Components of Hachimi-jio-gan (Ba-Wei-Di-Huang-Wan) and changes in blood flow in the human central retinal artery

Hideyuki ISOBE,[*a,b)] Kazuhiko YAMAMOTO[b)] and Jong-Chol CYONG[a)]

[a)]*Department of Bioregulatory Function, Graduate School of Medicine, University of Tokyo,*
[b)]*Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo,*
7-3-1 Hongo, Bunkyou-ku, Tokyo 113-8655, Japan.

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Abstract

We found an increase in blood flow in the central retinal artery attributable to Hachimi-jio-gan (HJG) extract granules, using the latest ultrasonic diagnosis device. A further examination was added concerning the relation between HJG components and the increase of blood flow. The decoction of HJG produced an increased blood flow in the central retinal artery, as did the extract granules. This increase, however, was not observed in the case of a decoction or extract granules of Rokumi-gan (RG). Central retinal artery exhibited a decrease in vascular resistance after administration of decoctions of Cinnamon Bark and of Aconite Tuber. The increased blood flow in the central retinal artery, however, occurred to a lesser extent with a decoction of 2 crude drugs (Cinnamon Bark and Aconite Tuber) and with a decoction of 7 crude drugs that added Cinnamon Bark or Aconite Tuber to RG (which contains neither Aconite Tuber nor Cinnamon Bark, unlike HJG which contains both). It is suggested that the cause of increased blood flow in the central retinal artery attributable to HJG is shown by the result, which means that all 8 ingredients (RG, Cinnamon Bark, and Aconite Tuber) are needed.

Key words Hachimi-jio-gan (Ba-Wei-Di-Huang-Wan), Rokumi-gan (Liu-Wei-Wan), components, human central retinal artery, ultrasonic diagnosis device, blood flow velocity, resistance of blood vessel.

Abbreviations HJG, Hachimi-jio-gan (Ba-Wei-Di-Huang-Wan), 八味地黄丸; PI, Pulsatility Index; RI, Resistive Index; RG, Rokumi-gan (Liu-Wei-Wan), 六味丸.

Introduction

Hachimi-jio-gan (HJG, Ba-Wei-Di-Huang-Wan) is widely used for Jinkyo, which is one indication category in Kampo medicine. It is used especially often for the aged, being effective in the treatment of various kinds of morbidity associated with age. It is also often used in eye diseases, such as cataract. It is well known that although its efficacy is admitted, improvement in the objective symptoms is rarely shown, in contrast to the improvement in the subjective symptoms. The action mechanism of HJG has not been clarified.

We examined the effects of the extract granules (Tsumura) of HJG on the increase of the blood flow in the central retinal artery, using an ultrasonic diagnosis device.[1)] The progress of ultrasonic diagnosis devices in recent years is remarkable, and it is now possible to observe circulation in a minute blood vessel in a noninvasive way, in real time.

HJG consists of eight crude drugs: Rehmannia Root, Corus Fruit, Dioscorea Rhizome, Alisma Rhizome, Hoelen, Moutan Bark, Cinnamon Bark and Aconite Tuber. We tried this time to determine from the constitution of the crude drugs which of these drugs is mainly related to the increase of the blood flow in the central retinal artery.

Rokumi-gan (RG, Liu-Wei-Wan) consists of 6 crude drugs that constitute HJG but without the Cinnamon Bark and Aconite Tuber. It is a prescription similar to HJG. No increase in blood flow in the central retinal artery was seen after treatment with RG extract

*To whom correspondence should be addressed. e-mail: isobe-tky@umin.ac.jp

granules (Tsumura) however. It was conceivable that the inclusion of Cinnamon Bark and Aconite Tuber, which are not included in RG, is important in producing the increase of blood flow due to HJG. When Cinnamon Bark and Aconite Tuber are added to RG it becomes HJG, which can be considered as [RG + Cinnamon Bark + Aconite Tuber]. We therefore examined all the decoctions and compared the effects of each on the blood flow in the central retinal artery. Decoctions observed included [RG], [Cinnamon Bark], [Aconite Tuber] as well as each pair in combination ([RG + Cinnamon Bark], [RG + Aconite Tuber] and [Cinnamon Bark + Aconite Tuber]), and finally [HJG]. From the results we determined which of the crude drugs or combinations were necessary to produce the effect of HJG.

Materials and Methods

Blood flow in the human central retinal artery was measured from before administration until 30 minutes after administration of Kampo medicines as a decoction.

The subjects were healthy adult volunteers. We received informed consent from all subjects. After the experiment, all subjects agreed that they experienced no problems.

Rehmannia Root (*Rehmannia glutinosa* LIBOSCHITZ), Corus Fruit (*Cornus officinalis* SIEBOLD), Dioscorea Rhizome (*Dioscorea batatas* DECAISNE), Alisma Rhizome (*Alisma orientale* JUZEPCZUK), Hoelen (*Poria cocos* WOLF), Moutan Bark (*Paeonia suffruticosa* ANDREWS), Cinnamon Bark (*Cinnamomum cassia* BLUME), Aconite Tuber (*Aconitum carmichaeli* DEBFAUX) were used in this study. The crude drugs for the decoctions were provided by Uchida Wakan-yaku Co. Ltd (Tokyo, Japan).

The quantity of crude drugs in the decoctions conformed to that in the extract granules (Tsumura).

The crude drugs were decocted with 500ml of distilled water until the contents was reduced by half.

In administration of the extract granule, 2 packages (2/3 of the quantity for a day) were taken at one time, so lukewarm water was added to a decoction quantity equaling 2/3 of the quantity for a day; the resulting liquid was taken at the time in a quantity similar to the lukewarm water (180 ml) given with the extract granules.

As a control, lukewarm water was used in the same quantity as in the decoction (180 ml, 34℃ to 36℃).

The kinds of decoction administered were as follows:

(1) HJG (decoction of HJG)

The quantities of crude drugs are similar to those of extract granules of HJG: Rehmannia Root 6 g, Corus Fruit 3 g, Dioscorea Rhizome 3 g, Alisma Rhizome 3 g, Hoelen 3 g, Moutan Bark 2.5 g, Cinnamon Bark 1g, Aconite Tuber 0.5 g.

(2) RG (decoction of RG)

The quantities of crude drugs are similar to those of extract granules of RG: Rehmannia Root 5 g, Corus Fruit 3 g, Dioscorea Rhizome 3 g, Alisma Rhizome 3 g, Hoelen 3 g, Moutan Bark 3 g.

(3) Decoction of Cinnamon Bark only

The quantity of the crude drug is only 1 g Cinnamon Bark, in conformity with extract granules of HJG.

(4) Decoction of Aconite Tuber only

The quantity of the crude drug is only 0.5 g Aconite Tuber, in conformity with extract granules of HJG.

(5) Decoction of 2 crude drugs: Cinnamon Bark and Aconite Tuber

The quantities of crude drugs are Cinnamon Bark 1 g and Aconite Tuber 0.5 g, in conformity with extract granules of HJG.

(6) Decoction of 7 crude drugs, with Cinnamon Bark added to RG same as HJG except without Aconite Tuber

The quantities of crude drugs are Rehmannia Root 6 g, Corus Fruit 3 g, Dioscorea Rhizome 3 g, Alisma Rhizome 3 g, Hoelen 3 g, Moutan Bark 2.5 g, Cinnamon Bark 1 g, in conformity with extract granules of HJG.

(7) Decoction of 7 crude drugs with Aconite Tuber added to RG same as HJG except without Cinnamon Bark

The quantities of crude drugs are Rehmannia Root 6 g, Corus Fruit 3 g, Dioscorea Rhizome 3 g, Alisma Rhizome 3 g, Hoelen 3 g, Moutan Bark 2.5 g, Aconite Tuber 0.5 g, in conformity with extract granules of HJG.

At the time of administration, subjects did not know which decoction was being given.

The measurement device was a wide-range ultrasonic diagnosis device, LOGIQ 500 (GE Yokogawa Medical), and a linear probe, LA 39 was used.

The items measured were blood flow velocity (systolic velocity [S], diastolic velocity [D], mean velocity [MN]), and resistance of the vessel ([PI], [RI]) in the central retinal artery (of the right eye).

[PI] is the Pulsatility Index, in other words, the

resistance index of the pulse flow. [RI] is the Resistive Index, in other words, the resistance index of the laminar flow. They were used together to evaluate blood flow. The calculation formulas are [PI]=([S]-[D])/[MN] and [RI]=([S]-[D])/[S].

The right eye was measured in all subjects for blood flow in the central retinal artery, because no significant differences were found between the right and left eyes in our measurement or in the other reports.[2)]

For the measurement, the subjects sat in a chair, closed their eyes, and kept still. The person performing the measurement sat on the opposite side and aimed the probe directly at the upper eyelid. The position of the eyeball and the optic nerve behind the eyeball were confirmed. Next, the central retinal artery that runs beside the optic nerve was identified so the blood flow velocity and vascular resistance in the central retinal artery could be measured.

Measurement was performed before administration and every 5 minutes after administration, from 5 to 30 minutes after.

ANOVA and Bonferroni/Dunn test were used for the statistical analysis. Values were considered to be significantly different when the p value was less than 0.05.

Results

(1) Decoctions of HJG and RG

(a) Decoction of HJG

The subjects were 10 healthy adults; the male-to-female ratio was 5:5. The average age was 28.3 ±4.7 years.

The systolic velocity, diastolic velocity, and mean velocity in the central retinal artery showed an increase after administration of the decoction of HJG.

A significant increase from Pre in blood flow velocity was observed after 20 minutes and 25 minutes for systolic velocity, after 20 minutes for diastolic velocity, after 20 minutes and 25 minutes for mean velocity. Vascular resistance showed no significant change. (Fig. 1)

(b) Decoction of RG

The subjects were 10 healthy adults; the male-to-female ratio was 5:5. The average age was 28.8 ±5.1 years.

No increase in blood flow in the central retinal artery was observed after administration of the decoction of RG. No obvious change was observed in vascular resistance. No increase in blood flow in the central retinal artery was observed even after the decoction of RG that is similar to the extract granules. (Data not shown.)

A comparison of the change of the blood flow in the central retinal artery between the decoctions of HJG and RG is shown in Fig. 2. As a control, lukewarm water was used. In the graph of the rate of change, the value before administration is denoted as 1.

First, no significant change after administration of RG was observed in the systolic velocity. On the other

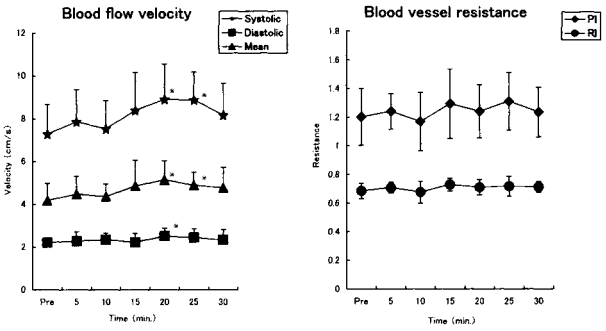

Fig. 1 Effects of decoction of HJG on blood flow in the central retinal artery.

After the administration of HJG, a significant difference was observed in the blood flow velocities. Vascular resistance showed no change (mean±S.D., n=10).

* Difference of $p<0.05$ was considered statistically significant from Pre.

[PI], Pulsatility Index; [RI], Resistive Index.

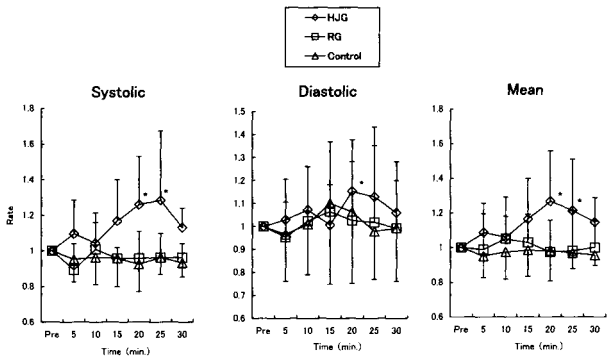

Fig. 2 Comparison of effects on blood flow in the central retinal artery of a decoction of HJG with those of a decoction of RG.

The graph shows rate of change, with the value before administration as 1. After administration of RG, blood flow velocities showed no change; on the other hand, after administration of HJG, blood flow velocities significantly increased (mean±S.D., n=10).

★Difference of $p<0.05$ was considered statistically significant from control.

hand, the flow velocity clearly increased after administration of HJG and a significant increase from control was shown 20 minutes and 25 minutes later.

For diastolic velocity, although no large change was observed in the case of RG, the increase of blood flow was shown in the case of HJG, and a significant difference from control was observed after 20 minutes.

For mean velocity, although the change in blood flow was not so large after administration of RG, after administration of HJG the increase was marked, and a significant increase from control was observed 20 minutes and 25 minutes later.

(2) Decoction of Cinnamon Bark only and Aconite Tuber only

(a) Decoction of Cinnamon Bark only

The subjects were 8 healthy adults; the male-to-female ratio was 4:4, and the average age was 27.8 ± 4.2 years.

After the administration of Cinnamon Bark, no significant difference was observed in systolic, diastolic and mean velocity in the central retinal artery. The vascular resistance showed a decrease; significant decreases from Pre in the PI were observed 5 minutes and 15 minutes after administration. (Fig. 3)

(b) Decoction of Aconite Tuber only

The subjects were 8 healthy adults; the male-to-female ratio was 3:5, and the average age was 30.5 ± 4.6 years.

After the administration of Aconite Tuber, no large change was observed in blood flow velocity. The vascular resistance showed a decrease; significant decreases from Pre in PI were observed 5 minutes and 20 minutes after administration, in RI after 5 minutes. (Fig. 4)

A decrease in the vascular resistance in the central retinal artery was observed after administration of both Cinnamon Bark and Aconite Tuber. These changes in blood flow are compared with the blood flow at the time of administration of HJG in Fig. 5. In the graph of the rate of change, the value before administration is given as 1.

A significant change in blood flow velocity is not observed after administration of Cinnamon Bark and Aconite Tuber. On the other hand, the increase in blood flow velocity after HJG was large and obvious.

For vascular resistance, the change in PI was small after HJG, but a significant decrease was shown after Cinnamon Bark and Aconite Tuber were given together.

(3) Decoction of 2 crude drugs Cinnamon Bark and Aconite Tuber; decoction of 7 crude drugs consisting of Cinnamon Bark added to RG (equivalent to HJG without Aconite Tuber); decoction of 7 crude drugs consisting of Aconite Tuber added to RG (equivalent to HJG without Cinnamon Bark)

(a) Decoction of 2 crude drugs, Cinnamon Bark and Aconite Tuber

The subjects were 8 healthy adults; the male-to-female ratio was 4:4, and the average age was 30.0 ± 3.8 years.

A decrease was shown in the systolic, diastolic, and mean velocities in the central retinal artery after admini-

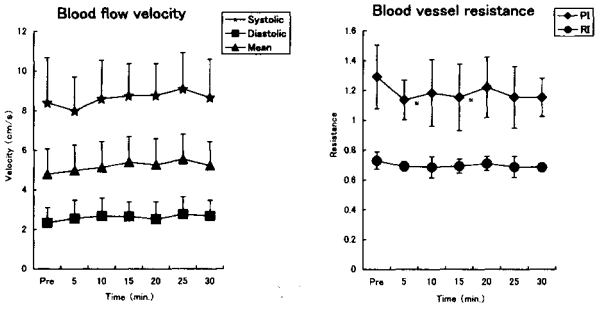

Fig. 3 Effects of decoction of Cinnamon Bark on the blood flow in the central retinal artery.

After the administration of Cinnamon Bark, no significant difference was observed in the blood flow velocity. The vascular resistance showed a significant decrease in PI (mean±S.D., n=8).

* Difference of $p<0.05$ was considered statistically significant from Pre.

[PI], Pulsatility Index; [RI], Resistive Index.

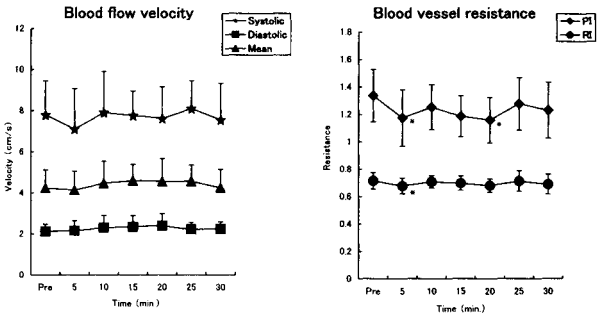

Fig. 4 Effects of decoction of Aconite Tuber on blood flow in the central retinal artery.

After the administration of Aconite Tuber, no significant difference was observed in the blood flow velocity. The vascular resistance showed a significant decrease in both PI and RI (mean±S.D., n=8).

* Difference of $p<0.05$ was considered statistically significant from Pre.

[PI], Pulsatility Index; [RI], Resistive Index.

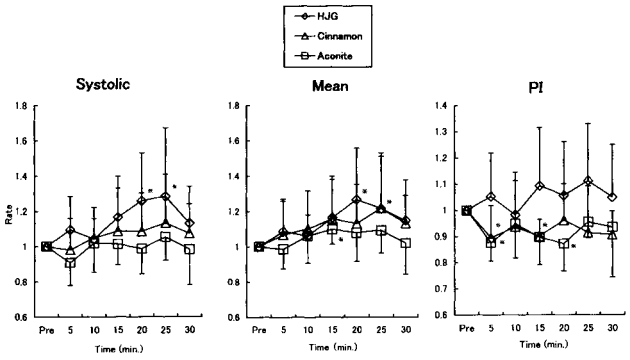

Fig. 5 Comparison of effects on blood flow in the central retinal artery among decoctions of Cinnamon Bark, Aconite Tuber, and HJG.
The graph shows rate of change, with the value before administration as 1. After administration of Cinnamon Bark and Aconite Tuber, a decrease in vascular resistance was shown. On the other hand, after administration of HJG, the change in vascular resistance was not large but the increase in blood flow velocity was remarkable (mean±S.D.).
* Difference of $p<0.05$ was considered statistically significant from Pre.
[PI], Pulsatility Index.

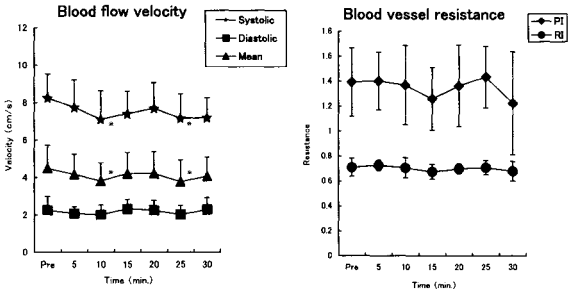

Fig. 6 Effects of decoction of Cinnamon Bark and Aconite Tuber on blood flow in the central retinal artery.
A decrease was shown in the central retinal artery after the administration of Cinnamon Bark and Aconite Tuber. A significant decrease was observed in the systolic and mean velocities. No significant difference was observed in the vascular resistance (mean±S.D., n=8).
* Difference of $p<0.05$ was considered statistically significant from Pre.
[PI], Pulsatility Index; [RI], Resistive Index.

stration of [Cinnamon Bark + Aconite Tuber]. A significant decrease from Pre in the systolic velocity was observed 10 minutes and 25 minutes after administration; that in the mean velocity occurred at 10 minutes and 25 minutes. The vascular resistance showed no significant change. (Fig. 6)

After the administration of [Cinnamon Bark + Aconite Tuber] together there were no such effects observed for Cinnamon Bark and Aconite Tuber separately, though the blood flow velocity in the central retinal artery showed a decrease.

(b) Decoction of 7 crude drugs consisting of Cinnamon Bark added to RG (equivalent to HJG without Aconite Tuber)

The subjects were 8 healthy adults; the male-to-female ratio was 4:4, and the average age was 25.8 ± 4.8 years.

No large change was observed in systolic, diastolic, or mean velocity in the central retinal artery after the administration of [RG + Cinnamon Bark]. No significant change was observed in vascular resistance. (Data not shown.)

(c) Decoction of 7 crude drugs consisting of Aconite Tuber added to RG (equivalent to HJG without Cinnamon Bark)

The subjects were 8 healthy adults; the male-to-female ratio was 4:4, and the average age 27.0 ±5.3 years.

No significant change was observed in blood flow in the central retinal artery after administration of [RG + Aconite Tuber]. No large change was observed in the vascular resistance. (Data not shown.)

The increase in blood flow in the central retinal artery that is observed with HJG was not seen with any combination of two elements among RG, Cinnamon Bark, and Aconite Tuber.

Discussion

The results showed an obvious increase in the blood flow of the central retinal artery after administration of the decoction of HJG. There was no large change in vascular resistance. These results are similar to those observed after administration of the extract granules. A clear effect of increase in the blood flow of the central retinal artery was seen after administration of the decoction of HJG.

We also observed the change of blood flow until 60 minutes after administration of the decoction of HJG. But the increase of blood flow was comparatively prompt and the change of blood flow was mainly observed within 30 minutes. So we examined relations between the increase of blood flow and HJG components until 30 minutes after administration.

HJG consists of 8 crude drugs: Rehmannia Root, Corus Fruit, Dioscorea Rhizome, Alisma Rhizome,

Hoelen, Moutan Bark, Cinnamon Bark and Aconite Tuber. It is used in Jinkyo which is one category in Kampo medicine. In modern medicine, Jinkyo is a wide category centering on the urogenital and endocrine systems. Its main standards for use are lumbago, pain, hyposthenia, chill of lower extremities, urinary disturbance, impotence, and thirst *etc.*

The range of clinical application is wide, and the indications for HJG are variable: for example, diabetes mellitus, benign prostatic hyperplasia, male sterility, senile cataract, hypertension, lumbago, menopause, osteoporosis, vaginitis, and others. It is used especially often for the aged and is useful in treating the various kinds of morbidity associated with age, such as senile vaginitis, benign prostatic hyperplasia, lumbago, pain, hyposthenia, palsy, chill of extremities, and mental disorders.

Research reports supporting the efficacy of HJG are accumulating. For instance, in humans, improvement of spermatogenesis,[3] and in animals, prevention of experimental osteoporosis induced by ovariectomy in rats,[4] and an effect on experimental amnesia in mice[5] have been reported.

Senile cataract is one disease that can be treated with HJG. It is known, however, that the objective symptoms hardly improve, although improvement of subjective symptoms affecting eyesight and cognition has been proven. Delay of the formation and progress of cataract in rats and mice have been reported in animal experiments.[6,7] It is conceivable that HJG improves the function of the eye, including transmission in the optic nerve, by improving the circulation of the whole eye fundus centering around the retina and especially by increasing the blood flow in the central retinal artery.

Because an ultrasonic diagnosis device can catch the circulation in various kinds of blood vessel in real time, such devices have been widely used to determine changes due to morbidity and to evaluate the effects of medicine. Observation of even minute blood vessels is now possible through the remarkable improvement in accuracy in recent years. Because the measurement is non-invasive, repeated measurement is possible, making the ultrasonic diagnosis device one of the best inspection devices for evaluation of the circulation.

Measurements using an ultrasonic diagnosis device in the ophthalmological field, regarding blood flow in the central retinal artery, have been carried out, and the relation between various kinds of disease have been reported. In previous reports concerning blood flow in the central retinal artery, although there was no significant correlation with gender, blood pressure, or pulse, *etc.*, blood flow velocities decreased and vascular resistance increased with age.[2,8]

It has been reported that central retinal artery blood flow velocities clearly decrease, and resistances clearly increase, in comparison with healthy adult volunteers, in cases of glaucoma,[9,10] diabetic retinopathy, Behcets disease,[11,12] macular degeneration,[13] and retinitis pigmentosa,[14] *etc.*

It has also been reported that late glaucoma showed significantly decreased blood flow velocities as compared with early glaucoma,[15] and that eyes with progressive visual field defects with normal-tension glaucoma had significantly lower blood velocities than those with nearly stable visual field defects.[16]

Although decrease of blood flow velocities and increase of vascular resistance are known to be found in diabetic retinopathy,[17,18] it has been reported that the resistive index of the central retinal artery in patients with diabetes mellitus was also larger than that of normal subjects and with diabetic retinopathy, the resistive index became even larger.

It has been reported that blood flow velocities in the central retinal artery decreased remarkably even in patients with ocular symptoms, although decrease of blood flow velocities and increase of vascular resistance were observed in patients with internal carotid artery stenoses. Furthermore, hemodynamic changes in patients with internal carotid artery stenoses showed clear improvement after carotid endarterectomy.[19,20]

Many reports have tried to evaluate the influence of drugs on the blood flow in the central retinal artery in the treatment of glaucoma. Reports of the improvement of the blood flow have been accepted, but there are more reports that no change in blood flow was observed.

Yamamoto *et al.* stated that 4 weeks of treatment with nilvadipine significantly increased the diastolic velocity, and significantly reduced the resistance index, of the central retinal artery in glaucoma.[21] Nicolela *et al.* used timolol or lantanprost for 7 days in ocular hypertensive and glaucoma patients, using a double-masked crossover design; although timolol and lantanprost reduced the intraocular pressure, no change in blood flow

velocity was observed in the central retinal artery.[22] Lachkar *et al.* reported that no change in blood flow velocity was observed, even when they used brimonidine tartrate for ocular hypertensive patients and reduction of the intraocular pressure was achieved.[23] There was a report concerning treatment with oral nifedipine in glaucoma, stating that a decrease of resistance in the central retinal artery was observed after administration for one month,[24] and another report states that there was no change in the blood flow velocity after administration for 3 to 6 weeks.[25,26]

There has been a report that with anesthesia at the time of operation for cataract, blood flow velocities were significantly reduced in the central retinal artery within short periods (1 and 5 minutes) after peribulbar anesthesia.[27] Our findings in the present study, however, showed that no change in blood flow was observed in a short period after the administration of drugs.

Decrease of blood flow velocity and increase of vascular resistance are often observed in the aged and in many eye diseases, according to reports regarding blood flow in the central retinal artery. It is recognized that a tendency toward decreased blood flow in the central retinal artery becomes more marked with progress of the disease. It is suggested that reduction of the blood flow in the central retinal artery is fundamentally related to the development and progress of eye disease. It is possible, therefore, that many eye diseases can be treated by increasing the blood flow in the central retinal artery. In other words, when blood flow in the central retinal artery is increased by the administration of HJG, this may be considered to show the efficacy of HJG in treatment of eye diseases.

The central retinal artery is a small branch of the internal carotid artery, so it is conceivable that changes in blood flow in the central retinal artery reflect the blood flow in the brain. When blood flow in the central retinal artery is increased by HJG, we can infer that blood flow in the brain is also increased. This viewpoint regarding increasing the blood flow of the brain implies that it is possible that HJG acts on the visual fields of the cerebral cortex and improves cognition. In other words, HJG causes improvement of eyesight at the cortical level also.

As mentioned above, HJG is highly useful in the improvement, and prevention of deterioration, of morbidity due to aging, not only in the case of cataract. It is considered that the increase in blood flow in the brain by treatment with HJG can bring about promotion of function and revitalization of the central nervous system overall. Hirokawa *et al.* report the effect of HJG on an experimental model of cerebral anoxia, showing that HJG inhibits the reduction of acetylcholine in the frontal lobe cortex,[28,29] and it is suggested that the increase in blood flow in the brain due to HJG is related to this effect.

RG consists of 6 crude drugs: Rehmannia Root, Corus Fruit, Dioscorea Rhizome, Alisma Rhizome, Hoelen, and Moutan Bark. It does not contain Cinnamon Bark and Aconite Tuber, which are both present in HJG, but it is a prescription similar to HJG. The increase of blood flow in the central retinal artery was small after the administration of RG, however, and the remarkable effect on blood flow that followed the administration of HJG was not observed with RG. RG and HJG have been commonly used in Jinkyo. The indication category of RG is JinInkyo, however, and that of HJG is JinYokyo. RG is assumed to be suitable for all ages. In comparison with HJG, the frequency of clinical use of RG for the aged and for eye diseases is low. It can be thought that the effects seen after HJG and not after RG reflect the difference in frequency of such prescription.

A significant decrease in vascular resistance was observed after the administration of both Cinnamon Bark only and Aconite Tuber only. As stated above, an increase in vascular resistance is observed with aging and in various diseases. Reducing the resistance of blood vessels is considered to be connected with improvement in morbidity. Although no significant decrease in vascular resistance was observed after the administration of HJG, it is conceivable that the increase of blood flow velocity is much larger than the decrease of vascular resistance.

Expansion of blood vessels and increase in blood flow are reported to be effects of the cinnamic aldehyde of Cinnamon Bark,[30] although expansion of blood vessels and improvement of peripheral circulation are known to be effects of Aconite Tuber. Thus, these drugs have been thoroughly shown to improve the blood flow velocity in the central retinal artery.

The obvious effect of increase in the blood flow shown by HJG was not observed after either Cinnamon Bark or Aconite Tuber, so it is conceivable that the effect

of HJG is partly independent of Cinnamon Bark and Aconite Tuber.

Although the blood flow velocity in the central retinal artery showed a decrease after administration of [Cinnamon Bark + Aconite Tuber], no major change was observed in vascular resistance. No decrease of resistance was observed in blood flow that was observed independently after Cinnamon Bark or Aconite Tuber.

No increase of blood flow in the central retinal artery appeared after the administration of [RG + Cinnamon Bark] or [RG + Aconite Tuber]. No large change in vascular resistance was observed. The decrease of vascular resistance that was observed after Cinnamon Bark and Aconite Tuber were given separately was not seen after adding RG to each of them.

It is considered that for RG, Cinnamon Bark and Aconite Tuber, which are constituents of HJG, no combination of two constituents shows a large increase in blood flow; instead, the combinations rather restrained the independent effects of Cinnamon Bark or Aconite Tuber.

On the other hand, [RG + Cinnamon Bark], and [RG + Aconite Tuber] are also "HJG without Aconite Tuber" and "HJG without Cinnamon Bark", and even eliminating only Cinnamon Bark or only Aconite Tuber from HJG causes the increase in blood flow that HJG shows to disappear. It is suggested that the increase in blood flow in the central retinal artery due to HJG is brought about only when all the constituents of RG, plus Cinnamon Bark and Aconite Tuber participate, bringing the number of crude drugs to 8.

It is considered that this effect, brought about by adding Cinnamon Bark and Aconite Tuber to RG, making 8 constituent crude drugs, gives the constitution of the prescription called HJG its meaning and ensures its effect.

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和文抄録

我々は，最新の超音波画像診断装置を用いて，八味地黄丸のエキス顆粒に，網膜中心動脈の血流増加作用を見出した。そこで，八味地黄丸の構成生薬とその作用の関連性について，煎じ薬を用いて検討を加えた。

八味地黄丸の煎じ薬（八味地黄丸料）は，エキス顆粒と同様，網膜中心動脈の血流増加作用を示した。しかし，六味丸の煎じ薬（六味丸料）やエキス顆粒には，網膜中心動脈の血流増加作用は認められなかった。

また，桂皮，附子各（一味）の煎じ薬の投与により，網膜中心動脈は，血管抵抗の減少を認めた。しかし，桂皮と附子を合わせた二味の煎じ薬や，六味丸に桂皮か附子を加えた(八味地黄丸から附子か桂皮を除いた)七味の煎じ薬では，かえってその作用は打ち消されてしまうようで，血流増加作用はみられなかった。

八味地黄丸の血流増加作用は，六味丸，桂皮，附子すべてがそろって八味になることによって，はじめて現されるものと考えられた。

*〒113-8655 東京都文京区本郷 7-3-1
東京大学医学部生体防御機能学 磯部秀之

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