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Effects of Red Ginseng upon Vascular Endothelial Function in Patients with Essential Hypertension

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Abstract: This study is to estimate the effect of Korean red ginseng on vascular endothelial cell dysfunction in patients with hypertension. Seventeen patients with hypertension who were divided into ginseng-treated (7) and non-treated (10) groups and 10 normotensive subjects were included. To assess the function of the vascular endothelial cell, changes of forearm blood flow to infusion of acetylcholine, sodium nitroprusside and bradykinin in incremental doses were measured by venous occlusion plethysmography. In the ginseng-treated hypertensive group, forearm blood flows at the highest dose of acetylcholine and bradykinin were significantly higher than those of the non-treated hypertensive group and were not different from those of the control group. In the case of sodium nitroprusside infusion, no significant differences were observed between the control, non-treated and treated groups. In conclusion, Korean red ginseng can improve the vascular endothelial dysfunction in patients with hypertension possibly through increasing synthesis of nitric oxide.

Hypertension is one of the independent risk factors of atherosclerosis and the predisposing factors of thromboembolic cerebrovascular disease, ischemic heart disease such as angina pectoris, myocardial infarction, and peripheral vascular obstructive disease (Management Committee, 1980; Medical Research Council Working Party, 1985; MDFP, 1984; IPPPSH, 1985). Before the development of overt atherosclerotic lesion under hypertensive condition, the functional abnormality of vascular endothelium develops and it reportedly causes dysregulation of blood flow by impairing local physiologic response to vasoactive substances and reducing vasodilatory reserve (Furchgott *et al.,* 1980; Furchgott *et al.,* 1983; Zeiher *et al.*, 1991; Vita *et al.,* 1990). The functional role of nitric oxide in maintaining vascular vasodilatory reserve has been extensively studied and the synthesis and release of nitric oxide in response to vasoactive substances has been shown to be impaired in the

presence of hypertension, atherosclerosis or hyperlipidemia (Palmer *et al.,* 1988; Fujii *et al.,* 1992; Moncada *et al.*, 1991; editorial, 1991; Star *et al.*, 1993; Moncada *et al.,* 1993; Lowenstein *et al.,* 1994). The dysfunction of vascular endothelium precedes hypertrophic change of vascular wall in atherosclerosis (Palmer *et al.,* 1987), suggesting endothelial dysfunction might be an antecedent factor of atherosclerotic change.

Reports have been made recently on the pharmacological effects of Korean red ginseng and its extracts on vascular tone, which showed that Korean red ginseng could enhance endothelium-dependent vasodilatory reserve in *ex vivo* experimental model using rabbit or mouse (Kim *et al.,* 1992; Kang *et al.*, 1995; Kim *et al.,* 1994). However, the effect of Korean red ginseng on vascular endothelium has not been studied in an *in vivo* human study.

In this study, we estimated the vasodilatory reserve of hypertensive patients with and without administration of Korean red ginseng by measuring the forearm blood flow using vein occlusion plethysmography (Kiowski, 1991; Linder *et al.*, 1990) and we report that Korean red ginseng can significantly improve endothelial dysfunction in patients with essential hypertension.

Subject and Method

Subject

Twenty patients diagnosed with essential hypertension were enrolled in this study. After washout of antihypertensive medication for 4 weeks, all subjects showed mild to moderate hypertension (> 140/90 mmHg and diastolic blood pressures lower than 110 mmHg). Twenty-four-hour ambulatory blood pressure monitoring was done in all subjects to exclude white coat hypertension. Twenty hypertensive patients were randomized into either red ginseng treated group or non-treated group. Ten healthy volunteers were also enrolled.

Informed consents were obtained from all subjects before enrollment. Exclusion criteria were as follows: 1) Age under 18 or over 70, 2) being pregnant or planning pregnancy, 3) secondary hypertension, 4) malignant or accelerated hypertension, 5) nephrotic syndrome, 6) history of stroke within 3 months, 7) history of acute myocardial infarction or unstable angina within 3 months, 8) congestive heart failure, 9) renal dysfunction of more than moderate degree (serum creatinine > 150 μmol/L), 10) hepatic dysfunction (AST/ALT more than two-fold of normal value), 11) dementia, 12) alcoholics or other drug abusers, 13) inability to maintain medication during the study period, 14) failure to obtain informed consent

Among the 10 treated patients, two did not consent to plethysmographic examination and examination was impossible in one patient due to failure of arterial cannulation. Plethysmography and evaluation of endothelial function was successfully done in the remaining 7 patients. The study was completed in the non-treated hypertensive group and the normal control group, with 10 patients each.

All subjects had no evidence of ischemic heart disease or atherosclerosis. The possibility of secondary hypertension and coexisting diseases was ruled out by history taking, physical examination, electrocardiography, chest X-ray, and blood chemistry. Table 1 shows age, sex, blood pressure, serum creatinine, and total cholesterol and blood glucose of

Table 1. Clinical Information of Ginseng-treated Hypertensive Group (n=7)

No.	Sex/ Age	Mean BP (mmHg)	Duration of treatment (months)	Fundus change (degree)	Serum Cr (mg/dl)	Glucose (mg/dl)	Cholesterol (mg/dl)
1	M/52	127	24	2	0.8	93	216
2	F/60	104	21	0	0.7	160	184
3	F/47	138	26		0.8	92	138
4	M/72	127	24	0	1	98	133
5	F/59	139	23		0.8	88	132
6	M/67	130	27	3	1.1	89	170
7	F/58	125	23		0.8	80	160
Average	59.3	127.14	24.0		0.86	100.00	161.86
SD	8.4	11.60	2.0		0.14	27.02	31.05

SD: standard deviation

the subjects, duration of ginseng treatment, fundus findings and blood chemistry of the ginseng-treated hypertensive group.

Table 2 summarized the finding of ambulatory blood pressure monitoring in the Ginseng-treated group.

Table 2. Blood Pressures of Ginseng-treated Hypertensive Group on 24-Hour Ambulatory Blood Pressure Monitoring (n=7)

	Daytime BP			Pressure Load	
	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)	SBP %	DBP %
Cho, J.K.	144	97	112	70	76.6
Park, B.N.	124	74	90	6.6	3.3
Kim, O.M.	159	93	115	83.8	67.7
Lee, W.M.	167	100	122	100	93.5
Lee, H.H.	165	99	121	90.6	78.1
Lee, J.H.	161	101	121	93.5	93.5
Seo, B.S.	145	98	113	78.1	84.3
Average	152.1	94.6	113.4	74.7	71.0
SD	15.4	9.4	11.1	31.6	31.3

SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, SD: standard deviation

Daytime; 8 am–11 pm

Pressure Load; promotion that SBP over 140 mmHg and DBP over 90 mmHg, respectively.

The ginseng-treated hypertensive group was significantly older than the other groups, with a mean age of 59.8 ($p < 0.05$), and showed significantly higher mean arterial pressure

($p < 0.001$). There was no significant difference of total cholesterol and blood glucose between the 3 groups. Two in the normal control group, 2 in the non-treated hypertensive group and 1 in the treated hypertensive group showed total cholesterol values higher than 200 mg/dL (Table 3).

Table 3. Clinical Information on All Subjects

	Control	Non-treated hypertensive	Ginseng-treated hypertensive	p value
N	10	10	7	
Age	40.6 ± 10.0	48.0 ± 10.0	59.3 ± 8.4	< 0.05
Sex (M:F)	5:5	2:8	3:4	NS
Mean arterial pressure	99.7 ± 6.6	129.0 ± 6.6	127.1 ± 11.6	< 0.001
Cr (mg/dl)	0.92 ± 0.2	0.88 ± 0.1	0.86 ± 0.1	NS
Cholesterol (mg/dl)	187 ± 28	194 ± 27	162 ± 31	NS
Glucose (mg/dl)	101 ± 10	102 ± 18	100 ± 27	NS

Values are mean ± SD

P values; hypertensive vs control group

Administration of Red Ginseng

In the red ginseng-treated group, the mean duration of red ginseng administration was 24 months (ranging 21–27 months). Red ginseng was prepared in capsular formulation, 300 mg each. The administered dose was 5 capsules, three times per day (4.5 g/day). No adverse effect was observed.

Measurement of Forearm Blood Flow

Plethysmography (Hokanson EC-R5, Issaquah, Washington) was used to measure forearm blood flow. At the time of examination, the subject had been administered red ginseng for at least 18 months.

Examination was done in a quiet room with the subject in a supine position and the forearm fixed at the same level as the right atrium. The brachial artery was cannulated with a 23-guage needle and perfused with a 5% dextrose water solution at the rate of 1 ml/min. A blood pressure cuff for adults was placed on the arm, a pediatric blood pressure cuff on the wrist, and a strain guage around the widest part of the forearm. The arm cuff was connected to a rapid cuff inflator (Hokanson E-10), the wrist cuff to a usual sphygmomanometer, and the strain guage to plethysmography. During the forearm blood measurement, the wrist cuff was inflated over systolic blood pressure to cut off the blood flow, the arm cuff was inflated abruptly to 40 mmHg to obstruct venous flow, and then the volume change of the forearm compartment was recorded. The measurement was done for 7 sec, repeated after a 15-sec pause for 7 times, and averaged.

Three vasodilating substances, acetylcholine (Ach), bradykinin (BK) and sodium nitroprusside (SNP) were used in this study. The vasodilators were administered in randomized order. A micro-infusion pump was used for intraarterial administration. Infusion rates for acetylcholine, endothelium-dependent vasodilatory substances were 7.5 μg/min(Ach 1),

15 μg/min (Ach 2) and 30 μg/min (Ach 3); for sodium nitroprusside 0.8 μg/min (SNP 1), 1.6 μg/min (SNP 2) and 3.2 μg/min (SNP 3); for bradykinin 100 ng/min (BK 1), 200 ng/min (BK 2) and 400 ng/min (BK 3). The concentrations of the drugs were adjusted so that infused volume per time at each particular step was the same for the three drugs, that being 0.25, 0.5, 1 ml/min. The duration of infusion was 5 min for each dose level with a 15-min pause taken between one drug and the next. Blood flow measurements were done during the last 2 min of each dose level.

Statistical Analysis

The Mann-Whitney U test was used for comparison of blood chemistry value and forearm blood flow according to the groups and dose levels. A p-value of less than 0.05 was considered to be significant.

Results

Arterial Blood Pressure Changes

Arterial blood pressure did not change significantly in any of the three (control, non-treated hypertensive and ginseng-treated hypertensive) groups with infusion of any three vasoactive substances (Ach, BK and SNP) used.

Forearm Blood Flow Change to Acetylcholine

The forearm blood flow of the ginseng-treated group at basal state did not differ significantly from the non-treated hypertensive group, but was significantly higher than the control group. As the infusion rate of acetylcholine increased, the forearm blood flow of the ginseng-treated group became significantly greater than that of the non-treated hypertensive group.

The forearm blood flow of the non-treated group at the highest dose (Ach 3) was 5.29 ± 1.86 ml/min/100 ml forearm tissue, which was significantly smaller than that with a lower dose (5.9 ± 3.4 in Ach 1, 6.2 ± 3.1 in Ach 2). In the comparison with the control group, blood flows at Ach 2 and Ach 3 were significantly smaller than the control group ($p < 0.05$).

Maximal blood flow rates of the control, non-treated hypertensive and treated hypertensive groups were 11.0 ± 2.5, 5.3 ± 1.9, 13.7 ± 4.0 ml/min/100 ml forearm tissue respectively (p value between non-treated and treated groups = 0.001).

The blood flow of the ginseng-treated group at Ach 3 was 13.73 ± 3.97 ml/min/100 ml forearm tissue, which was significantly higher than that of the non-treated hypertensive group ($p=0.0008$) but did not differ significantly from that of the control group ($p=0.14$). The difference of blood flow when compared to the non-treated hypertensive group was also significant at a lower dose level of acetylcholine ($p=0.001$ in Ach 1, $p=0.0001$ in Ach 2).

More vasodilatory reserve of the ginseng-treated group was shown at the lower dose level of acetylcholine (Ach 1, Ach 2) compared to the control group ($p=0.0003$ in Ach 1, $p=0.0004$ in Ach 2). After correction for the baseline blood flows that were significantly different between the ginseng-treated and control groups, degrees of blood flow change were not significantly different. Such a finding was not observed at the highest dose level (Ach 3) (Figure 1 and Tables 4 and 5).

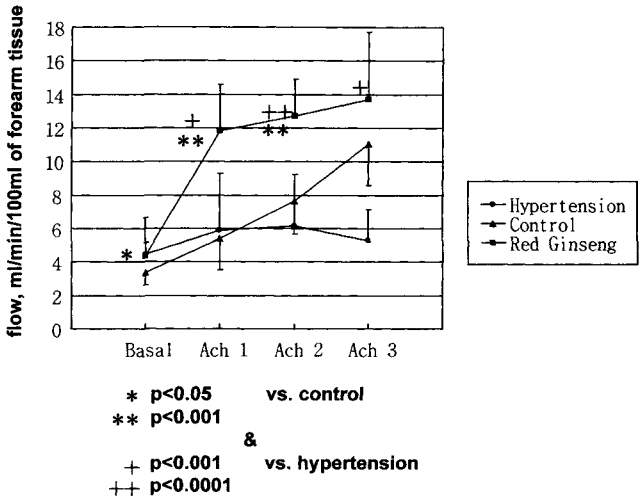

Figure 1. Forearm blood flow responses to acetylcholine (Ach) (mean, SD).

Table 4. Forearm Blood Flow Responses to Acetylcholine (Ach), Bradykinin (BK) and Sodium Nitroprusside (SNP)

	Control	Non-treated hypertensive	Ginseng-treated hypertensive	p-value for ginseng-treated group vs. control	p-value for ginseng-treated group vs. non-treated
Basal	3.4 ± 0.7	4.5 ± 2.2	4.4 ± 0.8	0.02	0.91
Ach 1	5.4 ± 1.9	5.9 ± 3.4	11.8 ± 2.8	0.0003	0.001
Ach 2	7.7 ± 2.0	6.2 ± 3.1	12.7 ± 2.2	0.0004	0.0001
Ach 3	11.0 ± 2.5	5.3 ± 1.9	13.7 ± 4.0	0.15	0.0008
Basal	3.4 ± 0.7	4.5 ± 2.2	4.4 ± 0.8	0.02	0.91
BK1	8.1 ± 2.0	7.9 ± 3.5	10.1 ± 3.9	0.24	0.26
BK2	10.6 ± 2.1	9.2 ± 3.2	12.8 ± 4.0	0.22	0.07
BK 3	12.5 ± 1.9	12.0 ± 3.6	16.2 ± 4.0	0.05	0.04
Basal	4.5 ± 2.2	3.4 ± 0.7	4.4 ± 0.8	0.02	0.91
SNP 1	7.6 ± 3.9	6.3 ± 1.4	8.7 ± 1.0	0.0007	0.41
SNP 2	8.9 ± 3.8	8.2 ± 1.6	10.0 ± 2.5	0.12	0.48
SNP 3	10.6 ± 3.7	10.5 ± 2.4	12.0 ± 2.8	0.29	0.41

Scale of flow; ml/min/100 ml of forearm tissue

Forearm Blood Flow Change to Bradykinin

During infusion of bradykinin at lower doses (Ach 1 and 2), blood flow of the ginseng-treated group was not significantly different from those of the control and non-treated groups. Blood flow of the non-treated group at the highest dose of bradykinin (BK 3) was 11.96 ± 3.57 ml/min/100 ml forearm tissue, which was similar to the control group

Table 5. Comparison of Percent Increase of Forearm Blood Flow Responses to Acetylcholine (Ach), Bradykinin (BK) and Sodium Nitroprusside (SNP) Between Control (n=10) and Red Ginseng (n=7) Groups

	Control	Ginseng-treated hyptertensive	p value
Ach 1	67.8 ± 76.9	178.2 ± 83.8	0.02
Ach 2	137.6 ± 89.9	199.4 ± 76.6	0.15
Ach 3	241.1 ± 106.8	230.5 ± 140.0	0.87
BK 1	152.3 ± 98.7	130.0 ± 71.3	0.59
BK 2	208.8 ± 114.0	191.1 ± 60.4	0.69
BK 3	200.0 ± 162.6	273.9 ± 74.7	0.23
SNP 1	95.9 ± 79.0	105.8 ± 43.5	0.74
SNP 2	156.6 ± 92.6	131.3 ± 41.1	0.46
SNP 3	227.7 ± 117.1	178.8 ± 64.3	0.29

Scale of flow; % increase compared to basal flow

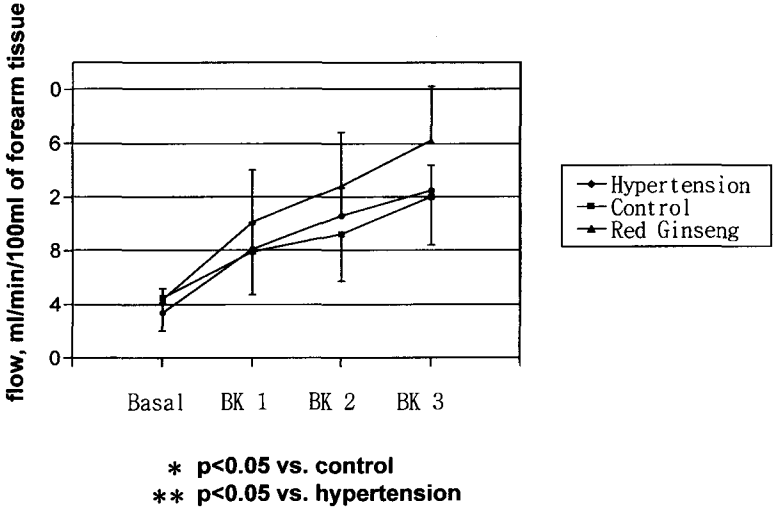

Figure 2. Forearm blood flow responses to bradykinin (BK) (mean, SD).

(p=0.69). Forearm blood flow of the ginseng-treated group at the highest dose level of bradykinin (BK 3) was 16.2 ± 4.0 ml/min/100ml forearm tissue, which was higher than the non-treated hypertensive group with marginal significance (p=0.04) (Figure 2 and Tables 4 and 5).

In the control group, forearm blood flow response to bradykinin was not significantly different from that to acetylcholine.

Forearm Blood Flow Change to Nitroprusside

Blood flow of the non-treated hypertensive group during infusion of nitroprusside, an endothelium-independent vasodilator, at lower doses, was not significantly different from those of the control group. Blood flow at the highest dose (SNP 3) was 10.5 ± 2.4 ml/min/100ml forearm tissue, which was also similar to the control group (p=0.94).

The ginseng-treated hypertensive group did not show any significant difference in forearm blood flow at all dose levels. Forearm blood flow at the highest dose level of nitroprusside was 11.97 ± 2.83 ml/min/100 ml forearm tissue (Figure 3 and Tables 4 and 5).

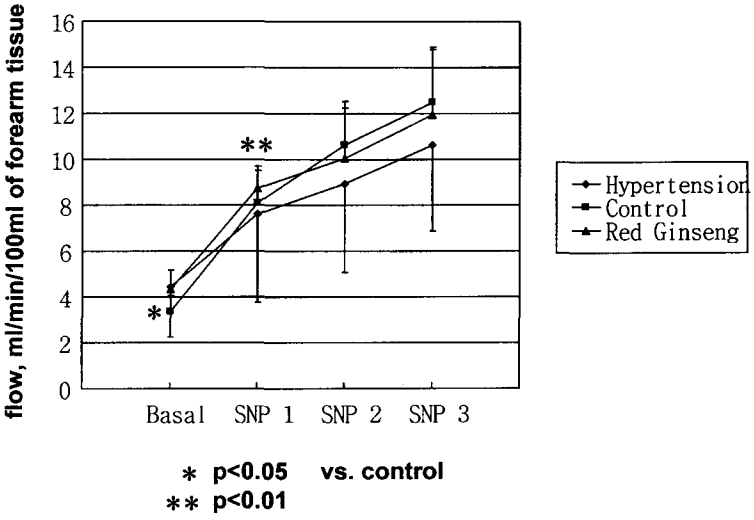

Figure 3. Forearm blood flow responses to sodium nitroprusside (SNP) (mean, SD).

Discussion

The remarkable result of this study is that, while the vasodilatory response to acetylcholine, endothelium-dependent vasodilatory substance was impaired in the non-treated hypertensive group, the ginseng-treated hypertensive group vasodilatory response was not so impaired, and was even comparable to that of the normal control group. This finding suggests that endothelial dysfunction due to hypertension can be improved by administering Korean red ginseng, i.e., secretion and/or synthesis of nitric oxide, endothelium-derived relaxing factor or vascular responsiveness to NO can be recovered to a normal level.

Extracts of Korean red ginseng have been proved to enhance NO synthesis and secretion from endothelial cells in animal experiments and *ex vivo* experiments using an organ chamber. Kim *et al.* (1992) showed that ginsenoside was effective in reducing free radical injury in rabbit pulmonary circulation model and its effect disappeared on administration of nitro-L-arginine, NO synthase inhibitor, and that cultured bovine aortic endothelial cells increasingly transformed L-arginine into L-citrulline on the addition of ginsenoside (10 μg/ml), suggesting ginsenoside can enhance NO secretion. Kang *et al.* (1995a) reported results of a study using an organ chamber model that, while acetylcholine-induced vasodila-

tion was impaired in thoracic vessel from rabbits fed with a high-cholesterol diet for 8 wks, normal vascular responsiveness was observed in a ginsenoside-treated (50/mg/kg/day) rabbit's vessel. Kang *et al.* (1995b) reported that the protopanaxatriol group among ginsenosides enhanced the endothelial synthesis of NO, which caused an increase in cyclic GMP in smooth muscle cells and subsequent vasodilation. Our study is the first study that shows the ability of Korean red ginseng to increase synthesis and release of NO, which enhances vascular vasodilation and reverses the endothelial dysfunction due to endothelial dysfunction.

The forearm blood flow of the non-treated hypertensive group at Ach 3 was lower than the blood flow at the lower doses. This phenomenon is possibly due to the pathological states of the arteries of hypertensive subjects. It is known that acetylcholine stimulation of endothelial cells in spontaneously hypertensive rats results in the production and release of prostaglandin H_2, which is a strong candidate for endothelium-derived contracting factor (Kato *et al.,* 1990). Another study reported that superoxide anion is an endothelium-derived contracting factor in canine cerebral arteries (Katusic *et al.*, 1990).

Unlike the previous study, pulverized red ginseng, not extract of red ginseng, was administered in our study, and the administered dose was 4.5 g/day, which was smaller than the empirical dose extrapolated from a dose of 50 mg/kg ginsenoside in previous animal experiments. Therefore, it is suggested that the pharmacological effect can be shown in humans with a smaller dose than the previously administered empirical dose.

Another considerable result was that the vasodilatory response to bradykinin, endothelium-dependent vasodilatory substance other than acetylcholine, was reserved in hypertension irrespective of ginseng treatment. Considering the equivalent vasodilatory effect with acetylcholine and bradykinin in the control group, this suggests the selective inhibition of acetylcholine-induced vasodilation.

Acetylcholine and bradykinin have different intracellular pathways of signal transduction. Acetylcholine stimulates muscarinic receptors of endothelial cells and G_i proteins, and bradykinin stimulates kinin receptors and G_q proteins (Tkachuk *et al.,* 1991; Shimokawa *et al.,* 1990). An experimental animal model using porcine coronary artery showed an impairment of the vasodilatory response to a substance which operated through G_i protein and a reserved response to bradykinin and other vasoactive substances in the initial phase of hyperlipidemia, which also decreased late in advanced atherosclerosis (Tanner *et al.,* 1991). In hypercholesterolemic patients without atherosclerosis, the vasodilatory response was blunted to acetylcholine but not to bradykinin (Palmer *et al.,* 1987). These studies suggest that hyperlipidemia in the initial phase selectively inhibits acetylcholine-stimulated intracellular signal transduction pathway.

In arterial hypertension, Kelm *et al.* (1996) reported that endothelium-dependent, NO-mediated dilation of resistance arteries and cutaneous microvessels of the forearm vasculature is heterogeneously impaired, depending on the type of endothelial receptor stimulated. In our study, the non-treated hypertensive group included initially diagnosed cases, and their vasodilatory responses to bradykinin were shown to be reserved. It was suggested that endothelial dysfunction was not selective, i.e., vasodilatory responses to both acetylcholine and bradykinin were impaired in studies including hypertensive patients whose duration of disease was 5 years or more (Panza *et al.,* 1990; Panza *et al.,* 1993a; Panza *et al.*, 1993b). Therefore, endothelial dysfunction due to hypertension is thought be selective initially, similar to that caused by hyperlipidemia.

Considering that the ginseng-treated group had a duration of disease of more than 3 years and was of a relatively old age (mean 59.3 of age), their normal response to bradykinin was remarkable. This result suggests that the effect of Korean red ginseng on endothelial function is related not only to intracellular signal transduction activated by acetylcholine as previously noted, but also to that simulated by bradykinin. Bradykinin is a locally active, intrinsic hormone, which stimulates release of not only NO but also prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) resulting in vasodilation (Ignarro *et al.,* 1987). Further study is needed to clarify whether red ginseng has an influence on bradykinin-associated intracellular transduction pathway, comparing vasodilatory response with and without arginine analogue, selective NO inhibitor.

In our results, the forearm blood flow response to bradykinin was greater in the ginseng-treated group, but with marginal significance. This may be due to the relatively small sample size and unbalanced group size.

The results of forearm blood flow with nitroprusside, an endothelium-independent vasodilator, showed that red ginseng has no significant effect on the vasodilatory response to exogenous nitric oxide in hypertensive patients.

One of the limitations of this study is that despite the definite improvement of endothelial dysfunction due to hypertension by Korean red ginseng, it could not be shown whether Korean red ginseng can *prevent* the development of endothelial dysfunction due to hypertension, or improve endothelial dysfunction in patients with advanced atherosclerosis.

Another limitation is the relative small sample size. However, plethysmography has been known to be highly accurate with few false positives in evaluating endothelial function, and also highly reproducible. We averaged 7 repeated measurements in each patient at each dose level, so we do not consider accuracy and/or precision to be a serious problem.

In conclusion, results of our study show that long-term administration of Korean red ginseng can improve endothelial dysfunction associated with essential hypertension. It is expected that treatment with Korean red ginseng can prevent or decrease the development of atherosclerosis due to hypertension, and a large-scale clinical trial is warranted to confirm this expectation.

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