表1 GLANT研究におけるDelapril群とCa拮抗薬群の脳心血管系イベント

降圧薬投与前に脳血管障害や心筋梗塞の既往のある例，狭心症を有する例，血清クレアチニンが2.0mg/dL以上の腎障害例を除外した症例（Delapril群988例，Ca拮抗薬群981例）において脳心血管系イベントの発症を検討したところ，脳心血管系イベントはCa拮抗薬群で多い傾向がみられるが，有意差はない．

	Delapril群 (n = 988)		Ca拮抗薬群 (n = 981)	
	発症例数	死亡例数	発症例数	死亡例数
脳血管障害	5 (0.5%)	0	11 (1.1%)	3 (0.3%)
脳出血	1 (0.1%)		2 (0.2%)	1 (0.1%)
脳梗塞・血栓	3 (0.3%)		8 (0.8%)	2 (0.2%)
TIA	1 (0.1%)		1 (0.1%)	
心疾患	5 (0.5%)	2 (0.2%)	7 (0.7%)	0
心筋梗塞	1 (0.1%)	1 (0.1%)		
突然死	1 (0.1%)	1 (0.1%)		
狭心症	1 (0.1%)		3 (0.3%)	
心不全			2 (0.2%)	
不整脈	2 (0.2%)		2 (0.2%)	
眼底出血	1 (0.1%)		0	

GLANT：The evaluation Group of Long-term Antihypertensive Treatment，TIA：一過性脳虚血発作，Ca：カルシウム

（文献2，3より）

圧160mmHg以上かつ拡張期血圧90～114mmHgで，原則50～80歳の本態性高血圧患者である。最終的にACE阻害薬群988例と，Ca拮抗薬群981例が解析対象となった。薬剤の割り付けは，担当医師が臨床背景の似通った2例を選び，1例にdelapril，他方に市販のCa拮抗薬を投与するオープン試験の形式として，1年間追跡した。単剤で効果不十分の時は，β遮断薬か利尿薬，または両方を併用した。

試験開始時と終了時の血圧は，ACE阻害薬群170/99→147/86mmHg，Ca拮抗薬群171/99→142/83mmHgであり，有意にCa拮抗薬群の降圧度が大きかった。脳心血管イベントの発症率は，脳血管障害がACE阻害薬群5例，Ca拮抗薬群11例，心疾患がACE阻害薬群5例，Ca拮抗薬群7例と，Ca拮抗薬群で高い傾向があったものの，有意差はなかった。（表1）。副作用はACE阻害薬群で19.6%，Ca拮抗薬群で13.0%であった。

この研究は無作為ではなく追跡期間が短いが，Ca拮抗薬群で降圧効果が高かったにもかかわらず，ACE阻害薬群で脳血管障害発症頻度が低い傾向が見られた。ACE阻害薬が，Ca拮抗薬よりも臓器保護に優れている可能性を示唆し，また，Ca拮抗薬が忍容性では優れていることを示している。

4．PATE-Hypertension

PATE-Hypertension（Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension）は，60歳以上の本態性高血圧患者を3年間，ACE阻害薬のdelaprilまたはCa拮抗薬のmanidipineで治療し，脳心血管イベントの発症率と，薬剤の副作用について検討した研究である[4]。薬剤は主治医の選択で，非盲検的に投与された。

総死亡は両群間で有意差はなかった。脳心血管イベントはACE阻害薬群が699例中34例（22.5/1,000例/年），Ca拮抗薬群が1,049例中50例（19.7/1,000例/年）であり，やはり有意差はなかった。治療期間中の血圧と心血管イベントの関係は，過

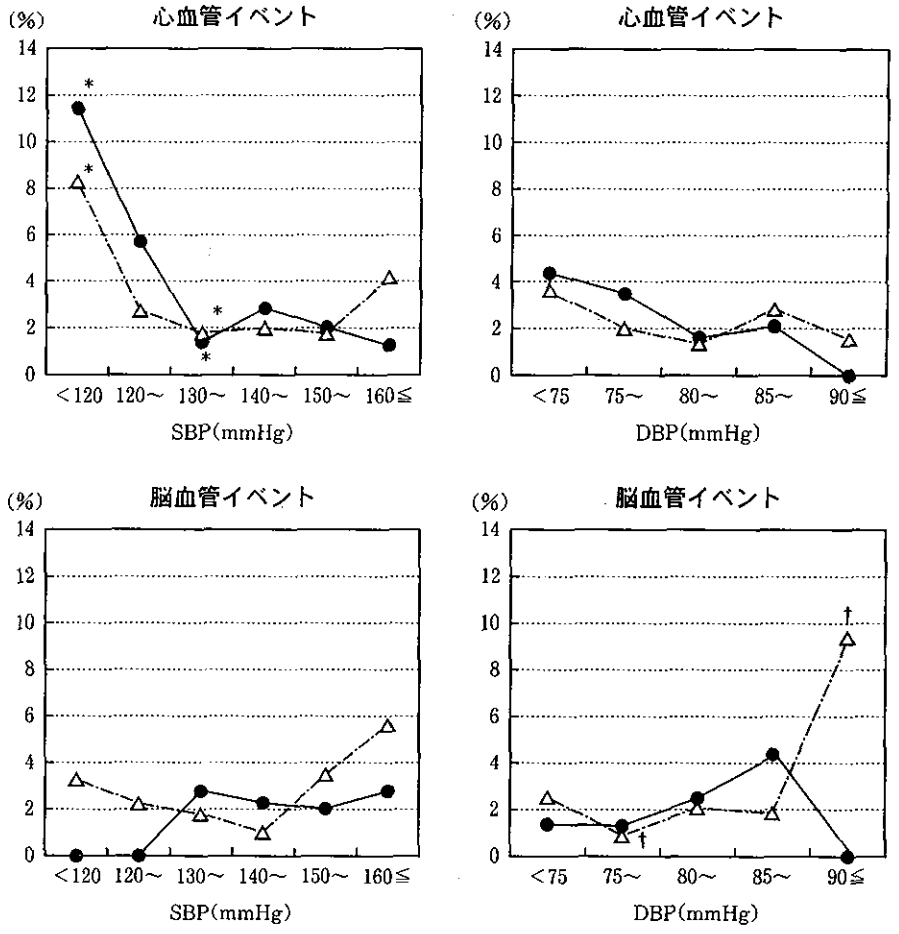

図2　PATE-Hypertension 研究における治療中の血圧値と心血管イベントとの関係

上段：心血管イベントは，収縮期血圧 120mmHg 未満において 130 ～ 139mmHg よりも有意に（$p < 0.01$）頻度が高かった．（＊印）．

下段：脳血管イベントは Ca 拮抗薬群においては拡張期血圧 75 ～ 79mmHg で，90 mmHg 以上よりも有意に（$p < 0.01$）頻度が低かった．（†印）．ACE 阻害薬群では同様の関係は認められなかった．

●：ACE 阻害薬群，△：Ca 拮抗薬群，上段：心血管イベント，下段：脳血管イベント

PATE-Hypertension：Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension，SBP：収縮期血圧，DBP：拡張期血圧

（文献 4 より）

度の降圧でも発症率の上昇を認める，いわゆる J-curve を呈した。副作用は，Ca 拮抗薬群よりも ACE 阻害薬群で多かった。

この研究は，目標降圧レベルが設定されていないが，ACE 阻害薬と Ca 拮抗薬は，高齢者高血圧における予後には差がなく，ACE 阻害薬は忍容性で劣ることを示唆している。また，過度の降圧は有害である可能性が示唆された。（図 2）。

5．JATE および JATE Ⅱ

JATE(Japanese Trial on the Efficacy of Antihypertensive Treatment in the Elderly) 研究は，高齢者（70 ～ 80 歳）軽症高血圧に対する治療効果を評価するために，Ca 拮抗薬（nitrendipine，nisoldipine，manidipine）のプラセボ対照の無作為二重盲検試験として，1992 年に開始された[5]。目

標登録患者数は2,000例と設定されたが，329例が登録されたのみで，1998年に追跡を終了した。

心血管イベントの発生率では，明らかな差はなかった。参加表明医師へのアンケート調査も行われ，症例登録が困難であった理由として，プラセボ対照試験に対する国民・医師両者のコンセンサスが得られていなかったこと，患者に利益がないことなどがあげられた。

この研究では十分な症例登録が得られず，本邦でプラセボを用いた臨床試験を実施することの困難さが示された[6]。

JATE Ⅱは，JATEの後を受けて行われた，高齢者高血圧を対象とするオープンの臨床試験である。プラセボは用いられず，Ca拮抗薬（上記3種に後にnifedipine CRが追加）を基礎薬として，治療期間は3年間である。661例が登録され，頭部CT（computed tomography）を含む臓器障害や心血管イベント，QOL（quality of life）などが評価された。2002年に終了し，解析結果の発表が予定されている。

6．J-MIND

J-MIND（Japan Multicenter Intervention of Antihypertensive Treatment for Nephropathy in Diabetics）は，高血圧を伴う2型糖尿病患者における尿アルブミン排泄量（AER），および心血管イベントに対するCa拮抗薬（nifedipine持効錠）とACE阻害薬（enalapril）の効果を，2年間にわたり検討した研究である[7]。対象は，尿蛋白正常または微量アルブミン尿を伴う436例で，nefedipine持効錠群（N群），enalapril群（E群）に無作為に割り付けられた。目標血圧は140/90mmHg未満とし，目標に達しない場合はfurosemideまたはα遮断薬を追加した。

AERはN群（45→64mg/日），E群（42→74mg/日）と，ともに増加した。両群間で差はなかった。脳心血管イベントはN群で5例（2.2%），E群で8例（3.8%）に認められ，有意な差はなかった。この研究は，糖尿病性腎症の進展に対する効果は，Ca拮抗薬とACE阻害薬との間にあまり差がないことを示唆している。しかし，両者ともに腎症の進行を阻止できなかった。

7．J-MIC（B）

J-MIC（B）〔Japan Multicenter Intervention for Cardiovascular Disease（B）〕は，冠動脈疾患を有する高血圧患者に，nifedipineとACE阻害薬を無作為に割り付け，予後を比較したものである[8]。観察期間は3年で，一次エンドポイントは心臓死，虚血性心疾患発症，冠動脈血行再建術および重症不整脈とし，二次エンドポイントは脳卒中，腎障害，心血管疾患以外の疾患および総死亡である。

Nifedipine群（N群）828例，ACE阻害薬群（A群）822例が解析対象となり，一次エンドポイントの発症率はN群で8.13/1,000例/年，A群で9.24で両群に有意差はなかった。虚血性心疾患を伴う高血圧患者の予後への効果は，Ca拮抗薬とACE阻害薬との間に差がないことが示唆された。

8．進行中の大規模臨床試験

1）JATOS

JATOS（Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients）は，高齢者高血圧治療における至適降圧レベルを検討するために企画された[9]。65～85歳の本態性高血圧患者を対象に，efonidipineを基礎薬として，降圧目標を収縮期血圧140mmHg未満，140～160mmHgの二群に分け，2年間の脳心血管疾患および腎障害の発症を評価比較する無作為臨床試験である。目標登録症例数は4,000例で，2001年4月に開始され，既に登録症例数は目標を達成している。2004年12月に終了する予定である。この研究は，ガイドラインにより異なっている，高齢者高血圧の降圧目標への答えになるものとして注目される。

2）CASE-J

CASE-J（Candesartan Antihypertensive Survival Evaluation in Japan）研究は，アンジオテンシンⅡ受容体拮抗薬（ARB）であるcandesartanと，Ca拮抗薬のamlodipineの効果を比較する試験である[10]。糖尿病，脳血管障害，冠動脈疾患，または腎障害を持つ，20～85歳の高リスク本態性高血圧患者が対象である。目標症例数は4,000例で，2001年9月に開始され，2005年12月に終

表2　海外と日本の高齢者高血圧の臨床試験における心血管イベントの発症率
わが国では欧米に比べて心血管イベントが少ない傾向がある．

	臨床試験	年齢（歳）	脳心血管合併イベント		脳血管イベント		心血管イベント	
			プラセボ	実薬*	プラセボ	実薬*	プラセボ	実薬*
海外	EWPHE	60～96	114.8	74.2 '	36.3	20.7 †	22.0	18.5
	SHEP	≧60	68.3	49.3 '	14.9	9.7 §	20.2	14.8 †
	STOP-Hypertension	70～84	55.5	33.5 '	31.3	16.8 '	16.5	14.4
	MRC Ⅱ	65～74	25.2	21.0 †	10.8	8.1 *	12.7	10.3
	臨床試験	年齢（歳）	プラセボ	カルシウム拮抗薬	プラセボ	カルシウム拮抗薬	プラセボ	カルシウム拮抗薬
	Syst-Eur	68～98	33.9	23.3 §	13.7	7.9 *	20.5	15.1 †
	Syst-China	≧60	33.3	21.4 '	20.8	13.0 *	10.8	6.9
日本	臨床試験	年齢（歳）	ACE阻害薬	カルシウム拮抗薬	ACE阻害薬	カルシウム拮抗薬	ACE阻害薬	カルシウム拮抗薬
	GLANT	60±10	12.7	22.7	4.9 †	14.7	4.9	2.9
	PATE-Hypertension	70±7	22.5	19.7	9.3	9.1	13.3	10.7

*利尿薬またはβ遮断薬，'$P < 0.01$，†$P < 0.05$，§$P < 0.001$

EWPHE：European Working Party on High Blood Pressure in the Elderly trial

SHEP：The Systolic Hypertension in the Elderly Program

STOP-Hypertension：Swedish Trial in Old Patients with Hypertension

MRC Ⅱ：Medical Research Council Trial of treatment of hypertension in older adults

Syst-Eur：Systolic Hypertension in Europe，Syst-China：Systolic Hypertension in China

GLANT：The evaluation Group of Long-term Antihypertensive Treatment

PATE-Hypertension：Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension

（文献4より）

了する予定である。この研究においても，既に目標症例数は達成されている。ARBとCa拮抗薬を比較する大規模臨床試験は海外でも進行中であるが，日本人におけるエビデンスをもたらすであろう。

3）HOMED-BP

HOMED-BP（Hypertension Objective Treatment based on Measurement by Electrical Devices of Blood Pressure Study）は，家庭血圧をベースに，降圧レベルと降圧薬の効果を評価する大規模研究である[11]。40～80歳の高血圧患者9,000例を登録し，それら患者をCa拮抗薬，ACE阻害薬，ARBいずれかの薬剤群と，家庭血圧135/85 mmHg未満と125/80mmHg未満の降圧目標とに無作為に割り付け，7年間追跡する。また，すべての参加施設をインターネットでホストコンピュータに接続し，降圧薬の処方や増・減量の判断を中央で管理するという，新しい手法がとられている。

2001年5月よりパイロット研究が開始され，2002年3月に本試験が開始された。2002年末で約1,400人が登録されている。この研究は，家庭血圧による至適降圧レベルと降圧薬の効果についての，重要な知見を提供してくれるであろう。

4）HOSP

HOSP（Hypertension Control Based on Home Systolic Pressure Study）研究は，家庭収縮期血圧の至適血圧レベルを検討し，同時にCa拮抗薬amlodipineと，ARBのlosartanの効果を比較する無作為臨床試験である[12]。パイロット研究が2000年4月に開始され，約170例が登録された。本試験は，国立循環器病センターと全国の国立病

院，国立療養所の共同研究として2003年に開始される。目標症例数2,000例で，5年間調査される。サブスタディの中間解析では，厳格な降圧群における尿アルブミン排泄量の，有意な現象が認められている[13]。本研究もHOMED-BPと同様に，家庭血圧と降圧薬についてのエビデンスをもたらすことが期待される。

9．おわりに

わが国におけるこれまでの，および進行中の主な高血圧治療の臨床試験について述べた。降圧療法における日本人のエビデンスはまだ乏しいが，高血圧患者の予後への効果はCa拮抗薬，利尿薬，ACE阻害薬との間にはあまり差がなく，副作用や忍容性の面ではCa拮抗薬が優れていることが示されている。また，わが国における治療中の高齢者高血圧患者の心血管イベントの発症は，欧米の臨床試験に比べて低い傾向が見られている。（表2）[4]。

現在進行中の，大規模臨床試験の結果が得られれば，ARBを含めた降圧薬治療の日本人における評価が，より明らかになるであろう。特に，高齢者高血圧や家庭血圧について，至適降圧レベルを検討する無作為臨床研究は，日本のみならず世界的にみても，重要な知見をもたらすものとして期待される。

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Original Article

Microalbuminuria and Cardiovascular Events in Elderly Hypertensive Patients without Previous Cardiovascular Complications

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To assist in the development of better treatments for elderly hypertensive patients, we studied the degree to which the baseline values of urinary albumin excretion (UAE) and other cardiovascular risk factors were predictive of cardiovascular complications in a cohort of elderly hypertensive patients. In 1994, we adopted 144 elderly hypertensive patients, who had been treated for more than 6 years at various clinics and more than 1 year at the National Cardiovascular Center, Osaka, Japan. They were divided into 2 groups: a NA group (n=111) with normoalbuminuria (UAE<30 mg/day) and an MA group (n=33) with microalbuminuria (UAE 30–300 mg/day). At baseline, the two groups were similar with respect to systolic and diastolic blood pressure (SBP/DBP), pulse pressure (PP), age, ratio of males to females, serum creatinine, uric acid, total cholesterol, fasting plasma glucose (FPG), and creatinine clearance (CCr). PP was calculated as SBP minus DBP. The efficacy of blood pressure (BP) control was similar in both groups during the 8-year follow up period; however, a total of 14 cardiovascular events occurred in the MA (6/33) and NA (8/111) groups, with the MA group showing the higher incidence rate by multiple logistic regression analysis (p<0.05). At 8 years of follow-up, PP and age were correlated with UAE (p<0.05, p<0.001). At the same time point, CCr was correlated with UAE at baseline (p<0.05). The results indicated that, in elderly hypertensive patients without previous cardiovascular complications, microalbuminuria can be a predictor of cardiovascular events irrespective of conventional BP control. (*Hypertens Res* 2003; 26: 603–608)

***Key Words*: microalbuminuria, hypertension, cardiovascular events, renal function**

Introduction

It has been well established that proteinuria plays a pathophysiological role in both renal and cardiovascular diseases. In addition, it has been shown that an appreciable proportion of patients with hypertension have a greater degree of urinary albumin excretion (UAE) than normotensive subjects (*1–4*). In addition to severe proteinuria, microalbuminuria is also considered to have relevance as a predictor of the progression of cardiovascular diseases (*5*). In diabetic subjects, microalbuminuria appears to be an important sign of early nephropathy that triggers end-stage renal disease (ESRD) and increases the incidence of cardiovascular deaths and total mortality (*6*). Furthermore, there is growing evidence that microalbuminuria can be used as a predictor of atherosclerosis and premature death even in non-diabetic patients and the general population (*5*, *7*). In hypertension research, most

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studies on UAE have been clinical investigations into the relationship between UAE and renal insufficiency, because renal insufficiency deteriorates hypertension and *vice versa*. There is substantial evidence that a slight increase in UAE further increases the risk of ischemic heart disease in hypertensive subjects (*8*). Indeed, a retrospective cohort analysis has suggested that hypertensive patients with microalbuminuria manifest a greater incidence of cardiovascular events and a greater decline in renal function than hypertensive patients with normal UAE (*9*). Thus, blood pressure control and concomitant treatment for renal protection are important for a large majority of the population of hypertensive patients. It has been reported that good long-term control of blood pressure by conventional treatment in middle-aged hypertensive patients appears to protect the kidney from progressive decline in creatinine clearance (CCr) and increase in UAE (*10*). As the above evidence suggests, establishing an effective treatment for elderly hypertensive patients is another important target of research because of the complexity of the disease features in such patients. Furthermore, the pathophysiological mechanism by which microalbuminuria acts as a predictor of hypertension and related vascular and renal diseases in the elderly remains to be clarified.

A recent epidemiologic study based on the use of urine ultrafiltration indicated that there is a strong relationship between systolic and diastolic blood pressure (SBP/DBP) and microalbuminuria (*11*). For years, DBP has been considered a more important measurement than SBP for assessing the development of organ damage secondary to hypertension (*12*). Recent data suggest that pulse pressure (PP) could be a greater risk factor (*13*, *14*). In the present study, we analyzed the findings of an 8-year follow-up analysis of elderly patients with essential hypertension without previous cardiovascular complications. The patients had been treated with antihypertensive drugs for more than 6 years, and their SBPs had been well controlled. The aim of the study was to assess the predictive impacts of microalbuminuria and blood pressure on the subsequent development of cardiovascular events and the decline of renal function in elderly hypertensive patients receiving antihypertensive therapy.

Methods

Patient Population

We conducted a prospective cohort analysis to determine whether there was an association among blood pressure, microalbuminuria, cardiovascular events, and loss of renal function in elderly patients with essential hypertension. In 1994, blood pressure, urinary albumin excretion, and other atherosclerotic risk factors were measured in 172 elderly hypertensive patients 65 years old and over, who had been treated for more than 1 year at the outpatient clinic of the National Cardiovascular Center, Osaka, Japan. A diagnosis of secondary hypertension was ruled out based on the findings of routine blood chemistry analysis, urinalysis, and plasma renin activity and catecholamine concentration. Individuals were excluded from this analysis if they, at baseline, had cardiovascular disease (angina pectoris, myocardial infarction, or stroke), diabetes mellitus or renal disease. Angina pectoris was diagnosed by the presence of myocardial ischemia according to typical anginal symptoms or reversible ischemic changes on ECG. Myocardial infarction was diagnosed by QRS change on ECG (abnormal Q or poor R progression), hypokinesis of wall motion on echocardiogram, or elevation of serum myocardial enzyme (creatinine kinase-MB) levels. Stroke (cerebral infarction and hemorrhage) was diagnosed by the clinical history, neurological examination, and findings of computerized tomography as described elsewhere (*15*, *16*). Diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, and/or a fasting plasma glucose (FPG) level >126 mg/dl. Renal disease was defined from the clinical history, the presence of proteinuria, which was defined as a protein level $>1(+)$ by the dye-impregnated paper strip method, and the presence of renal insufficiency, which was defined as a serum creatinine level >1.5 mg/dl. In this manner, a total of 144 patients were selected for this study. All patients gave their informed consent to participate in this study.

With patients in the sitting position, SBP and DBP were measured 3 times with a sphygmomanometer and appropriately sized cuff, once a month throughout the follow-up period of the study. DBP was recorded at the disappearance of the Kortokoff sounds (phase V). Pulse pressure was calculated as SBP minus DBP.

Urine in patients with no sign of urinary infection was collected at 24-h periods at baseline and again after 8 years, and urine albumin excretion was measured by radioimmunoassay. Patients with hypertension were considered to have microalbuminuria if their UAE was in the range of 30–300 mg/24 h, and normoalbuminuria if their UAE was less than 30 mg/24 h. Patients were classified into two groups: a NA group with normoalbuminuria ($n=111$) and an MA group with microalbuminuria ($n=33$).

Weight, height, body mass index (BMI), smoking habits, fasting serum creatinine levels, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides levels, fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c) were obtained once a year throughout the follow-up period. CCr was calculated by measuring intrinsic creatinine in serum (SCr) and in urine. Smoking habits were obtained from the medical records.

Follow-Up

A total of 144 subjects were followed up once a month to monitor blood pressure, effectiveness of antihypertensive therapy, and prevalence of cardiovascular events. Blood pressure levels were controlled based on the fifth report of JNC V (*17*).

Table 1. Baseline Clinical Characteristics of Elderly Hypertensive Patients

	NA group (n=111)	MA group (n=33)
Age (years)	72±1	73±1
Male gender (%)	47 (42)	19 (58)
Height (m)	1.57±0.01	1.59±0.01
Weight (kg)	61.1±1.0	60.9±2.0
BMI (kg/m^2)	24.6±0.3	24.0±0.6
Duration of hypertension (years)	22±1	22±1
Family history of hypertension (%)	75 (68)	21 (64)
Current smokers (%)	44 (40)	18 (55)
Use of CCBs (%)	82 (74)	28 (85)
Use of ACE inhibitors (%)	25 (23)	9 (27)

NA, normoalbuminuria; MA, microalbuminuria, BMI, body mass index; CCBs, calcium channel blockers; ACE, angiotensin-converting enzyme.

In August of 2002, end points were collected from the admission records or the medical records of the outpatient to verify the diagnosis of cardiovascular and renal events and cause of death. Myocardial infarction was diagnosed using either ECG or echocardiograms, and angina pectoris was diagnosed from both symptoms and ECG. Cerebral infarction and hemorrhage were diagnosed from both neurological findings and computerized tomography. Atherosclerotic obliteration (ASO) was defined as the presence of both symptomatic claudication and an ankle/brachial pressure index less than 0.9. Dissection of the abdominal aorta was diagnosed by typical clinical history and computerized tomography findings. For all subjects who died, the cause of death was recorded.

Statistical Analysis

All analyses were performed with the program Stat-View 5.0. Differences in baseline characteristics between the groups were compared by analysis of variance (ANOVA) for continuous variables and by the χ^2 test for categorical variables. Values of $p<0.05$ were considered to indicate statistical significance. Survival during the follow-up period was calculated by Kaplan-Meier curves for different groups and differences were tested by the log rank test. Relationships between UAE or CCr at 8-year follow-up and other clinical characteristics were evaluated using linear regression analysis. Cox proportional hazard regression analysis was performed to examine the relationship between cardiovascular events and several cardiovascular risk factors, *i.e.*, age, gender, smoking, BMI, DBP, PP, uric acid, total cholesterol, FPG, CCr, and UAE. Results are described as relative risks (RRs) (hazards ratio) with 95% confidence intervals (CIs). The results are expressed as the means±SEM.

Results

Table 1 shows the baseline clinical characteristics of the two groups of patients. Age, gender, BMI, duration of hypertension, family history of hypertension, and smoking status did not differ significantly between groups. The use of angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) also did not differ significantly. Although treatments with antihypertensive drugs throughout the follow-up period changed occasionally, the total number of prescriptions for ACE inhibitors and CCBs did not change substantially between groups in either group. Table 2 shows the clinical characteristics at baseline and at the 8-year follow-up for both groups. Blood pressure was not different between groups at either measurement. Creatinine concentrations of the MA group at baseline and at the 8-year follow-up were greater than those in the NA group ($p<0.005$). UAE values (as defined above) in the MA group at baseline and at the 8-year follow-up were greater than those in the NA group ($p<0.0001$). CCr in the MA group at the 8-year follow-up was lower than that in the NA group ($p<0.01$). Serum levels of uric acid, total cholesterol, triglycerides, FPG, and HbA1c did not differ significantly. Table 2 also shows the differences in UAE and CCr between the baseline and 8-year follow-up period. UAE increased in both groups ($p<0.05$). CCr decreased in both groups ($p<0.05$). The decline of CCr from baseline to 8-year follow-up in the MA group was significantly greater than that in the NA group ($p<0.05$).

Table 3 shows the relationships between UAE at the 8-year follow-up and other clinical characteristics. The relationships between UAE at the 8-year follow-up and each of age, SBP at 8-year follow-up, DBP at baseline, PP, UAE at baseline, and CCr were significantly positive in linear regression analysis. Table 4 shows the relationships between CCr at the 8-year follow-up and other clinical characteristics. Linear regression analysis showed that age, UAE, DBP at baseline, and CCr at baseline were significantly correlated to CCr at the 8-year follow-up.

The incidence of cardiovascular events was significantly greater in the MA group than in the NA group ($p<0.05$) (Fig. 1). At the 8-year follow-up, 6 of 33 patients (18%) in the MA group had experienced major cardiovascular events: one had acute myocardial infarctions, three had cerebral infarction, and two had dissection of the abdominal aorta. In the NA group, 8 of 111 patients (7%) experienced major cardiovascular events: one had acute myocardial infarctions, two had angina pectoris, one had cerebral infarction, three had cerebral hemorrhage (one fatal), and one had atherosclerotic obliteration (Table 5). Two patients in the MA group died due to colon cancer; these deaths were not cardiovascular in origin. Cox proportional hazard regression analysis showed that UAE at baseline was related to the incidence of cardiovascular events (Table 6).

Table 2. Clinical Characteristics of Elderly Hypertensive Patients

		NA group	MA group	*p*
SBP (mmHg)	Baseline	144±1	145±3	0.83
	8-year follow-up	143±1	142±3	0.93
DBP (mmHg)	Baseline	84±1	85±1	0.56
	8-year follow-up	81±1	81±1	0.98
PP (mmHg)	Baseline	60±1	60±3	0.83
	8-year follow-up	61±1	61±3	0.93
Creatinine (mg/dl)	Baseline	0.78±0.02	0.91±0.05	<0.005
	8-year follow-up	0.73±0.02	0.90±0.07	<0.005
Uric acid (mg/dl)	Baseline	5.6±0.1	5.9±0.2	0.29
	8-year follow-up	5.7±0.1	5.9±0.2	0.44
UAE (mg/24 h)	Baseline	13±1	92±11	<0.0001
	8-year follow-up	25±4#	200±60#	<0.0001
CCr (ml/min)	Baseline	93.8±2.3	89.8±4.4	0.46
	8-year follow-up	73.4±2.1#	60.6±4.2#	<0.01
Total cholesterol (mg/dl)	Baseline	203±3	192±5	0.08
	8-year follow-up	205±3	203±4	0.62
Triglycerides (mg/dl)	Baseline	132±7	152±15	0.21
	8-year follow-up	133±6	162±21	0.08
HDL-cholesterol (mg/dl)	Baseline	56±2	52±3	0.39
	8-year follow-up	52±2	48±2	0.20
FPG (mg/dl)	Baseline	101±1	105±2	0.08
	8-year follow-up	104±2	105±2	0.52
HbA1c (%)	Baseline	5.6±0.1	5.7±0.2	0.77
	8-year follow-up	5.5±0.1	5.6±0.1	0.83

NA, normoalbuminuria; MA, microalbuminuria, SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; UAE, urinary albumin excretion; CCr, creatinine clearance; HDL, high-density lipoprotein; FPG, fasting plasma glucose. # $p<0.05$ *vs.* baseline.

Table 3. Relationships between UAE at 8-Year Follow-Up and Other Clinical Characteristics

Variables	*r*	*p*
Age	0.30	<0.001
SBP at baseline	0.11	0.21
SBP at 8-year follow-up	0.14	<0.05
DBP at baseline	0.16	<0.05
DBP at 8-year follow-up	0.13	0.12
PP at baseline	0.19	<0.05
PP at 8-year follow-up	0.22	<0.01
UAE at baseline	0.33	<0.0001
CCr at baseline	0.17	<0.05
CCr at 8-year follow-up	0.20	<0.05

Definitions are as Table 2.

Table 4. Relationships between Creatinine Clearance at 8-Year Follow-Up and Other Clinical Characteristics

Variables	*r*	*p*
Age	0.33	<0.0001
SBP at baseline	0.08	0.31
SBP at 8-year follow-up	0.01	0.95
DBP at baseline	0.27	<0.05
DBP at 8-year follow-up	0.13	0.12
PP at baseline	0.05	0.53
PP at 8-year follow-up	0.08	0.34
UAE at baseline	0.20	<0.05
UAE at 8-year follow-up	0.20	<0.05
CCr at baseline	0.45	<0.0001

Definitions are as Table 2.

Discussion

In Japan, hypertension has been shown to be a significant predictor of stroke, myocarial infarction, and ESRD (*18*, *19*). Arguments have been made as to whether microalbuminuria can predict the prognosis of hypertensive patients. One retrospective study reported a greater incidence of stroke and other cardiovascular events in non-diabetic elderly subjects with increased UAE than in those with normal UAE (*20*). A recent prospective study showed that microalbuminuria was an independent risk factor of cardiovascular and all-cause mortality, especially among hypertensive subjects (*21*). However, in elderly hypertensive patients with microalbuminuria, prediction of prognosis in clinical practice is difficult because of the complexity of the features of the disease. Thus, whether microalbuminuria is a strong marker for potential progression of disease and/or eventually emerging cardiovascular events remains to be investigated.

The present study dealing with 144 hypertensive patients aged 65 years or older without previous cardiovascular complications revealed that patients manifesting microalbuminuria at baseline (MA group) had a higher incidence (6/33:18.2%) of cardiovascular events than those with nor-

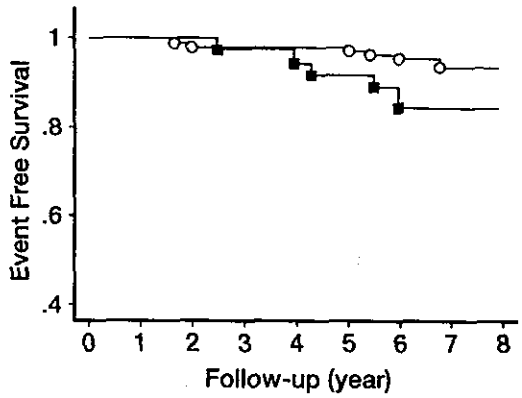

Fig. 1. *Cardiovascular event-free survival curves for elderly hypertensive patients with microalbuminuria (MA group: closed square) and patients without microalbuminuria (NA group: open circle). The difference between the two groups was significant in terms of the Kaplan-Meier survival curves and by log rank test* ($p<0.05$).

Table 5. Cardiovascular Events in Elderly Hypertensive Patients with and without Microalbuminuria

Events	NA group (n=111)	MA group (n=33)
Myocardial infarction	1	1
Angina pectoris	2	0
Cerebral infarction	1	3
Cerebral hemorrhage	3	0
Arteriosclerosis obliteration	1	0
Dissection of abdominal aorta	0	2
Total	8	6

Definition are as Table 2.

moalbuminuria (NA group) (8/111: 7.2%) during the 8-year follow-up period. The degree of UAE at the 8-year time point was closely related to UAE at baseline as well as to the age of patients, SBP at 8-year follow-up, DBP at baseline, and PP at baseline, indicating that microalbuminuria was not restored despite the therapeutic blood pressure control. Thus, microalbuminuria at baseline reflected the cardiovascular and renal events as endpoints during the 8-year follow up. Indeed, the CCr levels at baseline were related to the CCr levels at 8 years as well as to the age of patients and DBP at baseline (Table 4). UAE at baseline and UAE at 8 years were significantly correlated with CCr at 8 years, indicating that, in elderly hypertensive patients, mild renal impairment was retained during throughout the follow-up period. As shown in Table 6, cardiovascular events emerging during the 8-year period were closely correlated with the degree of UAE at baseline, as revealed by Cox proportional hazard regression analysis. Other risk factors, such as advanced age, gender, obesity, smoking, DBP, PP, CCr, dyslipidemia, and FPG, were not significantly related with cardiovascular events.

Table 6. Relative Risks by Cox Proportional Hazard Regression Analysis of 8-Year Cardiovascular Events Associated with Potential Risk Factors

Risk factors	Relative risk (95% CI)	p
Age at baseline	1.10 (0.92–1.24)	0.37
Gender (male)	2.93 (0.61–14.04)	0.18
BMI	0.96 (0.76–1.21)	0.71
Current smokers	2.25 (0.45–11.15)	0.32
DBP at baseline	0.94 (0.84–1.05)	0.24
PP at baseline	1.00 (0.95–1.05)	0.91
UAE at baseline	1.10 (1.00–1.20)	<0.005
CCr at baseline	1.02 (0.99–1.05)	0.11
FPG at baseline	0.97 (0.91–1.03)	0.32
T-chol at baseline	1.00 (0.98–1.03)	0.67

T-chol, total cholesterol. Other definitions are as Table 2.

Several factors are thought to be involved in the mechanism of elevated UAE, including renal hemodynamic changes with increased intraglomerular pressure, changes in perm selectivity of the glomerular filter due to structural changes in glomerular tufts that are often associated with nephrosclerosis, and so on (*3*). All these factors are known to be associated with high blood pressure, and high blood pressure can affect renal function through functional and morphological changes of nephrons. Thus, proteinuria is a crucial factor for the pathogenesis of hypertension and renal insufficiency.

Numerous studies have provided evidence of a relationship between microalbuminuria and hypertension. In several studies on non-diabetic hypertensive subjects, the prevalence of microalbuminuria has been reported to be 20% to 40% or more, and UAE has been shown to be increased with age and with severity and duration of hypertension (*22*). Other studies have shown a significant correlation between UAE and office blood pressure values (*11*, *23*), continuous ambulatory blood pressure measurements (*24*), or PP (*25*). In our present study patients whose averaged age was 72.7 years at baseline had been treated for more than 6 years, and their blood pressure was well controlled, at least during the successive 8-year follow-up period. Pulse pressure showed a positive relationship to UAE at the 8-year follow-up. The prevalence of microalbuminuria was almost 25% at baseline, and 41% at the 8-year follow-up, showing almost same percentage as described with the both percentages being almost identical to those described in the previous report (*22*). The elderly hypertensive patients adopted in the present study were thus general. Nonetheless, the occurrence of cardiovascular events was higher in the group having microalbuminuria at baseline, independent of their blood pressure control.

Our present study did not indicate a positive relation between smoking and cardiovascular events. Again, gender, lipid metabolism, and FPG were not correlated with cardio-

vascular events. However, we do not conclude that all these parameters have little relevance to cardiovascular events and prognosis of elderly hypertensive patients, because in the present study the total number of patients in the MA group was about 1/3 of that in the NA group, and thus there may have been an unexpected, underlying bias. Further investigation is therefore necessary with a larger number of patients and a longer period of follow up.

In conclusion, in the present study elderly hypertensive patients without previous cardiovascular complications, whose risks (except smoking) were not very high (no diabetes mellitus, and blood pressure was controlled) but who had microalbuminuria, manifested a greater incidence of cardiovascular events and a greater decline in renal function than those with normoalbuminuria in an 8-year follow up. Although the mechanism by which microalbuminuria influences the prognosis of hypertension in the elderly population is unclear, microalbuminuria might more properly express already existing microvascular lesions than serum cholesterol or glucose levels. Microalbuminuria may be a good of cardiovascular events in elderly hypertensive patients receiving long-term conventional antihypertensive therapy. Our results suggest that UAE measurements should be considered as an important adjunct to the evaluation of elderly patients with essential hypertension.

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Original Article

Association between Left Ventricular Diastolic Dysfunction and Renal Hemodynamic Change in Patients with Treated Essential Hypertension

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The heart and kidneys are important target organs in hypertension. Early signs of hypertensive target organ damage can be detected by evaluating left ventricular (LV) diastolic function and intrarenal hemodynamics using Doppler ultrasonography. However, it has not been sufficiently clarified whether cardiac damage and renal impairment progress in parallel, especially from the early stage. In the present study, Doppler echocardiography and renal Doppler ultrasonography were performed in 99 patients with treated essential hypertension, and LV diastolic filling parameters, *i.e.*, the velocity ratio of atrial filling to early diastolic filling (*A/E*), and the deceleration time of the E wave (DcT) and renal Doppler parameters, *i.e.*, the diastolic to systolic ratio (*D/S*) and resistance index (RI), were determined. *D/S* was negatively correlated and RI was positively correlated with *A/E* and DcT. These cardiac and renal Doppler parameters were also associated with age, diastolic blood pressure, creatinine clearance, and/or glucose levels. By multiple regression analysis, *D/S* was found to have a significant association with DcT, independent of other clinical parameters, including age. In subgroup analysis in which patients were divided by their glucose tolerance, a significant correlation between renal Doppler parameters and LV diastolic function was observed in subjects with normal glucose tolerance, but this correlation disappeared in those with impaired glucose tolerance and diabetes mellitus. The present findings show that there is a significant relation between LV diastolic function and renal Doppler parameters in treated hypertensive patients, and suggest that cardiac damage progresses in parallel with renal involvement in these patients from the early stage. (*Hypertens Res* 2003; 26: 971–978)

***Key Words*: hypertension, diastolic function, heart, vascular resistance, kidney**

Introduction

Both the heart and kidneys are very important target organs in patients with hypertension. Their damage is directly linked to heart failure or renal failure and is also associated with all cause mortality (*1*, *2*). As microalbuminuria is an independent predictor for not only renal complications but also cardiac complications (*3–6*), there may be a close relation between both impairments. However, it has not been fully elucidated whether cardiac damage progresses in parallel with renal involvement in hypertensive patients, particularly at the early stages.

Abnormalities in left ventricular (LV) diastolic filling have been described in patients with hypertension, even in the absence of left ventricular hypertrophy (*7–9*). Moreover, impaired LV diastolic relaxation is a prognostic indicator of cardiovascular risk (*10*). An increased intrarenal resistance index (RI) evaluated by renal Doppler ultrasonography has also been reported in patients with essential hypertension (*11*, *12*). Assessment of intrarenal vascular resistance is useful in determining the degree of intrarenal damage. High levels of RI are associated with subclinical end-organ damage—namely microalbuminuria, LV hypertrophy, and carotid atherosclerosis—in hypertensive patients (*13*, *14*). In addition, an RI value of ≥ 0.8 is a strong and independent

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predictor for the progression of renal disease (*15*). These previous studies suggest that it is important to evaluate both LV diastolic function and intrarenal Doppler parameters to detect hypertensive target organ damage at an early stage. However, there has been no study examining the association between these early cardiac and renal changes. Thus, we conducted the present study to investigate whether there is any relation between LV diastolic dysfunction and intrarenal hemodynamic change in patients with treated essential hypertension.

Methods

Patients and Study Design

We evaluated 99 Japanese patients who were admitted to our hospital for the evaluation and treatment of hypertension. Exclusion criteria were the presence of secondary hypertension, myocardial infarction, valvular heart disease, atrial fibrillation, congestive heart failure, renal artery stenosis, and renal insufficiency (serum creatinine ≥ 1.5 mg/dl). Diabetic patients receiving hypoglycemic medication or whose fasting plasma glucose was ≥ 200 mg/dl or HbA_{1c} was $\geq 8.0\%$ were also excluded from this study.

Hypertension was defined as an average blood pressure of $\geq 140/90$ mmHg on at least two different occasions or by the presence of antihypertensive treatment. Among the 99 patients, 88 (89%) were receiving antihypertensive drugs, including combination therapy in some cases. The other 11 patients were also treated with diet and/or exercise therapy. Blood pressure, blood chemistry, and 24-h urinary collection were measured and echocardiography and renal Doppler ultrasonography were performed during their admission. Antihypertensive medication was not discontinued on the days of these echographic examinations.

Patients with previously diagnosed diabetes mellitus and patients who received the 75-g oral glucose tolerance test during their admission were divided into two groups. Patients who had a fasting plasma glucose of <110 mg/dl and a plasma glucose level of <140 mg/dl at 2 h after a glucose load were defined as having normal glucose tolerance. The other subjects, *i.e.*, patients with impaired glucose tolerance or mild diabetes mellitus, were defined as having abnormal glucose tolerance.

All patients gave their informed consent to participate in the present study.

Biochemical Analysis

Blood samples were obtained in the morning after an overnight fast. Biochemical variables were measured using an autoanalyzer. Twenty-four-hour urinary collection was carried out to evaluate creatinine clearance. Urinary albumin excretion was evaluated as the albumin-to-creatinine excretion ratio.

Echocardiography

Two-dimensional echocardiography was performed using a cardiac ultrasound unit (Sonos 5500: Hewlett Packard, Andover, USA) as previously described (*16*). Measurements included interventricular septal thickness (IVSTd), posterior wall thickness (PWTd), LV diameter at end-diastole (LVDd), and LV diameter at end-systole (LVDs). LV relative wall thickness (RWT) was calculated as (IVSTd+PWTd)/LVDd. LV mass was estimated using the formula validated by Devereux and Reichek (*17*): LV mass (g) $= 1.04\times\{(\mathrm{IVSTd}+\mathrm{PWTd}+\mathrm{LVDd})^3-\mathrm{LVDd}^3\}-13.6$. LV mass was normalized for body surface area and expressed as *LV mass index (LVMI)*.

To assess LV diastolic function, the diastolic filling of LV was examined using Doppler echocardiography. The LV diastolic filling pattern was obtained with the sample volume at the tips of the mitral valve in the apical four-chamber view and recorded at the end-expiratory phase during quiet breathing (*18*). The peak velocity of the early diastolic filling wave (E wave) and the peak velocity of atrial filling (A wave) were recorded and the A-to-E ratio (*A/E*) was calculated. The deceleration time (DcT) was measured as the time between the top of the E wave and the point where the descending part of the E wave or its asymptote crossed the zero line.

Renal Doppler Ultrasonography

Ultrasound examinations using a duplex Doppler apparatus were performed with subjects in a supine position in the morning after overnight fasting. Images were obtained with a duplex Doppler apparatus (SSA-380A: Toshiba Inc., Tokyo, Japan; and System FiVe: VINGMED, Horten, Norway) with a 2.5–3.75 MHz convex or sector array probe in both real-time/color-coded Doppler and pulsed Doppler modes. The peak systolic flow velocity (PSV), the peak diastolic flow velocity (PDV), and the end-diastolic flow velocity (EDV) of the segmental arteries were evaluated according to the method described previously (*15*). The diastolic-to-systolic ratio ($D/S=\mathrm{PDV/PSV}$) and resistance index ($\mathrm{RI}=(\mathrm{PSV}-\mathrm{EDV})/\mathrm{PSV}$) were calculated as the average of 6 total measurements in randomly selected segmental arteries from the upper, middle, and lower portion of the bilateral kidneys. The intra-assay and inter-assay coefficients of variation of these renal Doppler parameters were 2.6% and 3.4% (*D/S*), and 2.7% and 3.2% (RI), respectively.

Statistical Analysis

Statistical analysis was performed using StatView Version 5 Software (Abacus Concepts Inc., Berkeley, USA). Values were expressed as the means $\pm$ SD. Relations between variables were assessed using univariate linear regression analyses and Pearson's correlation coefficient. Multiple regression

Table 1. Patient Characteristics and Echographic Data

Age (years)	61±13
Gender (male / female)	50 / 49
Duration of hypertension (years)	16±11
Diabetes mellitus	16%
Hyperlipidemia	41%
Current smoker	20%
Systolic blood pressure (mmHg)	134±12
Diastolic blood pressure (mmHg)	76±11
Heart rate (beats/min)	63±9
Blood urea nitrogen (mg/dl)	16±4
Serum creatinine (mg/dl)	0.7±0.2
Creatinine clearance (ml/min)	110±47
Fasting plasma glucose (mg/dl)	96±15
HbA_{1c} (%)	5.4±0.6
Antihypertensive drugs	
Ca channel blockers	65%
RAS inhibitors	58%
β-Blockers	34%
Diuretics	17%
α1-Blockers	11%
LVMI (g/m^2)	119±34
RWT	0.47±0.08
A/E	1.21±0.33
DcT (ms)	234±48
D/S	0.64±0.07
RI	0.64±0.08

RAS, renin angiotensin system; LVMI, left ventricular mass index; RWT, relative wall thickness; HbA_{1c}, hemoglobin A_{1c}; *A/E*, peak velocity ratio of the atrial filling wave-to-early diastolic filling wave; DcT, deceleration time of the E wave; *D/S*, diastolic-to-systolic ratio; RI, resistance index. Values are the mean±SD or percentage.

analyses were also performed to identify independent associations between LV diastolic function and renal Doppler parameters. The significance of differences between the two groups was estimated by unpaired Student's *t*-test. A value of $p<0.05$ was considered to indicate statistical significance.

Results

The clinical characteristics of all subjects are summarized in Table 1. Since most patients were receiving antihypertensive drug treatment and the others were treated with diet and/or exercise therapy, their average blood pressure was well controlled. The LV mass of the present subjects was within normal (LVMI <125 g/m^2), but a concentric change in LV geometry (RWT ≥ 0.44) was observed. Their hearts also had an abnormal relaxation pattern (*A/E* ≥ 1.0 and DcT ≥ 230 ms), which is a common change in diastolic function observed in hypertensive patients. In renal Doppler parameters, an increase in RI (≥ 0.70) and/or decrease in *D/S* (<0.50) were found in about one fourth of the subjects, although their mean values were within the normal range.

We examined the correlation between renal Doppler parameters and cardiac hypertrophy and diastolic function in all subjects. *D/S* had a negative correlation with both *A/E* ($r=-0.331$, $p<0.001$) and DcT ($r=-0.309$, $p=0.002$), two indices of LV diastolic dysfunction (Fig. 1). RI had a positive correlation with *A/E* ($r=0.325$, $p=0.001$) and DcT ($r=0.271$, $p=0.006$). The observed association between renal Doppler parameters and LV diastolic function was independent of the use of any type of antihypertensive drugs (Table 2). On the other hand, neither *D/S* nor RI showed a significant correlation with the indices of LV hypertrophy, *i.e.*, LVMI (*D/S*, $r=-0.061$, $p=0.550$; RI, $r=0.074$, $p=0.470$) and RWT (*D/S*, $r=-0.029$, $p=0.775$; RI, $r=0.027$, $p=0.791$).

As for the associations with other clinical parameters, *A/E* was correlated with age, diastolic blood pressure, and creatinine clearance, and DcT was correlated with age and creatinine clearance (Table 3). Both *D/S* and RI were correlated with age, diastolic blood pressure, creatinine clearance, fasting plasma glucose, and HbA_{1c} (Table 4). We investigated whether the observed relation between renal Doppler parameters and LV diastolic function was also independent of such factors as age, blood pressure, renal function, and glucose levels using a multiple regression analysis in all subjects. As shown in Table 5, *D/S* had a significant association with DcT ($\beta=-0.240$, $p=0.044$) independent of age and other variables, although when RI was included as an independent variable in place of *D/S* the association was not significant. As for the *A/E*, another index of LV diastolic dysfunction, only age was an independent determinant.

Eighty subjects were divided into two groups by the absence or presence of abnormalities in glucose tolerance. No intergroup differences were found in clinical and echographic parameters except for fasting plasma glucose, HbA_{1c}, and urinary albumin excretion (Table 6). We examined the correlation between renal Doppler parameters and LV diastolic function in each group. *D/S* and RI were significantly correlated with *A/E* and DcT in the subject group with normal glucose tolerance (Table 7). In the subgroup with abnormal glucose tolerance, however, the significant association between renal and cardiac Doppler parameters disappeared.

Discussion

The present study has demonstrated that LV diastolic dysfunction is associated with intrarenal hemodynamic change in patients with treated essential hypertension. Several studies have reported a relation between cardiac damage and renal damage in hypertensive patients. Echocardiographically determined LV mass and geometry have been associated with serum creatinine in patients with essential hypertension (*19*, *20*). LV mass has also been related to proteinuria and microalbuminuria in such patients (*5*, *21*, *22*). As for LV

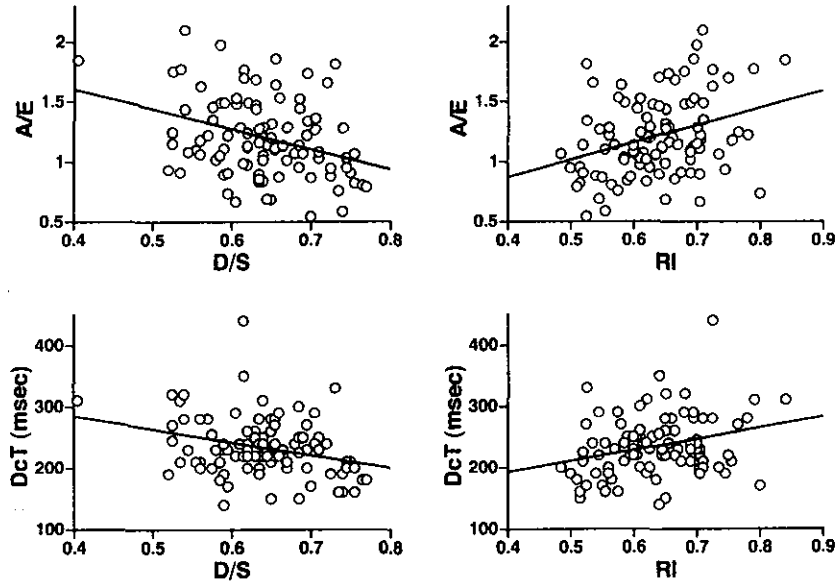

Fig. 1. *Correlation between renal Doppler parameters* (D/S *and RI) and left ventricular diastolic function* (A/E *and DcT) in all subjects.* D/S *was negatively correlated with* A/E ($r=-0.331$, $p<0.001$) *and DcT* ($r=-0.309$, $p=0.002$). *RI was positively correlated with* A/E ($r=0.325$, $p=0.001$) *and DcT* ($r=0.271$, $p=0.006$).

Table 2. Antihypertensive Drug-Independent Association between Renal Doppler Parameters and Left Ventricular Diastolic Function by Multiple Regression Analysis

	For *A/E*		For DcT	
	β	*p*	*β*	*p*
Model 1				
D/S	−0.303	0.004	−0.256	0.011
Ca channel blockers	0.053	0.595	0.123	0.204
RAS inhibitors	0.122	0.244	0.112	0.274
β-Blockers	−0.008	0.940	0.006	0.947
Diuretics	0.085	0.424	0.207	0.048
α1-Blockers	−0.023	0.821	0.038	0.696
Model 2				
RI	0.306	0.004	0.213	0.039
Ca channel blockers	0.027	0.788	0.113	0.258
RAS inhibitors	0.145	0.165	0.135	0.188
β-Blockers	−0.022	0.826	0.003	0.974
Diuretics	0.076	0.477	0.197	0.061
α1-Blockers	−0.013	0.901	0.049	0.617

A/E, peak velocity ratio of the atrial filling wave-to-early diastolic filling wave; DcT, deceleration time of the E wave; *D/S*, diastolic-to-systolic ratio; RI, resistance index; RAS, renin angiotensin system.

function, it has been reported that patients with renal insufficiency had both systolic and diastolic dysfunction (*23*). Furthermore, weak associations have been shown between microalbuminuria and indices of LV diastolic function (*5*). To our knowledge, however, the present study is the first to find a significant relation between LV diastolic function and renal Doppler parameters that are early markers of hypertensive target organ damage.

Both echocardiography and renal Doppler ultrasonography are noninvasive examinations that are frequently utilized for hypertensive patients. Echocardiography is usually used to evaluate LV asynergy, LV hypertrophy, and other cardiac complications. Renal Doppler ultrasonography is used as a screening test for renovascular hypertension due to renal artery stenosis. In addition, even if the patient's blood pressure is well controlled and there is no LV hypertrophy or re-

Table 3. Correlation between Left Ventricular Diastolic Function and Clinical Parameters

	A/E		DcT	
	r	*p*	*r*	*p*
Age	0.591	<0.001	0.409	<0.001
Systolic blood pressure	−0.119	0.244	−0.039	0.705
Diastolic blood pressure	−0.241	0.017	−0.103	0.314
Heart rate	0.093	0.382	0.019	0.855
Serum creatinine	0.183	0.069	0.150	0.138
Creatinine clearance	−0.294	0.003	−0.216	0.034
Urinary albumin excretion	0.118	0.252	0.039	0.708
Fasting plasma glucose	0.033	0.745	0.004	0.969
HbA_{1c}	0.136	0.187	0.126	0.222

A/E, peak velocity ratio of the atrial filling wave-to-early diastolic filling wave; HbA_{1c}, hemoglobin A_{1c}; DcT, deceleration time of the E wave.

Table 4. Correlation between Renal Doppler Parameters and Other Clinical Parameters

	D/S		RI	
	r	*p*	*r*	*p*
Age	−0.522	<0.001	0.618	<0.001
Systolic blood pressure	−0.085	0.406	0.190	0.061
Diastolic blood pressure	0.324	0.001	−0.332	<0.001
Heart rate	−0.108	0.307	−0.018	0.863
Serum creatinine	−0.006	0.957	0.004	0.966
Creatinine clearance	0.261	0.010	−0.429	<0.001
Urinary albumin excretion	0.050	0.628	−0.066	0.523
Fasting plasma glucose	−0.265	0.008	0.222	0.027
HbA_{1c}	−0.248	0.015	0.206	0.044

HbA_{1c}, hemoglobin A_{1c}; *D/S*, diastolic-to-systolic ratio; RI, resistance index.

Table 5. Independent Determinants for the DcT by Multiple Regression Analysis

	β	*p*
D/S	−0.240	0.044
Age	0.318	0.017
Systolic blood pressure	−0.128	0.261
Diastolic blood pressure	0.202	0.099
Creatinine clearance	−0.068	0.531
Urinary albumin excretion	0.040	0.685
Fasting plasma glucose	−0.169	0.216
HbA_{1c}	0.123	0.369

DcT, deceleration time of the E wave; *D/S*, diastolic-to-systolic ratio, HbA_{1c}, hemoglobin A_{1c}.

nal artery stenosis and dysfunction, minor alterations in LV diastolic filling and in renal Doppler parameters may indicate that there are early impairments in the heart and kidneys, because these abnormalities are considered early signs of hypertensive target organ damage. Thus, the significant association between the two observed in the present study suggests that cardiac and renal damage in essential hypertension might progress in parallel from an early stage.

There are several possible explanations for the mechanism of this association. In the present findings, age was a powerful determinant of both cardiac diastolic dysfunction and renal hemodynamic change. LV diastolic dysfunction (abnormal relaxation) in hypertensive patients is induced not only by LV hypertrophy but also by cardiac fibrosis with an increase in myocardial collagen matrix. It has been shown that the number and thickness of type I collagen fibers and intermolecular cross-linking of collagen are increased in the aged (*24*). In an autopsy study, the percentage of focal and global glomerulosclerosis, the extent of interstitial fibrosis, and the extent of tubular atrophy were all increased with age (*25*). These changes may cause an increase in blood flow resistance measurable at an upstream segmental artery. Another possible explanation for the mechanism is the effect of transforming growth factor (TGF)-β, which is well known to induce accumulation of extracellular matrix and tissue fibrosis (*26, 27*). Because of these properties, TGF-β has been linked to myocardial and renal fibrosis. Furthermore, a recent study reported that the increased levels of TGF-β in patients with

Table 6. Comparison of Clinical Findings between the Two Groups Divided by their Glucose Tolerance

	Normal GT	Abnormal GT	*p*
n	40	40	
Age (years)	61±13	62±12	NS
Systolic blood pressure (mmHg)	132±8	133±12	NS
Diastolic blood pressure (mmHg)	75±8	76±10	NS
Heart rate (beats/min)	64±8	62±8	NS
Serum creatinine (mg/dl)	0.7±0.2	0.8±0.2	NS
Creatinine clearance (ml/min)	112±48	116±45	NS
Urinary albumin excretion (mg/g Cr)	16±16	71±155	0.031
Fasting plasma glucose (mg/dl)	88±8	103±19	<0.001
HbA_{1c} (%)	5.2±0.4	5.8±0.7	<0.001
Antihypertensive drugs			
Ca channel blockers	65%	70%	NS
RAS inhibitors	53%	68%	NS
β-Blockers	33%	38%	NS
Diuretics	20%	20%	NS
α1-Blockers	10%	15%	NS
LVMI (g/m^2)	119±36	125±35	NS
RWT	0.47±0.08	0.48±0.08	NS
A/E	1.18±0.32	1.22±0.35	NS
DcT (ms)	242±54	230±42	NS
D/S	0.65±0.07	0.63±0.07	NS
RI	0.63±0.08	0.65±0.07	NS

GT, glucose tolerance; Cr, creatinine; HbA_{1c}, hemoglobin A_{1c}; RAS, renin angiotensin system; LVMI, left ventricular mass index; RWT, relative wall thickness; *A/E*, peak velocity ratio of the atrial filling wave-to-early diastolic filling wave; DcT, deceleration time of the E wave; *D/S*, diastolic-to-systolic ratio; RI, resistance index; NS, not significant. Values are the mean±SD or percentage.

Table 7. Correlation between Renal Doppler Parameters and Left Ventricular Diastolic Function in Each of the Two Groups

	D/S		RI	
	r	*p*	*r*	*p*
Normal GT (*n*=40)				
A/E	−0.347	0.028	0.398	0.011
DcT	−0.403	0.009	0.422	0.006
Abnormal GT (*n*=40)				
A/E	−0.306	0.055	0.306	0.054
DcT	−0.240	0.137	0.166	0.307

D/S, diastolic-to-systolic ratio; RI, resistance index; *A/E*, peak velocity ratio of the atrial filling wave-to-early diastolic filling wave; DcT, deceleration time of the E wave; GT, glucose tolerance.

essential hypertension contribute to the development of target organ damage (*28*). These findings suggest that humoral factors such as TGF-β, independently of age and hemodynamic factors, might influence both LV diastolic function and intrarenal vascular resistance.

In the present subgroup analysis, no significant correlation was observed between renal Doppler parameters and LV diastolic function in patients with abnormal glucose tolerance, including those with mild diabetes mellitus. A high level of plasma glucose, even if its elevation is slight, has been shown to deteriorate LV diastolic function in patients with treated essential hypertension (*29*). Interstitial accumulation of advanced-glycated end products, which include collagen, elastin, and other connective tissue proteins, may be responsible for alterations of the diastolic properties of the heart in persons with hyperglycemia (*30, 31*). On the other hand, glomerular dysfunction, intrarenal arteriosclerosis, interstitial fibrosis, and interstitial edema are related to the alteration in intrarenal hemodynamics in diabetic patients (*32–36*). Furthermore, many studies have reported that hyperinsulinemia and insulin resistance may contribute to both LV diastolic dysfunction (*37–39*) and glomerular hyperten-

sion and hyperfiltration (*40–42*). This abundance of glucose tolerance-related factors that modify LV diastolic function and renal Doppler parameters might have extinguished the relation between these two Doppler parameters in patients with glucose intolerance. In the present study, since an increase in plasma glucose levels was correlated with renal hemodynamic change rather than with LV diastolic dysfunction (Tables 3 and 4), mild abnormalities in glucose tolerance may have more selectively affected intrarenal hemodynamics than LV diastolic function.

The majority of patients in the present study had received antihypertensive drugs and their blood pressure was controlled. As a limitation of this study, therefore, some types of antihypertensive agents may have affected the cardiac function and renal hemodynamics apart from their actions on blood pressure. Angiotensin converting enzyme inhibitors and Ca channel blockers have been shown to inhibit cardiac and renal TGF-β expression and fibrosis in experimental models (*43–45*). In fact, previous studies reported that these types of drugs were effective in improving cardiac performance and intrarenal resistance in hypertensive patients (*39, 46–48*). In the present study, however, multivariate analyses proved that the association between renal Doppler parameters and LV diastolic function was independent of the use of specific types of antihypertensive drugs.

In conclusion, the findings of the present study demonstrated that cardiac diastolic dysfunction assessed by LV filling velocities was significantly associated with renal Doppler parameters related to the increase in intrarenal vascular resistance in patients with treated essential hypertension. Since these cardiac and renal indices evaluated using Doppler echographies are early markers of hypertensive target organ damage, the present findings suggest that cardiac damage and renal impairment in hypertensive individuals might progress in parallel from the primary stage.

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An Acyl-CoA Synthetase Gene Family in Chromosome 16p12 May Contribute to Multiple Risk Factors

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Abstract—We recently reported that genetic polymorphisms of SAH, an acyl-CoA synthetase for fatty acids, might contribute to multiple risk factors, especially hypertriglyceridemia. There are at least 4 members in this SAH gene family, *SAH*, *MACS1*, *MACS2*, and *MACS3*, and these 4 members are clustered in human Ch16p12. It is possible either that the previously observed associations were due to linkage disequilibrium with truly important polymorphisms in other members of the SAH gene family or that other polymorphisms in this gene family may also influence multiple risk factors. Thus, we performed association studies between genetic polymorphisms in this *SAH* region and multiple risk factors, using a large cohort representing the general population in Japan. The L513S polymorphism in *MACS2* was shown to significantly influence the triglyceride level and the waist-to-hip ratio. The previously observed associations between an *SAH* polymorphism and the waist-to-hip ratio appear to be due to linkage disequilibrium with the L513S polymorphism. Haplotype analysis indicated that a haplotype defined by the I/D polymorphism of *SAH* and the L513S polymorphism in *MACS2* was highly significantly associated with the triglyceride level. This study confirmed the importance of this chromosomal region in the pathogenesis of hypertriglyceridemia and visceral obesity. (***Hypertension.* 2003;41:1041-1046.**)

Key Words: epidemiology ■ fatty acids ■ genetics ■ hyperlipidemia ■ obesity

Differential screening was used to isolate *SAH* (Spontaneously hypertensive rat–Clone *A*–*H*ypertension-associated) from a genetically hypertensive rat strain, spontaneously hypertensive rat (SHR).[1] The expression of *SAH* in the kidneys of SHR is markedly higher than that in the kidneys of a normotensive control stain, Wistar-Kyoto rat. The rat *SAH* is localized on chromosome 1 near the most prominent QTL for blood pressure and had been expected to contribute to hypertension in SHR.[2,3] However, subsequent congenic analysis excluded rat *SAH* from the genes that contribute to hypertension in SHR.[4,5]

Recently, SAH protein has been reported to be significantly homologous to bovine xenobiotic-metabolizing medium-chain fatty acids: CoA ligase.[6] We revealed that human SAH had acyl-CoA synthetase activity toward medium chain fatty acids and that a genetic polymorphism of *SAH* might contribute to multiple risk factors, including hypertriglyceridemia, obesity, and hypertension.[7] It is likely that a genetic polymorphism of *SAH* might influence triglyceride metabolism, energy expenditure, and fat metabolism by influencing fatty acid metabolism.

A homology search of *SAH* in the human genome indicates that there are at least 4 members in this *SAH* gene family, *SAH*, *MACS1*, *MACS2*, and *MACS3* (Figure). Moreover, these 4 appear to be clustered in chromosome 16p12 (see Results). It is possible that the associations seen between the *SAH* polymorphism and multiple risk factors in the preceding study[7] might be due to linkage disequilibrium with genetic polymorphisms in other members of this gene family and that genetic polymorphisms in other members of this gene family might also contribute to multiple risk factors. Thus, to extend our previous work, we searched for genetic variations in this chromosomal region and performed association studies between polymorphisms in this region and multiple risk factors using a large cohort representing the general population in Japan.

Methods

DNA Studies

Genomic DNA from 36 subjects was used for sequence screening for polymorphisms. The promoter region and all of the exons of the *MACS1*[8] (Medium Chain Acyl-CoA Synthetase 1; MACS1) gene were sequenced according to the human draft sequence. The genome structures of *MACS2* (GenBank accession; AX451437) and *MACS3* (GenBank accession; AK000588) had not been determined at the beginning of the present study. We determined exon-intron boundaries on the basis of homology to *SAH* and *MACS1* and amplified intronic sequences by primers residing on the neighboring exons to determine the flanking sequences of exons. Based on the flanking sequences, all of the coding exons of *MACS2* and *MACS3* were amplified and sequenced. Primer sequences can be provided on request. The polymorphisms were determined by use of the TaqMan system (PE Applied Biosystems). The sequences of the primers and probes used in the TaqMan method can be provided on request.

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