was observed in the diet group (−8/−4 mmHg) but not in the troglitazone group (+1/+1 mmHg).

Therefore, weight reduction by restriction of the dietary intake causes clear reductions in BP of overweight hypertensives throughout the day. The effects of weight reduction may not be due to a reduction in calorie intake itself or an improvement in insulin sensitivity.

Exercise

Intervention studies have shown that exercise lowers BP in hypertensive and normotensive subjects. However, the antihypertensive effect of exercise appears to be modest. According to meta-analysis of controlled studies aerobic training causes a reduction in casual BP by an average of 5.3/4.8 mmHg, with a greater effect in hypertensive patients than normotensive subjects [8]. Several studies comparing the effects of exercise and weight reduction have shown that BP is decreased significantly by weight loss but not by exercise [9].

In a randomized crossover study, we examined the effects of daily walking (30–60 min for 4 weeks) in 65 hypertensive patients [10]. The number of steps increased from 5300–10 000/day in the walking period, while body weight did not change. Office, home, and 24-h BPs fell with the daily walking by 2.6/1.3 mmHg ($P<0.05$), 2.1/1.5 mmHg ($P<0.01$), and 2.4/1.8 mmHg ($P<0.01$), respectively. The changes in home BP and 24-h BPs were more significant than those in office BP. These results suggest that increasing physical activity acts to reduce 24-h and home BPs. However, the effect of exercise without weight loss appears to be small.

Sodium restriction

The antihypertensive effect of dietary salt restriction has been demonstrated in a number of clinical studies. In hypertensive patients, a decrease in office systolic BP of 1–2 mmHg can be expected with a reduction in salt intake by 1 g/day, while the fall in BP is less in normotensive subjects [11]. However, the effect of salt on BP varies widely among individuals as the known presence of salt-sensitive and non-salt-sensitive (or salt-resistant) hypertensives.

We studied the effects of a low-salt diet (25 mmol/day for 7 days versus 250 mmol/day) in 20 hypertensive patients [12]. The average 24-h BP decreased by 9/4 mmHg with the low-salt diet. This hypotensive effect was observed throughout the day. In non-salt-sensitive patients, 24-h heart rate and the LF/HF ratio of heart rate variability increased while the HF component decreased significantly. In salt-sensitive patients, the responses of heart rate and power spectral parameters to the low-salt diet were blunted.

In another study from our department, the nocturnal BP fall was absent in salt-sensitive patients but was preserved in non-salt-sensitive patients on a high-salt diet [13]. Dietary salt restriction caused greater reduction in nighttime BP than daytime BP in salt-sensitive patients.

Therefore, restriction of sodium intake is effective in the control of BP over 24 h. Salt-sensitive patients who are non-dippers on a high-salt diet may become dippers with sodium restriction.

Mineral supplementation

Potassium, calcium, and magnesium may have antihypertensive effects since dietary intake of these minerals has been shown to be inversely related to the level of BP [14,15]. Meta-analysis showed a significant reduction in casual BP with potassium supplementation [16]. The average reduction was 3.1/2.0 mmHg with 75 mmol/day of supplemented potassium. The effects of calcium supplementation on BP are not clear since conflicting results have been reported. In meta-analysis, pooled estimates of the effect of calcium supplementation (0.5–2 g/day) were only −0.9/−0.2 mmHg, and was significant only for systolic BP [17]. Inconsistent effects of magnesium supplementation on casual BP have also been reported [18].

We carried out a series of randomized crossover studies of mineral supplementation in 50–60 patients with hypertension (Table 1). Potassium supplementation (64 mmol/day for 4 weeks) decreased office, home and 24-h BPs [19]. Changes in home and 24-h BPs were highly significant ($P<0.001$) compared with office BP ($P<0.05$). Supplementation of magnesium (20 mmol/day for 8 weeks) also reduced office, home, and 24-h BPs significantly [20]. However, the effects of calcium supplementation (25 mmol/day for 8 weeks) were small and were significant only for home BP [21].

Increasing dietary intake of potassium, calcium, and magnesium appears to be beneficial in the management

Table 1 Effects of potassium, calcium and magnesium supplementation on 24-h ambulatory blood pressure in hypertensive patients

	K suppl. (64 mmol/day)	Ca suppl. (25 mmol/day)	Mg suppl. (20 mmol/day)
Office			
SBP (mmHg)	−2.7 ± 1.1*	−2.0 ± 1.0	−3.7 ± 1.3**
DBP (mmHg)	−1.4 ± 0.6*	−1.1 ± 0.7	−1.7 ± 0.7*
Home			
SBP (mmHg)	−3.6 ± 0.9***	−1.9 ± 0.7*	−2.0 ± 0.8*
DBP (mmHg)	−1.6 ± 0.5**	−1.3 ± 0.6*	−1.4 ± 0.6*
24-h			
SBP (mmHg)	−3.4 ± 1.0***	−1.2 ± 0.8	−2.5 ± 0.8**
DBP (mmHg)	−1.2 ± 0.5*	−0.9 ± 0.5	−1.4 ± 0.6*

mean ± SE, *$P<0.05$, **$P<0.01$, ***$P<0.001$ *vs* control period. SBP, systolic blood pressure; DBP, diastolic blood pressure [20].

of hypertension, although its antihypertensive effect may be small. Among those minerals, the effect of potassium may be greater than calcium or magnesium.

Alcohol restriction

The hypertensive effect of alcohol has been demonstrated in a number of observational studies. This effect was seen regardless of race and kind of alcoholic drinks, and was estimated to be approximately 1 mmHg per 10 ml of ethanol [22]. Intervention studies have also shown that reduction of alcohol intake lowers casual BP in hypertensive and normotensive subjects. However, alcohol has both pressor and depressor actions, and the latter are obvious in Asian subjects, especially in those who show alcohol flush [23].

We studied the effects of a single moderate dose of alcohol (1 ml/kg) in 16 hypertensive patients [23]. Blood pressure decreased and heart rate increased for several hours after alcohol ingestion. These changes were marked in patients showing facial flush but were small in patients without flush.

We also examined the effects of repeated intake of alcohol (1 ml/kg with dinner for 7 days) in 14 hypertensive patients under standardized conditions [24]. On day 7, BP decreased in the late evening (−13/−8 mmHg) but increased in the early morning (7/4 mmHg). Average 24-h BP did not change.

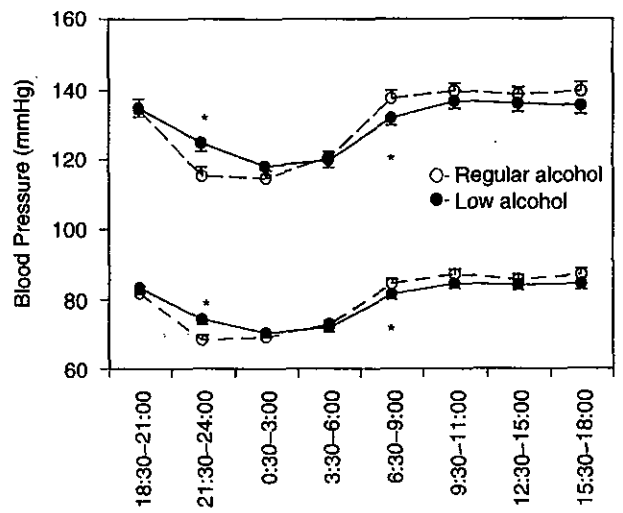
In a randomized crossover study, we investigated the effects of alcohol restriction for 4 weeks in 34 habitual drinkers with hypertension [25]. The mean ethanol intake decreased from 66 to 11 ml/day. Daytime BP fell by 3/2 mmHg but night-time BP rose by 4/2 mmHg (Fig. 1). The average 24-h BP did not change (−1/0 mmHg) while 24-h heart rate decreased by 4 b/min. The restriction of alcohol intake significantly increased the day–night BP difference, with a decrease in non-dippers and an increase in extreme-dippers.

Therefore, the effects of alcohol restriction on BP appear to be qualitatively and quantitatively different from other non-pharmacological measures such as sodium restriction, at least in Japanese subjects [26]. Although a small decrease in 24-h BP with alcohol restriction was observed in Caucasians [27], the hypertensive effect of alcohol may be overestimated by the conventional measurement of casual BP during the daytime.

Smoking cessation

In epidemiological studies, smokers usually do not show higher levels of BP than non-smokers. However, smoking acutely increases BP and heart rate through activation of the sympathetic nervous system. Studies using ambulatory

Fig. 1



Twenty-four hour blood pressure profile in hypertensive patients on regular alcohol consumption (66 ml/day) and on restricted alcohol intake (11 ml/day). * $P < 0.05$ between the two periods. Modified from *American Journal of Medicine*, **105**, Kawano Y *et al.*, Effects of alcohol restriction on 24 hour ambulatory blood pressure in Japanese men with hypertension, 307–311, Copyright 1998 with permission from Excerpta Medica Inc.

BP monitoring have revealed that daytime BP is higher in smokers than in non-smokers among hypertensive patients [28], and is higher on smoking than on non-smoking days in normotensive subjects [29].

We examined the effects of smoking cessation (one day) in 16 hypertensive smokers [30]. Daytime BP was significantly lower on the non-smoking day than the smoking day (by 7/5 mmHg), while night-time BP was comparable between the two periods. Daytime heart rate also decreased significantly. Smoking cessation significantly increased the day–night BP difference.

Thus, the hypertensive effect of smoking appears to have been underestimated. Cessation of smoking may improve BP control in hypertensive patients if they can maintain a constant body weight.

Conclusion

Monitoring of 24-h BP and home BP is useful in the non-pharmacological management of hypertension. These methods can detect small changes in BP in a moderate number of subjects. Effects of various lifestyle modifications on 24-h BP and home BP are qualitatively and quantitatively different. Ambulatory BP monitoring is particularly suitable in the assessment of changes in lifestyle affecting the circadian pattern of BP such as alcohol consumption and smoking.

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● Session I-3

本態性高血圧患者における家庭血圧コントロールと尿アルブミン排泄量

－HOSP Sub-Study－

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はじめに

高血圧患者における微量アルブミン尿は，初期の腎障害の指標であるとともに，心血管合併症の予知因子であることが知られている[1,2]。また，家庭血圧は日常生活での血圧を反映し，外来血圧より臓器障害や予後に強く関連している[3,4]。

しかし，これまでの腎と高血圧についての介入研究は外来血圧に基づいており，家庭血圧に基づいたものはない。また，腎硬化症による末期腎不全は増加しているが，腎機能低下がない本態性高血圧患者の腎保護に最適な血圧値や降圧薬は明らかではない。

本研究は，家庭血圧に基づいた介入試験 Hypertension Control Based on Home Systolic Pressure (HOSP) 研究の一部として，高血圧患者における家庭血圧コントロールの尿アルブミン排泄量(UAE)への影響を検討したもので，その中間結果を報告する。

1 方　法

HOSP 研究に登録された国立循環器病センターの本態性高血圧症例 72 名（年齢 64 ± 9 歳，m ± SE）を対象とした。明らかな腎機能低下や蛋白尿を有する例はなかった。

HOSP 研究は家庭血圧に基づいた高血圧治療の共同研究であり，厚生労働省循環器病委託研究「高血圧の大規模臨床試験研究施行のための総合的研究」の一部として行われている。高血圧患者を対象として家庭での収縮期血圧に基づいた二つのレベルの降圧目標を設定し，カルシウム (Ca) 拮抗薬とアンジオテンシン II (AII) 受容体拮抗薬を初期選択薬として降圧治療を行い，目標血圧値の達成度や忍容性，臓器障害，心血管事故などについて検討することを目的とするものである[5]。対象は未治療または休薬可能な本態性高血圧患者で，無投薬時の外来および朝の家庭収縮期血圧が 140mmHg 以上 200mmHg 未満の者である。年齢は40歳以上80歳未満で，脳卒中や心筋梗塞の既往，重篤な合併症を有する者は除く。follow-up は最低1年間で，5年間を予定している。

対象者には4週間の無治療期の後，降圧目標と降圧薬を無作為に割付けて治療を行った。降圧目標は，①朝の家庭収縮期血圧 140mmHg 未満，②同 130mmHg 未満とし，降圧薬は，I. アムロジピン 2.5 → 5mg，1 ×朝，II. ロサルタン 25 → 50mg，1 ×朝とした。はじめの3ヵ月間は

Key words：Essential hypertension, Urinary albumin excretion, Home blood pressure, Amlodipine, Losartan

国立循環器病センター内科高血圧腎臓部門

表1　降圧目標および降圧薬による各群の朝の家庭収縮期血圧の経過

	治療前	3ヵ月後	1年後
降圧目標			
140mmHg未満	150 ± 11	139 ± 12 *	133 ± 5 *
130mmHg未満	148 ± 6	135 ± 11 *	127 ± 5 *,+
降圧薬			
アムロジピン	149 ± 9	134 ± 8 *	129 ± 6 *
ロサルタン	149 ± 9	140 ± 14 *,+	130 ± 6 *

単位：mmHg，*：$p < 0.05$ vs 治療前，+：$p < 0.05$ vs 他群

表2　降圧目標および降圧薬による各群の尿アルブミン排泄量の経過

	治療前	3ヵ月後	1年後
降圧目標			
140mmHg未満	33 ± 37	41 ± 68	36 ± 28
130mmHg未満	42 ± 45	38 ± 42	27 ± 34 *
降圧薬			
アムロジピン	40 ± 43	36 ± 35	31 ± 25
ロサルタン	36 ± 21	43 ± 69	31 ± 36

単位：mg/day，*：$p < 0.05$ vs 治療前

単剤治療とし，降圧が不十分な場合には，以後I群はAII拮抗薬およびアンジオテンシン変換酵素（ACE）阻害薬以外，II群はCa拮抗薬以外の降圧薬を追加した。

外来血圧は坐位で2回測定され，平均値を用いた。家庭血圧はほぼ毎日，早朝と夜に各3回測定され，受診前3日間の平均値を求めた。また治療前および3ヵ月後（$n = 69$），1年後（$n = 40$）に血液生化学検査と24時間蓄尿を行い，血清クレアチニン濃度やUAE等を調べた。

データは平均値±標準偏差で表わした。統計解析はpairedおよびunpaired t-testにより，$p < 0.05$を有意とした。

2 結　果

治療前の血圧値は，外来159 ± 12/95 ± 9 mmHg，家庭朝149 ± 9/91 ± 8mmHg，家庭夜142 ± 13/87 ± 10mmHgであり，外来血圧は家庭血圧より，また家庭血圧の朝は夜より有意に高値であった。目標140mmHg未満群（$n = 36$）と130mmHg未満群（$n = 36$），アムロジピン群（$n = 34$）とロサルタン群（$n = 38$）との間に差はなかった（**表1**）。血清クレアチニン濃度は0.7 ± 0.2mg/dL，UAEは38 ± 42mg/dayであった。微量アルブミン尿（30～300mg/day）は36%に認められた。

3ヵ月後の血圧値は，いずれも治療前より低下した。目標140mmHg未満群と130mmHg未満群との差は有意ではなかった（**表1**）。アムロジピン群はロサルタン群より外来および朝の家庭血圧は有意に低値であり，夜の家庭血圧は両群で差はなかった。UAEは39 ± 55mg/dayで不変であった。

1年後の血圧値は，目標140mmHg未満群と130mmHg未満群との間に有意差がみられた（**表1**）。アムロジピン群とロサルタン群との外来および朝の家庭血圧の差は消失し，夜の家庭血圧は後者が低値となった。UAEは31 ± 31mg/dayと有意に減少し，微量アルブミン尿を呈する者は31%となった。UAEは目標血圧130mmHg未満群においては明らかに減少したが，140mmHg未満群においては不変であった（**表2**）。アムロ

ジピン群とロサルタン群は，UAEの変化には差がなかった。

3 考　　察

高血圧患者における降圧治療の臨床試験は，外来での拡張期血圧に基づいて行われてきたが，外来血圧より家庭血圧が，また拡張期血圧より収縮期血圧が，臓器障害や予後に強く関連することが明らかとなっている[3,4,6]。家庭血圧はまた，高血圧の薬物および非薬物療法の評価に有用であると考えられる[7,8]。本研究は家庭血圧に基づいた初の無作為介入試験HOSP研究のサブスタディであり，中間結果ではあるが朝の家庭血圧130mmHg未満へのコントロールによる本態性高血圧患者のUAEの減少が示された。

腎障害を伴った高血圧患者については，厳格な降圧治療の効果が示され，130/85mmHg未満へのコントロールが推奨されている[9]。しかし，腎障害のない高血圧患者においては，降圧治療によるUAEの減少は示されているが[10]，メタアナリシスでも腎障害予防効果は確認されず[11]，目標とする血圧レベルも明らかではない。本研究では，UAEは目標血圧130mmHg未満群では減少し，140mmHg未満群では不変であった。したがって，本態性高血圧患者においても，厳格な血圧コントロールが腎障害の進展の抑制に重要と考えられる。

腎障害を伴う高血圧に対してはACE阻害薬の有用性が確立し，高血圧性腎硬化症においてもACE阻害薬がCa拮抗薬より有効であることが示されている[12]。AII拮抗薬も糖尿病性腎症において，ロサルタンによる予後改善や，イルベサルタンがアムロジピンより効果的であったことが報告された[13,14]。腎機能低下のない本態性高血圧患者においては，ACE阻害薬がCa拮抗薬よりUAEの減少は大きいことが観察されているが[15]，各種の降圧薬は同等であったとの報告もある[10]。本研究では，UAEへの効果はアムロジピン群とロサルタン群との間に差はなく，腎障害の進展抑制には薬剤の種類より降圧自体がより重要であることが示唆される。

結　　語

腎障害を伴わない本態性高血圧患者を対象として，朝の家庭収縮期血圧に基づいた2段階の目標血圧（140および130mmHg未満）と2種類の降圧薬（アムロジピンおよびロサルタン）による降圧治療の無作為介入試験を行い，中間結果を解析した。

朝の家庭収縮期血圧を130mmHg未満にするには，多くの例で併用治療を要した。外来および朝の家庭血圧への効果は，アムロジピンがロサルタンより有意に大きかった。

尿アルブミン排泄量は降圧治療1年後に有意に減少した。この効果は目標血圧130mmHg未満群では明らかで，140mmHg未満群ではみられなかった。アムロジピン群とロサルタン群との間には差はなかった。

家庭血圧を130mmHg未満にコントロールすることが，本態性高血圧患者における腎障害の進展の抑制に重要と考えられる。

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文　　献

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Effects of Control of Home Systolic Blood Pressure on Urinary Albumin Excretion in Patients with Essential Hypertension

— Preliminary Results of the HOSP Sub-Study —

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To investigate the effects of home blood pressure (BP) control and those of a calcium antagonist and an angiotensin II receptor antagonist on the kidney, we examined urinary albumin excretion (UAE) in 72 patients with essential hypertension (64 ± 9 years old, m ±SD) as a part of Hypertension Control Based on Home Systolic Pressure (HOSP) study. The participants were randomly assigned to the mild control (morning home systolic BP <140mmHg) and stirict control (<130mmHg) groups, and to the amlodipine (2.5~5mg/day) and losartan (25-50mg/day) groups after 4 weeks of washout period. Additional antihypertensive drugs were added after 3 months of monotherapy. Amlodipine was more effective than losartan to control office and morning home BP, while the effect on evening home BP was comparable. UAE did not change after 3 months, but decreased significantly after 1 year (n = 40) of antihypertensive therapy. This effect was obvious in the strict control group (42 ± 45 vs 27 ± 34mg/day) but not in the mild control group (33 ± 37 vs 36±28 mg/day). The effect on UAE was not different between the amlodipine and losartan groups. These results suggest that to control home systolic BP to less than 130mmHg may be effective in the prevention of future nephrosclerosis in patients with essential hypertension.

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家庭血圧測定を診療にどう生かすか

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家庭血圧測定を診療にどう生かすか

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はじめに ●

家庭用の血圧計は広く普及し，家庭血圧を測定している高血圧患者は多い．家庭血圧からは日常生活における血圧値を知ることができ，診察室での随時血圧測定のみではわからない有用な情報が得られる．家庭血圧は外来血圧より低いことが多いが，両者が大きく異なる場合も少なくない．本稿では，家庭血圧について概説するとともに，それを診療に生かすための要点を示したい．

家庭血圧の意義 ●

家庭血圧は診察室での随時血圧に比べて種々の利点があり，高血圧の診断と治療に大きな意義を有している(**表1**)[1]．

まず，家庭血圧の測定により日常生活における血圧を知ることができる．白衣高血圧の診断や降圧治療の適応決定，治療効果の判定に役立つ．

次に，家庭血圧は再現性がよく，測定回数も多いことから，信頼性に優れている．臓器障害や予後は，外来血圧より家庭血圧との関連が強い[2]．

また，家庭血圧はいつでも測定でき，自覚症状と血圧との関係を評価できることも利点の一つにあげられる．

さらに，自己測定により患者の血圧への意識が高まり，高血圧治療への理解が深まることが期待できるであろう．

このように，家庭血圧は高血圧患者の診療に役立つところが大きい．ほとんどの高血圧患者には，血圧計を保有して家庭での血圧を測定することが勧められる．

家庭血圧と外来血圧 ●

家庭血圧は，一般に外来での随時血圧より低い値を呈する．われわれの施設における未治療の高血圧患者では，差の平均は10/5 mmHg程度であった[3]．しかし，外来一家庭の血圧差は個人差が大きく，50 mmHg以上にもなることがある(表1)．

表1　家庭血圧の特徴

- 家庭血圧は日常生活における血圧を表す
- 家庭血圧は数多く測定でき再現性がよい
- 家庭血圧は自覚症状との関係を評価できる
- 臓器障害や予後は家庭血圧との関連が強い
- 家庭血圧は外来血圧より一般に低い
- 外来と家庭の血圧差は個人差が大きい
- 高血圧の基準は家庭血圧では低くなる

治療中の高血圧患者においても，大部分の例では家庭血圧は外来血圧より低い．われわれの検討では，差が20/10 mmHg以上の例は約20%であった[4]．

外来一家庭の血圧差は，白衣効果によるところが大きいが，血圧の日内変動や降圧薬の影響もある．また一部の例では，家庭血圧が外来血圧より高い逆白衣現象がみられる．

家庭血圧は，朝が夜よりいくらか高い場合が多い．24時間血圧との比較では，家庭血圧の平均値は24時間血圧値より少し高く，日中血圧値よりやや低値であった[5]．

家庭血圧計と測定指導 ●

家庭用の血圧計は種々のものが市販されているが，精度は上腕用のものが優れている．手首用の機種はやや精度が劣り，指用の機種は誤差が大きい．したがって，血圧計は上腕用のものが勧められる．手首用の機種はあまり勧められないが，精度検定で信頼できれば用いてもよいであろう．指用のものは勧められない．また，購入時および1～2年ごとに精度検定を行うことが望ましい．

家庭血圧の測定には一定の基準はないが，同じ

◎家庭血圧測定は，高血圧の診断と治療に大きな意義を有している．
◎家庭血圧は外来血圧より低いことが多いが，両者の差は個人差が大きい．
◎家庭血圧による高血圧の基準や治療目標値は，低めに設定する必要がある．

時間帯に測定し，自覚症の変化時などに追加するとよい．朝(起床後から朝食前)と夜(夕食2時間後から就寝前)に測定することが望ましい．毎日測るほうがよいが，厳密である必要はなく，患者の都合や意向に従って実行してもらえばよいであろう．

家庭血圧では，高血圧の基準は随時血圧に比べて低くなる．まだ診断基準は統一されていないが，135/85 mmHg以上であれば高血圧と考えられる．

患者への指導の際には，カフを正しく装着することや静かにして測定すること，血圧が常に変動していることを教えておく．神経質な患者では，家庭血圧の数値に心配しすぎることがある．また，勝手に降圧薬を調節しないように注意しておくべきであろう．

家庭血圧に基づいた高血圧治療 ●

これまで述べたように，家庭血圧は臨床的に有用であり，高血圧患者の治療は外来血圧よりむしろ家庭血圧に基づいて行うことが勧められる．ただし，そのためには家庭血圧が正しく測定されていなければならない．

家庭血圧を診療に生かすには，その特性や変動についての理解を要する(表1)．朝が夜より高い例が多いが，この傾向は降圧治療により強くなることがある．また，治療中の者では昼に著しい血圧低下を認める場合もある．このような変動は，短時間作用性の降圧薬で大きく，長時間作用性の薬剤では小さい．生活習慣も，朝と夜の家庭血圧に関係する．特にアルコールは血圧を2相性に変化させ，夜の降圧と朝の昇圧をもたらす．

家庭血圧に基づいた高血圧治療の例としては，白衣高血圧者や白衣現象の著しい患者において，不要なあるいは危険な降圧薬の増量を避けることができる．また，モーニング・サージの大きな患者では，薬剤の種類や服薬時間を変更することにより改善が期待できよう．ただし，家庭血圧では目標血圧も低めになることに留意する必要がある．

おわりに ●

家庭血圧は高血圧の診断と治療に大きな意義を有しており，大いに推奨される．家庭血圧の測定は降圧治療の決定と評価に有用であり，自覚症状と血圧との関係を評価でき，治療へのコンプライアンス向上も期待できる．家庭血圧での高血圧の診断とコントロールは低めに設定する必要があるが，これを診療に生かすことによって，個々の高血圧患者によりよい治療を行うことができるであろう．

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Original Article

A Single-Nucleotide Polymorphism in C-Type Natriuretic Peptide Gene May Be Associated with Hypertension

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We conducted an association study between genetic variants of C-type natriuretic peptide gene (*CNP*) and hypertension in a Japanese population. We found four genetic variants, two in the promoter region, one missense mutation, and one in the 3′-untranslated region (3′-UTR), and genotyped all four variants in 2,006 subjects recruited from the Suita study. One of the variants, G2628A in 3′-UTR, was found to be associated with blood pressure. Multiple logistic analyses indicated that the genotype of the G2628A polymorphism (GG=1, GA+AA=2) (p=0.0034), sex (p=0.0288), alcohol consumption (p=0.0002), age (p<0.0001), and body mass index (p<0.0001) were predictors of hypertension. The odds ratio of the GA+AA genotype over the GG genotype for hypertension was 1.40 (p=0.0034, 95% confidence interval (CI) 1.12–1.75). Multiple logistic analyses in a younger subpopulation aged below 65 years indicated that the odds ratio of the GA+AA genotype over the GG genotype for hypertension was 1.58 (p=0.0024, 95%CI 1.18–2.12). Thus, the *CNP* G2628A polymorphism made an even greater contribution to hypertension in the younger subpopulation.
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***Key Words*: genetic variants, blood pressure, epidemiology**

Introduction

Interactions between genetic and environmental factors are thought to play important roles in the pathogenesis of hypertension. The use of association studies in large epidemiological cohorts with a large number of single-nucleotide polymorphisms throughout a single gene or throughout the entire genome is a new strategy for identifying genes that contribute to high blood pressure (*1–3*). In the present study, we applied this strategy to the C-type natriuretic peptide (CNP) gene (*CNP*) to examine whether its genetic variants influence blood pressure.

The natriuretic peptides play important roles in cardiovascular homeostasis. A-type and B-type natriuretic peptides (ANP and BNP) are mainly produced in cardiac tissues and directly influence blood pressure and body fluid homeostasis (*4*). Although CNP is produced in endothelial cells, its level in the peripheral circulation is very low and does not appear to be associated with blood pressure status (*5*). On the other hand, the expression level of CNP in the central nervous system has been reported to be high (*6*), and intracerebroventricular CNP has been reported to lower blood pressure (*7*). These observations strongly suggest that CNP functions as a neuropeptide in regulating blood pressure and body fluid homeostasis. Thus, *CNP* is a candidate gene for human essential hypertension.

In the present study, we thoroughly searched for polymorphisms of *CNP* and performed an association study using a large epidemiological cohort. To our knowledge, this is the first report to investigate associations between *CNP* genetic variants and blood pressure.

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Table 1. Genetic Variants in *CNP*

Polymorphism	TaqMan probe	PCR primer
G733A	Fam-attgttcccacagaaggagttcaccagcgg	5′-ctctaggttcacgttcagccgg-3′
	Tet-attgttcccacagagggagttcaccagcg	5′-cctgtgaaagtgcacaggatactgg-3′
G1612C	Fam-cactgggaccctgctcgccct	5′-gcagctgggagagatgcatg-3′
	Tet-cactgggaccgtgctcgccct	5′-gagcagagtcacgggctcag-3′
G2347T	Fam-agattggcgcccccgccc	5′-gtcagaagaagggcgacaag-3′
	Tet-agattggcgaccccgcccc	5′-gttggctcctttgtatttgcg-3′
G2628A	Fam-ccgcccagccagccttcgga	5′-cctcaagctggaccgaatcg-3′
	Tet-cgcccagccggccttcgga	5′-cctagcacaacttgagcaaaggc-3′

The nucleotide numbers of polymorphisms are given according to the sequence in the GenBank database (accession No. E03598). G733A and G1612C are in the promoter region, G2347T is in exon 2 and shows an amino-acid change of Gly61Val, and G2628A is in the 3′-untranslated region of CNP mRNA.

Table 2. Linkage Disequilibrium among Polymorphisms

	G733A	G1612C	G2347T	G2628A
G733A		945**	118**	55**
G1612C			2	25**
G2347T				6*

The degree of linkage disequilibrium (LD) was estimated by contingency table analysis (Pearson). χ^2 values are shown. * $p=0.06$, ** $p<0.0001$.

Table 3. Characteristics of the Study Population

	Control	Hypertension
N (%male)	1,235 (46.4)	771 (50.5)
Age**	57.1 (0.3)	64.8 (0.4)
BMI**	22.3 (0.1)	23.4 (0.1)
Alcohol*	14.4 (0.8)	16.4 (0.8)
TChol*	208.2 (0.8)	213.3 (1.2)
TG**	119.2 (2.9)	138.2 (3.7)
HDL	58.8 (0.4)	58.1 (0.6)
MI (%)**	0.57	2.46
CVA (%)**	1.21	3.63
G733A (GG/GA/AA)	830/365/40	512/238/21
G1612C (GG/GC/CC)	1033/186/16	652/114/5
G2347T* (GG/GT)	1210/25	764/7
G2628A** (GG/AG/AA)	972/243/20	555/196/20

Values are expressed as the mean (SEM). BMI, body mass index (kg/m^2); Alcohol, alcohol consumption (ethanol mg/day); TChol, total cholesterol (mg/dl); TG, triglycerides (mg/dl); HDL, high density lipoprotein cholesterol (mg/dl); MI, myocardial infarction; CVA, cerebrovascular accident. * $p<0.05$, ** $p<0.01$.

Methods

Subjects

The selection criteria and design of the Suita study have been described previously (2). In the present study, subject information was made anonymous. The present study was approved by the Ethics Committee of the National Cardiovascular Center and by the Committee on Genetic Analysis and Genetic Therapy of the National Cardiovascular Center. Informed consent on genetic analysis was obtained from about 3,700 subjects, and the genotype of *CNP* was determined in 2,006 consecutive subjects. Subjects were categorized as hypertensives when they had a systolic blood pressure of ≦140 mmHg or a diastolic blood pressure of ≦90 mmHg. Subjects who were taking hypertensive medication were also categorized as hypertensives.

DNA Studies

Genomic DNA from 24 subjects was used as a template for sequence analyses. The promoter (up to −1 kb) and coding regions (exons 1 and 2) were sequenced. The region of the promoter and exon 1 was amplified by the following primers: 5′-ggaagttgaccacctgtcacggct-3′ (570–594 according to GenBank accession No. E03598) and 5′-cttccctctctc ctgggtcctgc-3′ (1904–1882). The region of exon 1, intron 1, and exon 2 was amplified by the following primers: 5′-ctgcaaatggagttcccctgtg-3′ (1339–1360) and 5′-gaagccaggtgg gttcaaccag-3′ (2792–2770). Polymorphisms were determined by the TaqMan system. The primers and probes are summarized in Table 1.

Statistical Analyses

Values are expressed as the means±SEM. All statistical analyses were performed with the JMP statistical package (SAS Institute Inc., Cary, USA). Multiple regression and multiple logistic analyses were performed with other covariates. Residuals of blood pressure values were calculated by adjusting for sex, age, and body mass index (BMI). Differences in numerical data among the groups were calculated by one-way analysis of variance (ANOVA) and the unpaired *t*-test. Differences in frequencies and the degree of linkage disequilibrium were tested by contingency table analysis.

Table 4. Characteristics of a Younger Subpopulation (<65 years)

	GG	GA	AA	*p*
N (%male)	981 (44.4)	272 (45.6)	27 (44.4)	ns
SBP	124.1 (0.6)	127.3 (1.2)	128.1 (3.7)	0.0344
DBP	79.4 (0.4)	81.4 (0.7)	80.1 (2.1)	0.0318
PR	67.1 (0.2)	67.0 (0.5)	66.9 (4.5)	ns
Age	52.9 (0.3)	53.4 (0.5)	54.9 (1.7)	ns
Alcohol	17.1 (0.8)	17.1 (1.6)	16.9 (4.5)	ns
BMI	22.8 (0.1)	23.2 (0.2)	23.0 (0.6)	ns
HTN (%)	27.7	38.2	44.4	0.0013
HTN medication (%)	10.9	12.9	14.8	ns

SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); PR, pulse rate per minute; HTN, presence of hypertension; HTN medication, medication for hypertension. Other abbreviations are the same as in Table 3.

Results

CNP Polymorphisms

We found 4 polymorphisms in *CNP*, which are summarized in Table 1. We found two polymorphisms in the promoter region, one polymorphism in the coding region (exon 2) that accompanied an amino acid change from Gly to Val at amino acid position 61, and one polymorphism in the 3′-non coding region. The pairwise linkage disequilibriums are summarized in Table 2. The genotype frequencies are given in Table 3.

Association Study

Table 3 shows characteristics of the study population. The GT genotype of the G2347T polymorphism is more frequent in hypertensives. The frequencies of the AG and AA genotypes in G2628A polymorphism are higher among hypertensives. Multiple logistic analyses which included sex, age, BMI, alcohol consumption, and genotype of *CNP* indicated that sex ($p=0.0288$), age ($p<0.0001$), BMI ($p<0.0001$), alcohol consumption ($p=0.0002$), and A2628G genotype (GG=1, GA+AA=2) ($p=0.0034$) were predictors of hypertensive status. The odds ratio of the GA+AA genotype of the G2628A polymorphism for hypertension was 1.40 (95% confidence interval (CI) 1.12–1.75) over the GG genotype.

It is generally accepted that genetic effects are more evident among younger subjects, whereas the phenotypes of older subjects are more strongly influenced by environmental factors. Therefore, we analyzed the effects of genotypes on blood pressure among younger subjects. Table 4 shows characteristics of the study population aged below 65 years according to the G2628A polymorphism. Multiple logistic analysis in this younger subpopulation indicated that age ($p< 0.0001$), BMI ($p< 0.0001$), alcohol consumption ($p=0.0029$), and A2628G genotype (GG=1, GA+AA=2) ($p=0.0024$) were predictors of hypertensive status. The odds ratio of the GA+AA genotype of the G2628A polymorphism for hypertension was 1.58 (95% CI 1.18–2.12) over the GG genotype. Thus, the *CNP* G2628A polymorphism made an even greater contribution to hypertension in the younger subpopulation.

Discussion

CNP is abundantly expressed throughout the brain, with particularly high concentrations found in the anterior pituitary (*6*). Since the receptor for CNP with guanylyl cyclase activity (natriuretic peptide receptor B; NPRB) is abundant in tissues of neural origin and is scarce in peripheral vasculature, CNP has less of a direct peripheral depressor effect than ANP and BNP (*8*, *9*). However, intracerebroventricular infusion of CNP has been reported to lower blood pressure and aldosterone secretion (*7*). Therefore, it is possible that genetic variations of *CNP* may influence blood pressure through their effects on the central nervous system.

In terms of salt sensitivity, we have studied the influence of genetic variants of *SCNN1A*, *SCNN1G* and *CYP11B2* on blood pressure in the same study population (*10–12*). Our results showed that a genetic variant of *SCNN1A* had a significant influence on blood pressure. In future studies, it would thus be intriguing to study the relationship between the effectiveness of diuretic therapy and genetic variants of *SCNN1A* and *CNP*.

In the present work, we studied 4 polymorphisms of *CNP*, two in the promoter region, one in the coding region that is accompanied by an amino-acid change, and one in the 3′-untranslated region (3′-UTR). The missense mutation is outside the loop structure that is very important for biological activity (*4*), and may not have biological significance. Only the G2628A genotype in 3′-UTR was associated with blood pressure. We speculated that this 3′-UTR polymorphism may influence the stability of CNP mRNA (*13*). We constructed artificial luciferase genes which had CNP 3′-UTRs. Transient expression analyses indicated that this 3′-UTR poly-

morphism had no significant influence on luciferase activity, thereby dismissing the hypothesis described above (data not shown). The biological significance of this polymorphism is unclear at present. Variations in linkage disequilibrium with this 3′-UTR polymorphism may be more important and may have biological significance.

CNP has been reported to be located at chromosome 2q24-qter. Four other genes with unknown functions are reported to exist within 50 kb of *CNP* (contig NT_022157.7). The distance for tight linkage disequilibrium may vary according to the chromosomal region and race, and may be beyond 50 kb (*14*). In this sense, it may be necessary to sequence and genotype a wider range of this chromosomal region to identify the genetic variations that truly influence blood pressure.

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Epsilon 4 allele of apolipoprotein E gene associates with lower blood pressure in young Japanese subjects: The Suita Study

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Objectives **The apolipoprotein ε4 allele (*APOE/ε4*) increases plasma cholesterol level and the risk for the late onset type of Alzheimer's disease. However, the correlation between hypertension and *APOE/ε4* has not yet been clarified. To examine the *APOE/ε4* effect in the general population of Japan, we performed a large genetic epidemiological survey (the Suita Study).**

Design and methods **The Suita Study was a cohort study based on a random sample of 14 200 Japanese residents of Suita city. Subjects who gave informed consent for genetic analysis were recruited in the current study ($n = 3997$). *APOE* polymorphism was clearly determined by the TaqMan polymerase chain reaction method.**

Results **Subjects with *APOE/ε4* were significantly ($P < 0.03$) more frequent (19.7%) in normotensives than in hypertensives (16.9%), the estimated odds ratio for hypertension (with *APOE/ε4* versus without *APOE/ε4*) being 0.83 [95% confidence interval (CI), 0.70–0.98]. The significance of the association (OR = 0.64; 95% CI, 0.48–0.86) was increased in young subjects (≤60 years old) but disappeared in old subjects. *APOE/ε4* also significantly contributed to a 2.9% increase of total cholesterol, 11.8% increase of triglyceride and 3.2% of decrease of high-density lipoprotein-cholesterol.**

Conclusions **We concluded that *APOE/ε4* was associated with an increase of plasma lipid levels and with a decrease of systolic blood pressure. The final conclusion on whether *APOE/ε4* contributes to the risk for cardiovascular disease will be clarified by analysis of the cumulative incidence, which will be obtained in the future Suita Study.**
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Introduction

Apolipoprotein E (apoE), a main apoprotein of the chylomicron, binds to a specific receptor on liver cells and peripheral cells. The three major isoforms of human apolipoprotein E (apoE2, E3, and E4) are coded for by three alleles (*ε2*, *3*, and *4*) at the structural locus in the apolipoprotein E gene (*APOE*) [1]. At codon 112/158, apoE2, E3, and E4 contain cysteine/cysteine, cysteine/arginine, and arginine/arginine, respectively. These *APOE* polymorphisms have been associated with risk of elevated serum lipids [2,3], coronary artery disease [4], and Alzheimer's disease [5,6]. However, even if it is commonly accepted that the *APOE/ε4* allele increases low-density lipoprotein (LDL)-cholesterol level and predisposition to Alzheimer's disease, the precise mechanism of its involvement in the genetic predisposition to cardiovascular disease has not yet been clarified. Especially, the obtained results concerning the association between the *APOE* polymorphism and stroke risk are inconsistent, suggesting that the *APOE* polymorphism is not only a modifier of lipid metabolism. On the other hand, Kimura *et al.* [7] reported that the survival rate of diabetic patients with renal disease in *APOE/ε4* carriers was higher than that in non-carriers. In their reports, the *APOE* polymorphism and hypertension were identified as independent risk factors for the progression to renal failure. Their results suggested that the *APOE* polymorphism is associated with the progression of diabetic nephropathy, and the presence of the *APOE/ε4* allele is a protective factor and other alleles are risk factors. To clarify the effect of *APOE* polymorphisms

on cardiovascular risk, we examined precisely their effect in a large Japanese general population.

Methods

Study population

The Suita Study was based on a random sample of 14 200 Japanese urban residents of Suita City, which is located in Osaka prefecture, the second largest urban area in Japan. Participants between the ages of 30 and 79 years were selected at random from the municipality population registry, and stratified by sex and age groups of 10 years [8]. Basic sampling of the population started in 1989 with a cohort study base, and 51.7% ($n = 7347$) of the subjects had paid an initial visit to the National Cardiovascular Center by February 1997. In addition to performing routine blood examinations, we extracted DNA from an extra 5 ml of blood withdrawn from those who visited the National Cardiovascular Center between May 1996 and February 1998. All participants were Japanese, and only those who gave informed consent for genetic analysis of 13 genes including *APOE* and storage of a DNA sample were enrolled in the present study.

Blood pressure measurement and criteria for hypertension

After more than 10 min of rest, systolic and diastolic blood pressure were measured twice. According to the recent criteria of the sixth report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC/VI) [9], hypertension was defined as a mean systolic blood pressure (SBP) of ≥140 mmHg, a mean diastolic blood pressure of ≥90 mmHg, or current administration of antihypertensive medication. The remaining population was simply defined as normotensive. Family history of hypertension was defined as having a father, mother or sibling with a history of hypertension.

Determination of genotypes according to APOE/ε2, ε3, ε4 allele combinations

To deal with the 4013 samples, we used the TaqMan polymerase chain reaction (PCR) method [10]. The following primers and probes were included in the reaction: FC2 forward primer, 5′-CGG ACA TGG AGG ATG TGC-3′; FT3 forward primer, 5′-GCG GAC ATG GAG GAT GTG T-3′; R1 reverse primer, 5′-CTC GCG GAT GGC GCT GA-3′; *ε2* allele specific probe (158TF), 5′-Fam-CAC TGC CAG GCA CTT CTG CA-Tamra-3′; *ε3, 4* allele specific probe (158CT), 5′-Tet-CTG CCA GGC GCT TCT GCA-Tamra-3′. PCR was carried out using a Gene Amp 9700 (Applied Biosystems, Inc., Foster City, California, USA) under the following conditions: initial denaturation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 62°C for 60 s. During the PCR cycles, two TaqMan probes hybridize competitively to a specific sequence of the target DNA, and the reporter dyes separate from the quencher dye, resulting in an increase of fluorescence of the reporter. The fluorescence level of PCR products was measured using an ABI PRISM 7200 or 7900 Sequence Detector (Applied Biosystems), resulting in clear identification of six pairs of *APOE/ε2, 3,* and *4* alleles. As the quality control of TaqMan PCR method, we determined *APOE* genotype of volunteers ($n = 212$), with informed consent, using both TaqMan and classical PCR-RFLPs (restriction fragment length polymorphisms) and confirmed identical results between them.

Statistical analysis

All statistical analyses were conducted using Stat View 4.5J (SAS Institute Inc., Cary, North Carolina, USA) and JMP 3.1.5 (SAS Institute Inc.). Differences in genotype or allele between normotensives and hypertensives were examined by chi-squared analysis. The association between the *APOE* polymorphisms and clinical variables was examined by one-way analysis of variance. We assessed the quantitative effects of covariates by multiple logistic regression analysis using JMP.

Results

Study population

There was no significant difference in age, sex or blood pressure between those who participated in the genetic analysis and those who did not. From the 3997 subjects, 1518 hypertensives and 2479 normotensives were defined according to the criteria described above. In the comparison of characteristics between hypertensives and normotensives, age, percentage of males, body mass index (BMI), family history of hypertension (FH), alcohol consumption, past smoking habit, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (T-chol), triglyceride (TG), fasting plasma glucose (FPG) and creatinine were significantly higher in hypertensives (Table 1). In contrast, current smoking habit and HDL-cholesterol (HDL-chol) level were significantly lower in hypertensives (Table 1).

APOE polymorphism and hypertension

TaqMan PCR clearly detected the genotype of *APOE* and the obtained allele frequency of *APOE/ε2*, *ε3*, and *ε4* was 0.05, 0.85, and 0.10, respectively. The genotype distribution significantly satisfied Hardy–Weinberg's expectation (*ε2*: $\chi_1^2 = 1.11$, $P = 0.29$; *ε3*: $\chi_1^2 = 0.003$, $P = 0.95$; *ε4*: $\chi_1^2 = 0.17$, $P = 0.18$). *APOE/ε4* allele distribution was significantly different ($P < 0.02$) between hypertensive and normotensive subjects (Table 2). Marginal significant difference ($P = 0.067$) was observed in *APOE/ε3* allele distribution, while *APOE/ε2* allele frequency was similar in hypertensives and normotensives (Table 2). The prevalence of hypertension significantly ($P < 0.02$) decreased according to the number of *APOE/ε4* alleles (Fig. 1). In subjects with the *ε4* allele, the calculated odds ratio for hypertension was 0.83 (95% confidence interval (CI), 0.70–

Table 1 Clinical features of study subjects

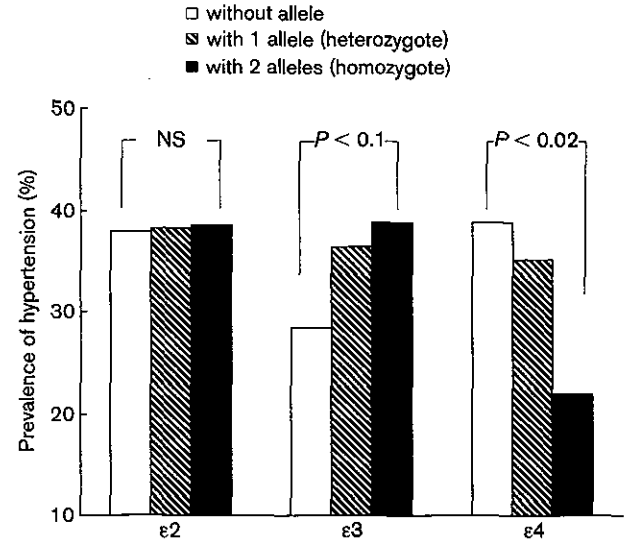
Variable	Hypertensives	Normotensives	*P* value
Number of subjects	1518	2479	
Age (years)	65 ± 10	57 ± 12	<0.0001
Sex (% male)	50	46	0.004
BMI (kg/m^2)	23 ± 3.2	22 ± 2.8	<0.0001
FH (%)	41	32	<0.0001
Drinking habit (%)	47	48	NS
Alcohol consumption (ml/day)	13 ± 24	11 ± 21	0.003
Smoking habit (%)			
Current	19	26	<0.0001
Past	22	15	<0.0001
Never	60	59	NS
SBP (mmHg)	149 ± 16	117 ± 12	<0.0001
DBP (mmHg)	89 ± 10	75 ± 7.9	<0.0001
T-chol (mmol/l)	5.5 ± 0.85	5.4 ± 0.85	<0.0001
TG (mmol/l)	1.6 ± 1.2	1.3 ± 0.95	<0.0001
HDL-chol (mmol/l)	1.6 ± 0.17	1.5 ± 0.18	0.0003
FPG (mmol/l)	5.5 ± 1.1	5.3 ± 1.0	<0.0001
Creatinine (μmol/l)	66 ± 26	62 ± 15	<0.0001

Variables are expressed as mean ± standard deviation.
FH, Family history of hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; T-chol, total cholesterol; TG, triglyceride; HDL-chol, HDL cholesterol; FPG, fasting blood glucose.
NS, no significant difference between hypertensives and normotensives.

Table 2 Genotype and ε2, 3, 4 allele distribution of *APOE* polymorphism in hypertensive and normotensive subjects

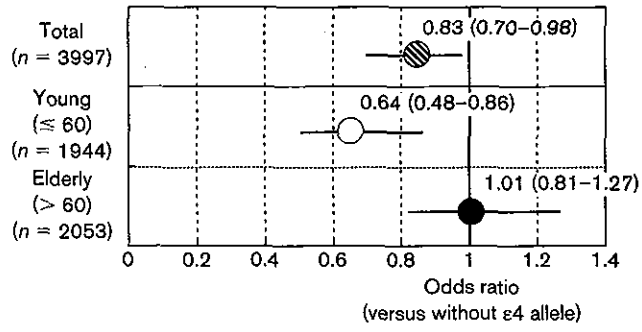
		Hypertensives		Normotensives	
APOE Genotype	Number of ε2 alleles	*n*	%	*n*	%
ε3/ε3, ε3/ε4, ε4/ε4	0	1371	90.3	2242	90.4
ε2/ε3, ε2/ε4	1	142	9.4	229	9.2
ε2/ε2	2	5	0.3	8	0.3
		$\chi^2 = 0.017$, $P = 0.99$			
Genotype	Number of ε3 alleles				
ε2/ε2, ε2/ε4, ε4/ε4	0	25	1.7	63	2.5
ε2/ε3, ε3/ε4	1	367	24.2	640	25.8
ε3/ε3	2	1126	74.2	1776	71.6
		$\chi^2 = 5.4$, $P = 0.067$			
Genotype	Number of ε4 alleles				
ε2/ε2, ε2/ε3, ε3/ε3	0	1262	83.1	1990	80.3
ε2/ε4, ε3/ε4	1	247	16.3	457	18.4
ε4/ε4	2	9	0.6	32	1.3
		$\chi^2 = 8.3$, $P = 0.016$			

Fig. 1



Prevalence of hypertension and *APOE* genotype. The significance of the difference among the three groups was examined by ANOVA (analysis of variance). NS, there was no significant difference among three groups: subjects without the ε2 allele, with a single ε2 allele and with two ε2 alleles.

Fig. 2



Effect of *APOE/ε4* allele on hypertension in young and elderly subjects. The odds ratio of the risk for hypertension was calculated for the subject with the ε4 allele versus the subject without an ε4 allele.

0.98). Dividing the subjects into two groups by age, the significance was strongly enhanced in young subjects (≤60 years old) and the calculated odds ratio was only 0.64 (0.48–0.86) (Fig. 2). The calculated odds ratio was similar in young subjects between males (0.66) and females (0.59). The attributable risk of lack of *ε4* allele for hypertension was 0.118 in the whole population and 0.294 in young subjects. The positive association with hypertension remained after adjustment for age and sex ($P < 0.03$), and after full adjustment for confounding factors (age, sex, BMI, smoking habit, alcohol consumption, T-chol, TG, HDL-chol, creatinine, and FPG) ($P < 0.05$). The APOE ε4 allele was also significantly associated with systolic blood pressure ($P < 0.013$), pulse pressure ($P < 0.02$) and heart rate ($P < 0.045$), but not with diastolic blood pressure (Table 3).

APOE polymorphism and plasma lipid levels

The *APOE/ε4* allele was significantly associated with an increase of total cholesterol ($P < 0.0001$) and triglyceride ($P = 0.0002$) levels and with a decrease of HDL-cholesterol level ($P = 0.003$) (Table 3). *APOE/ε4* increased total cholesterol by 0.16 mmol/l and triglyceride by 0.16 mmol/l, and decreased HDL-cholesterol by 0.05 mmol/l. However, *APOE/ε4* was not associated with any other clinical parameters.

Table 3 **Contribution of *APOE/ε4* allele to blood pressure and lipid levels**

APOE genotype	*ε4* allele (+)	*ε4* allele (−)	*P* value
Number of subjects	745	3252	
SBP (mmHg)	127.6 ± 19.6	129.6 ± 20.7	<0.013
DBP (mmHg)	79.6 ± 10.4	80.3 ± 11.2	NS
Pulse pressure (mmHg)	47.9 ± 14.7	49.3 ± 14.9	<0.02
Heat rate (beats/min)	66.6 ± 8.01	67.3± 8.26	<0.045
T-chol (mmol/l)	5.55 ± 0.86	5.39 ± 0.85	<0.0001
TG (mmol/l)	1.54 ± 1.31	1.38 ± 1.00	0.0002
HDL-chol (mmol/l)	1.50 ± 0.41	1.55 ± 0.41	0.003

Variables are expressed as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; T-chol, total cholesterol; TG, triglycerides; HDL-chol, high-density lipoprotein cholesterol.

Discussion

We have performed a large genetic epidemiological study of the Japanese general population and obtained the following results. (1) The estimated risk for hypertension in young subjects (≤60 years old) with the *APOE/ε4* allele was reduced by 36% compared with young non-carriers of *APOE/ε4*. (2) *APOE/ε4* carrier status versus non-carrier status was associated with a 2.9% increase of total cholesterol level, 11.8% increase of triglyceride level and 3.2% decrease of HDL cholesterol level.

Three common alleles of *APOE* have been stated as modulators of the lipid profile or as genetic predisposing factors for Alzheimer's disease. It has been considered that the *APOE/ε3* and *ε4* alleles increase plasma LDL-cholesterol level, suggesting that the *APOE/ε3* and *ε4* alleles are risk factors for atherosclerosis [11]. Therefore, gene polymorphism of *APOE* plays a key role in the development of cardiovascular disease [12], but the results obtained concerning *APOE* genotype and cardiovascular complications remain controversial. For cardiovascular disease, positive results for the association between coronary artery disease (CAD) and *APOE/ε4* allele have been frequently published [13]. A meta-analysis estimated that the odds ratio for CAD is 1.26 (95% CI, 1.13–1.41) in subjects with *APOE/ε4* [14]. In contrast, the association between *APOE* polymorphism and stroke has not been clarified. Kokubo *et al.* [15] recently reported, from genetic epidemiological results in a Japanese rural population, that the risk for cerebral infarction was increased in *APOE/ε2* carriers (odds ratio (OR) = 1.7) but not in *APOE/ε4* carriers (OR = 0.9). Despite the certain atherogenic effect of *APOE/ε4*, it is not clear why the results of investigations concerning the association between *APOE/ε4* and cerebral infarction have been inconsistent [16]. Our findings suggest a feasible explanation for the inconsistent results. *APOE/ε4* increased plasma LDL-cholesterol and triglyceride levels, and decreased HDL-cholesterol and blood pressure, with the result that the prevalence of hypertension was lower in young but not in elderly subjects in *APOE/ε4* carriers. In addition, Hanon *et al.* [17] examined the association between *APOE* polymorphism and arterial wall thickness, and found that *APOE/ε2* was related to hypertrophy of the carotid arterial wall despite having a favorable effect on the lipid profile. These results suggest that the unfavorable lipid profile did not simply reflect the progression of arteriosclerosis. Atherosclerosis in larger arteries is related mainly to lipid and blood pressure levels. Kessler [16] and Kokubo [15] reported that *APOE/ε4* was associated with atherothrombosis but not with lacunar infarction and cortical infarction. Therefore, we hypothesized that *APOE/ε4* enhances atherosclerosis in larger arteries via an unfavorable lipid profile, whereas it attenuates the risk for ischemia in smaller arteries via lower blood pressure. Another explanation for positive association in young subjects is that *APOE/ε4* might be associated with hypertensive death. However, it is difficult to arrive at a logical conclusion based on the current investigation.

On the other hand, the possible association with blood pressure only in systole, suggesting that the *APOE* polymorphism might be involved in modulation of peripheral arteriole resistance or cardiac output. Precise inspection of the results revealed that heart rate of *APOE/ε4* carriers was also lower than that of non-carriers ($P = 0.058$), suggested the possibility that sympathetic activity might be decreased in *APOE/ε4* carriers. A paper showed [18] that APOE elicits an increase in intracellular calcium levels and subsequent death of embryonic rat hippocampal neurons in culture, and similar effects on calcium were found when the APOE peptide was applied to chick sympathetic neurons. Of course, it is nothing more than a collateral evidence of our results but it can be a feasible explanation for the positive association with systolic blood pressure only in young subjects.

Previous investigations have always dealt with *APOE/ε4* as a 'risk' factor. However, the current study showed a protective effect against hypertension in young subjects, suggesting that the risk of genetic polymorphism should be discussed in the context of interaction with environmental factors, such as aging, excess salt intake, and obesity. Taking *APOE/ε4* carriers as an example, a genetically high cholesterol level and lower blood pressure offset each other in stroke susceptibility [19]. Presumably, an unfavorable lipid profile gradually reduces the effect of lower blood pressure, with the result that *APOE/ε4* shows no effect on hypertension in elderly subjects. Undoubtedly there are some study limitations in this cross-sectional analysis. The final conclusion on whether *APOE/ε4* modulates susceptibility to cardiovascular disease will be clarified in the analysis of cumulative incidence to be obtained in the future Suita Study.

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腎血管性高血圧症の診断と治療*

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はじめに

腎血管性高血圧（RVH）の頻度は高血圧全体の1%未満であるが，治癒する高血圧という点で興味を集めてきた。最近の診断上の進歩としては，①アスピリンレノグラム，②超音波ドップラー，③MR angiography（MRA）などが挙げられる。一方，治療上の進歩としては血管内インターベンションがある。これまでのバルーンを用いた経皮経管的腎動脈拡張術（PTRA）に加えて動脈硬化性病変に対してはステント挿入術が施行されるようになった。

I．RVHの成因

RVHは腎動脈狭窄(RAS)などによる腎血流障害を原因とする高血圧と定義される。腎血流障害の原因には粥状動脈硬化症，線維筋性過形成(FMD)，高安動脈炎などによるRAS，腎動静脈瘻，大動脈縮窄症などがある。そのうち，粥状動脈硬化症によるものが90%を占める。粥状動脈硬化は主に腎動脈起始部に出現し，時に大動脈壁のアテロームと融合する。粥状動脈硬化によるRASは放置すると進行し，10%程度[1]の例では完全閉塞に至る。

FMDは動脈壁で過形成を示す層によってintimal fibroplasia, medial fibromuscular dysplasia, periadventitial fibrosisに分類される。medial fibromuscular dysplasiaはFMDの90%以上を占め，若年から中年の女性に多い。数珠玉状の所見を呈し，腎動脈本幹のmid portionから末梢に認められる。

II．RVHの診断

1．臨床所見

高血圧に占めるRVHの頻度は低いので，高血圧症全例についてRVHのスクリーニング検査を行うことは，非効率的である。患者背景，病歴，身体所見よりRVHの手がかりを得ることが重要である。**表1**[2]にRVH疑診の程度毎に主な臨床所見を示した。

2．各種検査

RVHが疑われた場合，RASなどの血管病変を検出するための検査が行われる。このためのgold standardは造影剤を用いた腎動脈撮影である。最近は，造影剤が少量ですむことより，DSAが一般的となっている。RVHが中程度に疑われる症例では，よりリスクの低いカプトプリル・レノグラム，超音波ドップラー法，MRAなどの非侵襲的検査が適応となる（**表2**）。狭窄側ではレニン分泌が促進するが，末梢血のレニンが上昇するのはRVHの約半数に留まる。また，レニン分泌は

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