBP, CI and PVR, in the oketsu group are expressed in a), b), c) and d) respectively. Closed circles show the alteration in parameters in each subject before and after the Keishi-bukuryo-gan administration.

Discussion

The vasculature in the body consists of arteries and veins of various sizes which are connected to each other by a network of capillaries. Blood circulation in the network of microvessels invisible to the naked eye because of its small size is often referred to as "microcirculation."[12]

"Oketsu" or blood stagnation, one of the unique yet important entities in both the pathological and physiological concepts of Kampo medicine, has been enthusiastically investigated scientifically by many researchers,[2,3,6-8] and advancements in modern science are now providing explanations for some of the processes in this field. Recently quantitative measurement techniques for microcirculation have become greatly advanced, and can be applied to the intact human being.[3,13] Data obtained recently by Itoh *et al.*[7] from the direct observation of microvessels in the conjunctiva of the eye ball of both normal persons and oketsu state patients with a sophisticated video-microscope system revealed a number of abnormalities in the microcirculation. A series of Kampo formulas, which were suggested as being useful against blood stagnation illness, especially Keishi-bukuryo-gan, were seen to prove their efficacy through the improvement of microcirculation.[2,5,7]

Effects of these formulas on hemodynamics in "macrocirculation," *i.e.*, on cardiac functions, vasodilation, or vasoconstriction of large vessels, however, have hardly been explored. This may have been due to difficulties involved in carrying out the procedures for measuring cardiac output. Numerous methods used clinically so far, such as the direct Fick procedure, the dye-dilution method with cuvette oximeters,[14] and the thermodilution method by Swan-Ganze flow-tipped catheters,[15] were more or less technically difficult, time-consuming, or invasive for the examinee. RI angiography using ^{99m}Tc *in vivo* labelled red cells is now widely available at the daily clinical level, and is reported to provide closely comparable data to that obtained by the Swan-Ganz catheter procedure,[16] but it is costly and limited in usage to certain facilities.

The earpiece dye-dilution method that we applied in this study has its origin in the 1940s,[14] and has undergone successive improvements since then so as to be sufficiently credible, easy to use repeatedly at bed side, and the least invasive in today's clinical use.[9] The progressive improvement in the ischemic dual light photometric technique for more accurate detection of dye concentration in blood in the ear auricle by Sekilj in 1958, Reed-Wood in 1967, and Yamaguchi and Katori in 1977, the mechanism of which was applied to the present cardiac output computer model used in this study, have made the greatest contribution for the establishment of measurement accuracy in the earpiece dye-dilution method.

The results of the present trial, first with water load in the normal group, showed no significant change in any of the hemodynamic parameters. This proved that the earpiece dye-dilution method *per se* has no significant stimulation effect, though an examinee would possibly be under some stress during the hemodynamic examination with his ear heat-flushed by the biting ointment for hyperemization and the mildly heated ear oximeter.

The acute oral load of Keishi-bukuryo-gan in normal subjects as well as patients with a mild oketsu state induced no definite alteration in hemodynamics in this study. These data indicated that the formula has no direct effect either on the heart or on large vessels. The pharmacological properties of Keishi-bukuryo-gan suggest that the formula is neither ino-, chrono-tropical for the heart nor vasodilative for arterioles. No objective autonomic signs like flushing, palpitation or sweating were observed in any subject in this study.

According to a report by Tosa *et al.*,[17] blood viscosity measured with a cone-plate rotational viscometer decreased significantly in normal volunteers from its baseline value after the subacute administration of Keishi-bukuryo-gan. The relationship between cardiac output and blood viscosity has been well researched both in animal experiments[18] and in humans at the clinical level.[19]

The data from these reports concerning this relationship indicate a definite association between the increase in output and the decrease in blood viscosity. Prior to the present study, we expected that cardiac output would increase after the acute administration of Keishi-bukuryo-gan due to a decrease in blood viscosity. Contrary to our expectations, the cardiac output remained the same, with no change in peripheral vascular resistance. Taking into account our previous reports, the present study suggests as a conclusion that Keishi-bukuryo-gan has little effect on the hemodynamics in macrocirculation, while proving a definite improvement in microcirculation. The present results bring up a question of how the formula works to fulfill the increased demand, *i.e.*, to deliver an extra volume of blood to the peripheral vasculature for the facilitated microcirculation while keeping the supply, or the cardiac output, ultimately even. The answer to the question will be found in the mechanisms of the redistribution of blood flow in the peripheral vasculature, which will depend on results of future detailed studies.

Because of the lack of a direct effect on cardiac function and large vessels, Keishi-bukuryo-gan now has a chance to be used not simply as a "Ku-oketsu-zai" or an agent to eliminate stagnation of the blood, but also as a safe pro-circulatory drug for elderly patients with arteriosclerotic disorders[20] even when they are complicated by severe ischemic heart disease.

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和文抄録

桂枝茯苓丸証を呈する瘀血病態患者5人および健常者6人を対象に，自家製桂枝茯苓丸6gの急性負荷投与を行い，投与前後における循環動態の変動について検討した。イヤーピース色素希釈法による心拍出量測量計および自動血圧計を用いて，血圧，心拍数，心係数，総末梢血管抵抗を計測した。桂枝茯苓丸投与により，いずれの変数にも変動は認められず，本剤は循環動態には影響しないことが明らかになった。我々の従来の研究結果をも勘案すると，桂枝茯苓丸は心臓および大血管等の循環動態には変動を及ぼさずに，微少循環を改善することが示唆された。

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