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Rheological studies on "oketsu" syndrome
I. The blood viscosity and diagnostic criteria

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Abstract

In order to elucidate the rheological characteristics of the blood in "oketsu" (blood stagnant) syndrome, 82 patients and 10 volunteers were evaluated in this study. According to "Terasawa" diagnostic criteria, patients were classified into 3 groups : non-"oketsu," mildly affected and severely affected with "oketsu" syndrome. The viscosity values obtained were corrected by a regression equation to values at 45% of hematocrit and then compared. The results indicated that both whole blood and plasma viscosity were significantly elevated in the cases with "oketsu" syndrome. By using Casson's equation, we found that both values of Casson viscosity and Casson yield stress were significantly high in cases of "oketsu" synrome. The results suggested that the blood of "oketsu" syndrome has more difficulty in flowing in certain microcirculations, and if the flow has completely ceased within a given sequence of vessels, the blood may need stronger stress to re-start the flow than that needed in normal subjects.

Key words "oketsu" syndrome, blood stagnant syndrome, blood viscosity, Casson viscosity, Casson yield stress, hemorheology

Abbreviations Oketsu (Yu-Xue), 瘀血 ; Ketsu (Xue), 血 ; Kampoh formulation, 漢方方剤

Introduction

"Oketsu", blood stasis or stagnant syndrome, is one of the pathological physiological concepts existing only in Chinese medicine.[1,2] In traditional Chinese medicine, "ketsu," (blood), means human red body fluid containing life energy ("Ki"), that circulates in the body. A pathological state induced by circulatory failure of this "ketsu" is called "oketsu."

Although the definition of "oketsu" in terms of Western medicine is difficult, as it is a general name that could be given to a wide range of diseases, it has been recognized clinically as blood stagnation or disorders in the peripheral microcirculation. Since it has been claimed that traditional Chinese medicine is effective only when it is applied on the selected cases according to the

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classical definition, the studies to clarify the classical definition by modern aspects is one of the premise to evaluate the clinical evaluation of traditional Chinese medicine. The present report was undertaken in an attempt to elucidate rheological aspects of the blood in "oketsu" syndrome.

Materials and Methods

Clinical study of "oketsu" syndrome : Eighty-two patients were examined in our clinic of Sino-Japanese medicine during the study period. Those given anti-inflammatory drugs or analgesics, which may affect platelet functions or hematogenesis, were excluded. Eighty-two patients consisting of 28 men (17−70 y.o.) and 54 women (20−75 y.o.) were considered as appropriate subjects. The degree of the "oketsu" state was standerdized according to the diagnostic criteria presented by Terasawa *et al*.[3] (Table I).

Healthy volunteers : In patients group, the number of non- "oketsu" group was only 16, so that healthy volunteers (7 men and 3 women, aged 18−29) made up of staff members and students of this university, whose "oketsu" score were under 20, served as non- "oketsu" group. The ages of volunteers were rather young than those of patients group because of difficulty of collection of non-"oketsu" subjects in elder ages.

Table I Diagnostic criteria for "oketsu" syndrome.[3]

symptoms	score male	score female		score male	score female
dark shade around the eyes	10	10	tenderness of left navel region	5	5
pigmentation over the face	2	2			
rough skin	2	5	tenderness of right navel region	10	10
purple discoloration of lips	2	2	tenderness under the navel region	5	5
purple discoloration of gums	10	5			
purple discoloration of tongue	10	10	tenderness of iliocoecal region	5	2
telangiectasis, vascular spider	5	5			
susceptibility to subcutaneous bleeding	2	10	tenderness of hypochondrial region	5	5
redness of palms, palmar erythema	2	5	tenderness of sigmoid region	5	5
			hemorrhoids	10	5
			dysmenorrhea		10

Evaluation : 20 points and less : non-"oketsu" state.
21 points and above : mildly affected "oketsu" state.
40 points and above : severely affected "oketsu" state.

Blood samples : 10 ml of blood was withdrawn from the cubital vein into a plastic syringe with EDTA-2K (1.8 mg/ml). All blood samples were taken in the morning after overnight fasting. Each sample was divided into two parts, one for measuring whole blood viscosity and the other to examine plasma viscosity. All samples were examined at least one hour after sampling.

Measurement of viscosity : Viscosities of whole blood and plasma were measured by cone-plate rotational viscometer (Bio-rheolizer, Tokyo Keiki Co., Ltd., Tokyo). The measurements were carried out at a temperature of 37 ℃ and a cone angle of 1° 38′. Under this condition, the reproducibility of the data are high, as reported by Kawagoe.[4]

For calibration of the viscometer, standard oil solution JS 10 (Syowa Oil Co., Ltd., Tokyo, Lot No. 10) was employed.

In cases of measurement of whole blood viscosity, blood samples were measured at five different points of shear rates ($\dot{\gamma}$) (19.2, 38.4, 76.8,

192.0, 384.0, sec^{-1}). Further, apparent viscosity (η) was calculated through the averaging of three values estimated at each point of shear rate.

The values of plasma viscosity were measured at one point of shear rate (384 sec-1), and averaged values were calculated after three estimations.

Measurement of hematocrit and other parameters : The value of hematocrit was measured by the capillary high speed centrifugation method using the centrifugal separator KH-120M (Kubota Co., Ltd., Tokyo) and a micro-capillary tube (75 mm length, ELMA Co., Ltd., Tokyo). Every sample was measured for total protein, total cholesterol, triglyceride, red blood cell count and total fibrinogen values.

Results

Whole blood viscosity in "oketsu" syndrome

Using the diagnostic criteria of "oketsu" syndrome, 82 patients and 10 volunteers were divided into three groups, i.e., a non-"oketsu" group, a mildly affected group and a severely affected group of "oketsu" syndrome. The apparent blood viscosities in these three groups were listed in Table II. The results indicate that, as far as apparent viscosity is concerened, there are no

Table II The apparent viscosity in non-"oketsu" group, mildly affected "oketsu" group and severely affected "oketsu" group.

	non-"oketsu" group	mildly affected group	severely affected group	
	n=26	n=31	n=35	
Hematocrit	43.5±0.89	39.8±0.86	39.2±0.72	(%)
Shear rate				
19.2 sec^{-1}	6.60±1.13	5.95±1.24	6.06±0.88	(cP)
76.8 sec^{-1}	4.79±0.76	4.66±0.68	4.60±0.48	(cP)
384.0 sec^{-1}	3.80±0.49	3.64±0.55	3.56±0.34	(cP)

The values are expressed as mean and standard deviation.

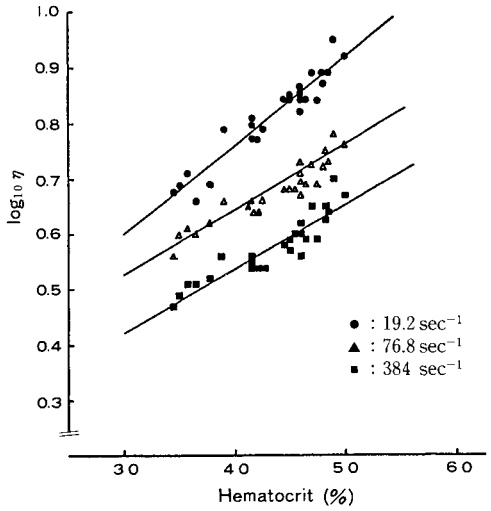

Fig. 1 Scatter diagram showing the measured blood viscosity of the non-"oketsu" group objects at their actual hematocrits.
The regression line shows the relationship of hematocrit to the logarithm of the viscosity.

differences among three groups.

Dormandy[5] has reported that the apparent values of blood viscosity and hematocrits are correlated in logarithmic manner. Fig. 1 shows the correlation between the apparent viscosities and hematocrits at three shear rates in the non-"oketsu" group. The regression equations obtained by using the method of least squares are as follows :

19.2 sec^{-1} $\log_{10}\eta = 0.0160Ht + 0.119$ $(r=0.949)$

76.8 sec^{-1} $\log_{10}\eta = 0.0111Ht + 0.197$ $(r=0.929)$

384.0 sec^{-1} $\log_{10}\eta = 0.0113Ht + 0.087$ $(r=0.914)$

These equations are changed into a more convenient form as follows :

19.2 sec^{-1} $\log_{10}\eta_{45} = \log_{10}\eta + 0.0160\ (45-Ht)$

76.8 sec^{-1} $\log_{10}\eta_{45} = \log_{10}\eta + 0.0111\ (45-Ht)$

384.0 sec^{-1} $\log_{10}\eta_{45} = \log_{10}\eta + 0.0113\ (45-Ht)$

Using these equations, each apparent viscosity is corrected to the values of 45 % of hematocrit. The corrected values of blood viscoisities among the non-"oketsu," mildly affected, and severely affected groups are listed in Table III. The results indicate that the corrected values of blood viscosity in the "oketsu" state are significantly elevated in comparison to the non-"oketsu" state.

Plasma viscosity in "oketsu" syndrome

Plasma is principally considered to be a Newtonian fluid which is not affected by shear rate. The plasma viscosities measured in each group are also listed in Table III. The data suggested that the plasma viscosity in the "oketsu" state is significantly higher than that of the non-"oketsu" state.

Table III Comparison of corrected values of blood viscosity and plasma viscosity in the three groups.

	non-"oketsu" group	mildly affected group	severely affected group	
Blood viscosity[#1]	n=26	n=31	n=35	
shear rate				
19.2 sec^{-1}	6.89±0.38	7.11±0.92	7.49±1.17*	(cP)
76.8 sec^{-1}	4.95±0.23	5.30±0.55**	5.32±0.54**	(cP)
384.0 sec^{-1}	3.94±0.21	4.15±0.42*	4.14±0.36*	(cP)
Plasma viscosity[#2]	n=15	n=28	n=29	
	1.35±0.05	1.49±0.16**	1.49±0.15**	(cP)

The values are expressed as mean and standard deviation.
The asterisks indicate significant difference of from non-"oketsu" group ; $*p<0.05$, $**p<0.01$
#1 ; corrected to standard hematocrit of 45 %, measured at various shear rates.
#2 ; measured at 384.0 sec^{-1}

Analysis using Casson's equation

In order to elucidate the rheometric characteristics of blood in the "oketsu" state, we used Casson's equation. Casson's equation is expressed as follows :

$\sqrt{\tau} = \sqrt{\tau_f} + \sqrt{\eta_c} \cdot \sqrt{\dot{\gamma}}$

τ : shear stress

η_c : Casson viscosity

$\dot{\gamma}$: shear rate τ_f : Casson yield stress

The shear stress of each subject is calculated by using the blood viscosity value at five points of shear rate, i.e., 19.2, 38.4, 76.8, 192.0 and 384.0 sec^{-1}. Then by using the approximation method, both Casson viscosity and Casson yield stress are estimated. The results obtained from each subject showed a good correlation with Casson's equation. The results further indicate that the rheometric characteristics of the blood in both the

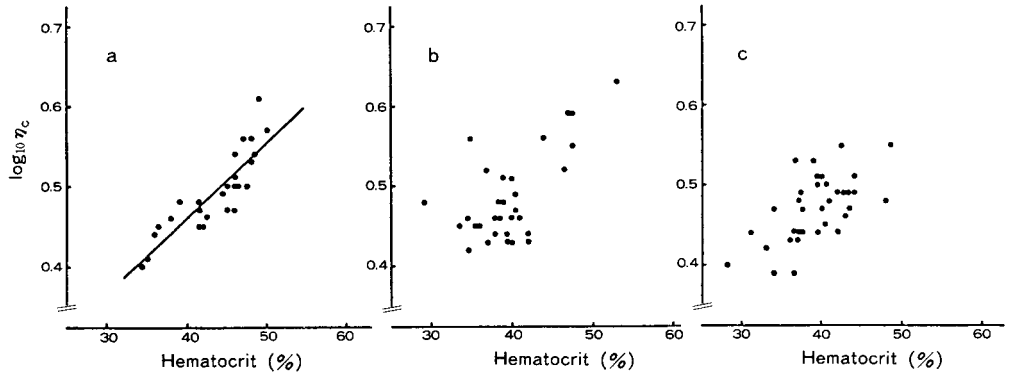

Fig. 2 Scatter diagram showing the Casson viscosity at the actual hematocrits.
(a) non-"oketsu" group ; the regression line shows the relationship of the hematocrit to the logarithm of the Casson viscosity. (b) mildly affected group. (c) severely affected group.

non-"oketsu" and "oketsu" states are able to be explained by two parameters, i.e., Casson viscosity and Casson yield stress.

Casson viscosity and Casson yield stress in the "oketsu" state

Since both the values of Casson viscosity and Casson yield stress are affected by the values of hematocrit, the data must be corrected before a comparison among different subjects is valid.

In cases of Casson viscosity, the mathematical correction method, the same as for apparent viscosity above, is employed. Correlation between Casson viscosities and hematocrit values are plotted in Fig. 2 and the regression line is expressed as the following equation :

$\log_{10}\eta_c = 0.00936\mathrm{Ht} + 0.0852 \quad (r=0.859)$

The above equation is changed into the following simpler form :

$\log_{10}\eta_{c45} = \log_{10}\eta_c + 0.00936\ (45-\mathrm{Ht})$

The correlations between Casson yield stress and hematocrit are shown in Fig. 3. The equation obtained is as follows :

$\tau_f = 0.00643\mathrm{Ht} - 0.149 \quad (r=0.8964)$

Then, the equation is changed as follows :

$\tau_{f45} = 0.00643\ (45-\mathrm{Ht}) + \tau_f$

Table IV shows the corrected Casson viscos-

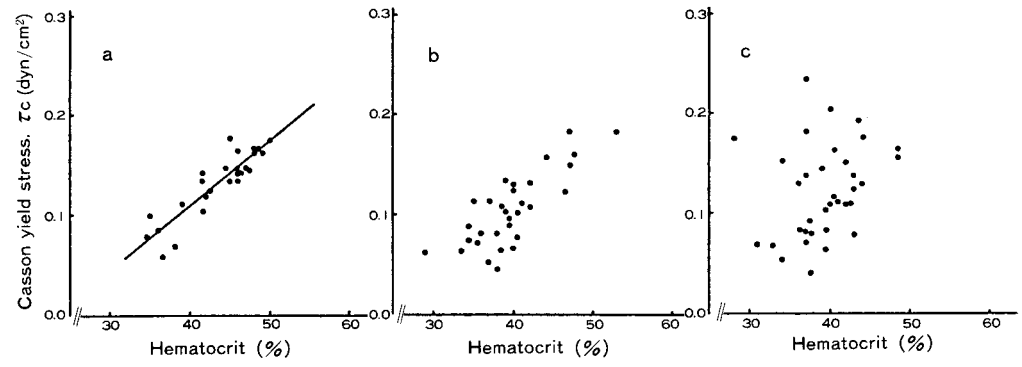

Fig. 3 Scatter diagram showing the Casson yield stress at the actual hematocrits.
(a) non-"oketsu" group ; the regression line shows the relationship of the hematocrit to the logarithm of the Casson yield stress. (b) mildly affected group. (c) severely affected group.

Table IV Comparison of corrected values of Casson viscosity and Casson yield stress in the three groups.

	non-"oketsu" group	mildly affected group	severely affected group	
	n=26	n=31	n=35	
corrected Casson viscosity	3.21±0.19	3.44±0.35*	3.36±0.28**	(cP)
corrected Casson yield stress	0.141±0.014	0.138±0.023	0.159±0.048***	(dyn/cm²)

The values are expressed as mean and standard deviation.
The asterisks indicate significant difference from non-"oketsu" group ; $*p<0.01$, $**p<0.05$ and $***p<0.1$, respectively.
***also means $p<0.05$ from mildly affected group.

ity and Casson yield stress in the non-"oketsu," mildly affected "oketsu" and severely affected "oketsu" groups. It was determined that both Casson viscosity and Casson yield stress are significantly elevated in "oketsu" state.

Changes in parameters of blood chemistry and hematological examinations in "oketsu" syndrome

There are no significant differences between non-"oketsu" and "oketsu" in regard to such parameters as total protein, total cholesterol, triglyceride in serum, total fibrinogen in plasma, and red blood cell count.

Discussion

According to the textbooks of traditional Chinese medicine,[1,2] the concept of "oketsu" syndrome suggests a close relationship between such disorders as arteriosclerotic, diabetic, climacteric, auto-immune and inflammatory diseases in modern Western medicine. Recently, pharmacological investigations of anti-"oketsu" Kampoh formulations (for treating the "oketsu" syndrome) have been widely performed. It has been clearly demonstrated that these formulations have anti-inflammatory[6] and immuno-modulating effects.[7]

Concerning hematological studies of the syndrome, it was elucidated that thromboxane synthesis in platelets of the patient with the syndrome is elevated, and anti-"oketsu" formulations correct the condition.[8] On the rheological aspects of the blood, there have been several reports which point out the elevation of blood viscosity in "oketsu" syndrome.[9] However, these reports were not based on recognized diagnostic criteria of the syndrome, so that, in a strict sense, the reliability of their results have been questionable. Our report presents the first trial for determining the rheological aspects of the "oketsu" syndrome by using specific diagnostic criteria related to the syndrome.

The blood is considered to be non-Newtonian fluid, and its apparent viscosity is significantly affected by hematocrit. In order to eliminate this influence of hematocrit, several methods have been adopted, i.e., a dilution technique using auto-plasma or physiological saline, and a mathematical method. In the present study, a mathematical method was employed, and the apparent values of viscosity were corrected by a regression equation. The corrected values of blood viscosity of the "oketsu" syndrome were significantly higer than those of the non-"oketsu" group. This means that the value of apparent viscosity in the patient of "oketsu" syndrome is significantly higer than that of non-"oketsu" subjects with the same hematocrit value.

Dormandy[5] has reported that erythrocytes exert considerable influence on blood viscosity at a low shear rate. The results obtained here showed that hyperviscosity is observed not only at a low shear but also at a high shear rate. This means that factors other than that only of the erythrocytes are responsible for hyperviscosity of

the blood in the syndrome. The present study has also revealed that the values of plasma viscosity are elevated in the syndrome, thus revealing this to be one of the factors which lead to hyperviscosity at a high shear rate in the syndrome.

From the viewpoint of the concept of "oketsu" syndrome as meaning stagnation or stasis of blood in peripheral circulation, it is important to estimate the characteristics of the blood flow at extremely low flow rates or stasis. Casson yield stress is thought to be a good parameter for estimating the features of the initiation of blood flow from stasis. The results indicate that the blood in "oketsu" syndrome needs stronger stress in order for the flow to begin. In other words, if flow has completely ceased within a given sequence of vessels, the blood affected by the syndrome needs stronger shear stress to re-start flow than that of normal subjects.

Through this investigation, the rheometric aspects of "oketsu" syndrome have been partially elucidated ; however, the reason for the elevation of viscosity yiled still remains unclear, so that further investigations on this problem are called for.

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和文抄録

瘀血症候群における血液レオロジー学的特性を明らかにする目的で，82名の患者と10名のボランティアを対象として検討した。寺澤の瘀血診断基準に基づき，対象を非瘀血群，軽症の瘀血群，重症の瘀血群の3群に分類した。血液粘度は補正式によってヘマトクリット45%に補正し，各群間の比較を行なった。その結果，瘀血症候群においては全血粘度，血漿粘度がともに有意に上昇していることが示唆された。Casson式を用いて，その流動特性を解析したところ，瘀血症候群においてはCasson粘度およびCasson降伏値がともに有意に上昇しているという成績を得た。これらの結果は，微小循環系において，瘀血症候群では血液が流れにくく，また，ひとたび血流が停止すると，その再開に要する力は非瘀血群に比べ，より大きなものを必要とすることを示している。

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