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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循環器薬の病態に応じた使い方

カルシウム拮抗薬

高血圧における使い方

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medicina
第40巻　第8号 別刷
2003年8月10日　発行

医学書院

〈カルシウム拮抗薬〉高血圧における使い方

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ポイント

- ▶ Ca 拮抗薬は大部分の高血圧患者に適しており，特に老年者に推奨される．
- ▶ Ca 拮抗薬は降圧効果が確実で，安全性と認容性に優れ，禁忌となることが少ない．
- ▶ Ca 拮抗薬は高血圧患者の予後を改善し，その効果は利尿薬や ACE 阻害薬と同等である．
- ▶ 24 時間の血圧コントロールには長時間作用性の薬剤が望ましく，夜の服薬も効果的である．

カルシウム(Ca)拮抗薬は高血圧の治療薬として広く用いられており，わが国では降圧薬のなかで最も汎用されている．Ca 拮抗薬は降圧効果が比較的確実で，副作用が少なく，禁忌となることがあまりない．初期の短時間作用性のものは安全性に疑問があったが，長時間作用性のものは高血圧患者の予後を改善することが示されている．本稿では，Ca 拮抗薬の特徴や高血圧治療におけるエビデンス，使い方，注意点について概説する．

作用機序と種類

Ca 拮抗薬の降圧機序は，血管平滑筋の電位依存性 L 型 Ca チャネルの阻害による血管拡張による．Ca 拮抗薬は心筋にも作用して心収縮や心拍数の抑制に働くが，血管選択性は薬剤により異なる．

Ca 拮抗薬は，ニフェジピンやアムロジピンなどのジヒドロピリジン系の薬剤と，ジルチアゼムやベラパミルなどの非ジヒドロピリジン系の薬剤に大別される．前者は血管選択性が強く心拍数は増加傾向となり，後者は心抑制作用が強く心拍数を減少させる．

Ca 拮抗薬は初期の薬剤は短時間作用性であったが，現在降圧薬として使われているものの多くは長時間作用性である．しかし後者の作用時間にも差があり，1 日 1 回の服薬では 24 時間後に効果が減弱するものもある．

一部の Ca 拮抗薬は，L 型以外の Ca チャネルにも作用する．シルニジピンは交感神経などに存在する N 型チャネルを，エフォニジピンは洞房結節などの T 型チャネルを阻害する．これらは心拍数への影響が少なく，腎保護作用を有することが示唆されている[1]．

高血圧治療におけるエビデンス

Ca 拮抗薬の高血圧治療における有用性は明らかであり，多くのガイドラインにおいて第一選択薬の一つとして推奨されている．その降圧効果は比較的確実であり，われわれの施設における検討ではニフェジピン徐放錠の効果はエナラプリル，アテノロール，トリクロルメチアジドに比べて大きく，特に老年者において明らかであった[2]．

プラセボを対照とした大規模臨床試験において，長時間作用性の Ca 拮抗薬は高血圧患者の予後を改善させることが示されている(表 1)[3]．その効果は老年者において明らかで，痴呆の予防に働くことも期待される[4]．

他の降圧薬との比較では，Ca 拮抗薬の予後改善効果はほぼ同等と考えられる(表 1)[3]．最近の ALLHAT 研究においても，アムロジピン群と利尿薬群は心血管イベントに差はなかった．ただし，脳卒中の予防は Ca 拮抗薬がやや優れ，心保

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0025-7699/03/¥500/論文/JCLS

護効果は少し劣ることが示唆されている．

腎保護効果に関しては，糖尿病性腎症や腎硬化症ではCa拮抗薬はACE阻害薬やAII拮抗薬に劣ることが報告されている．しかし，腎障害のない高血圧患者におけるわれわれの検討では，アムロジピンの尿中アルブミンへの効果はロサルタンと同等であった．

Ca拮抗薬の使い方

1．合併症のない高血圧患者

Ca拮抗薬は，合併症のない高血圧患者における第一選択薬の一つとして用いられ，特に高齢者においてはその使用が推奨されている．他の降圧薬と同様に，一般的には少量より開始し，降圧が不十分であれば増量する．

Ca拮抗薬は，他の降圧薬で治療を開始した場合の併用薬としても有用である．降圧効果や副作用を考慮すれば，β遮断薬やACE阻害薬，AII拮抗薬との併用が勧められる．ただし，ジルチアゼムとβ遮断薬の併用は，徐脈や心抑制に注意を要する．利尿薬との併用は，相加的に働くが効果は比較的小さい．

2．合併症を有する高血圧患者

Ca拮抗薬は代謝面の副作用はなく，禁忌となる病態も少ないため，合併症を有する高血圧患者においても，ほとんどの場合に良い適応となる(表2)[5]．使い方は，合併症のない場合に準じる．心不全や糖尿病性腎症を伴う患者においては，第一選択薬とはせずに併用薬として用いるほうがよい．

3．高血圧緊急症

悪性高血圧などの高血圧緊急症においては，ニカルジピンとジルチアゼムの注射薬が用いられる．少量から開始し，血圧と臨床症状をモニターしながら用量を調節する．

高血圧準緊急症は経口薬による治療でもよい．比較的速効性の薬剤が望ましいが，ニフェジピンのカプセル剤は急激な降圧をきたす可能性があり，徐放錠を用いる．

表1　高血圧治療の大規模臨床試験におけるCa拮抗薬の効果についてのメタアナリシス(文献3より)

	Ca拮抗薬の相対危険度		
	対プラセボ	対利尿薬/β遮断薬	対ACE阻害薬
脳卒中	0.61*	0.87*	0.98
虚血性心疾患	0.79*	1.12*	1.23*
心不全	0.72	1.12	1.22*
心血管イベント	0.72*	1.02	1.09
心血管死亡	0.72*	1.05	0.96
全死亡	0.87	1.01	0.97

＊：$p<0.05$

4．血圧日内変動

短時間作用性のCa拮抗薬は，服用後の血圧変動が大きく，好ましくない．長時間作用性の薬剤は1日1～2回の服用で安定した降圧が得られることが多いが，朝1回では翌朝に効果が減弱し，降圧不十分となっている場合がある．

このような場合には，①アムロジピンなどの超長時間作用性の薬剤を用いる，②長時間作用性の薬剤を朝と夜に分割する，③長時間作用性の薬剤を夜に投与する，が勧められる．夜の降圧薬投与に関しては，Syst-Eur試験およびSyst-China試験でニトレンジピンによる高齢高血圧患者の予後改善が示されている[4]．

使用上の注意点

長時間作用性のCa拮抗薬は比較的安全に使用できるが，いくつか注意すべき点がある．ジヒドロピリジン系の薬剤の副作用として，血管拡張による顔面紅潮や頭痛，動悸がよく知られている．より長時間作用性の薬剤では頻度は少ない．下肢浮腫は血管拡張と血管透過性の亢進によって起こり，用量依存性である．ACE阻害薬の併用により軽減する．歯肉腫脹をきたすこともある．また，薬剤によって異なるが，グレープフルーツは代謝に影響し，効果を増強させる．非ジヒドロピリジン系の薬剤では，徐脈性不整脈や心機能低下，便秘などに注意を要する．

表2　合併症を有する高齢者高血圧に対する第一選択薬と併用薬(文献5より)

合併症	Ca 拮抗薬(ジヒドロピリジン系)	ACE 阻害薬	利尿薬	β遮断薬	α遮断薬
脳梗塞慢性期	○	○			
脳出血慢性期	○	○			
虚血性心疾患	○	○		○*3	
心不全		○	○	△	
腎障害	○	○*1	○*2		
糖尿病	○	○	△	△	
高脂血症	○	○	△	△	○
痛風(高尿酸血症)	○	○	×		
慢性閉塞性肺疾患	○			×	
閉塞性動脈硬化症	○	○	△	×	
骨粗鬆症			○		
前立腺肥大					○

○：第一選択，△：使用に際して注意が必要，×：禁忌．
*1：クレアチニン2 mg/dl 以上は禁忌，*2：フロセミド，*3：冠攣縮性狭心症は禁忌．

●**おわりに**　Ca 拮抗薬は降圧薬として有効性，安全性，認容性が高く，高血圧患者の予後を改善することが確認されている．Ca 拮抗薬は，合併症の有無やその種類にかかわらず第一選択薬として用いられる場合が多く，また併用薬としても適している．Ca 拮抗薬には多くの種類があるが，長時間作用性のものが24時間の血圧コントロールからみて望ましい．N 型や T 型チャネルを阻害する薬剤の有用性については，今後の研究の進展が待たれる．

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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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Received October 8, 2002; Accepted in revised form April 15, 2003.

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-

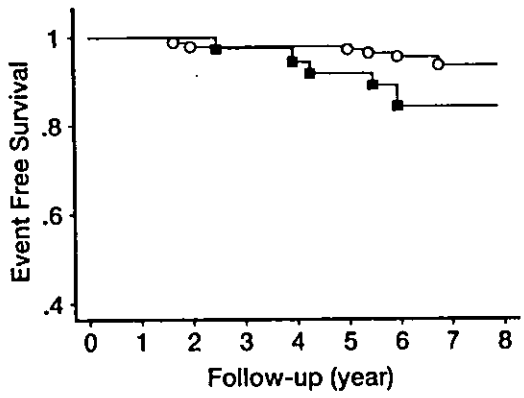

Fig. 1. *Cardiovascular event-free survival curves for elderly hypertensive patients with microalbuminuria (MA group: closed square) and patients without microalbuminuria (NA group: open circle). The difference between the two groups was significant in terms of the Kaplan-Meier survival curves and by 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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AJH 2003; 16:938–944

Influence of Low High-Density Lipoprotein Cholesterol on Left Ventricular Hypertrophy and Diastolic Function in Essential Hypertension

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Background: Left ventricular (LV) hypertrophy and LV diastolic dysfunction, which are common cardiac changes in hypertensive patients, are modified by several nonhemodynamic (eg, genetic, neurohumoral, and metabolic) factors. However, the influence of serum lipids on these LV changes has not been sufficiently studied. Although low high-density lipoprotein (HDL) cholesterol is well known to be a major risk factor for coronary heart disease, it is unclear whether HDL cholesterol plays a role in hypertensive heart disease.

Methods: In 274 patients with treated essential hypertension, two-dimensional and Doppler echocardiography were performed, and LV mass, ratio of peak velocity of atrial filling to early diastolic filling (A to E ratio [A/E]), and deceleration time of the E-wave were evaluated. The relationship of dyslipidemia, especially low HDL cholesterol, to LV hypertrophy and diastolic function was investigated in these patients.

Results: In a univariate regression analysis, HDL cholesterol was inversely associated with LV mass, A/E, and deceleration time. The association of HDL cholesterol with LV diastolic function was observed in both men and women. Its association with LV mass was gender-dependent, being significant only in women. Triglycerides were weakly correlated with LV mass and A/E, but total and low-density lipoprotein cholesterol had no correlations with these indices. In a multiple regression analysis, only low HDL cholesterol among several lipid levels was an independent predictor of both LV mass and LV diastolic dysfunction.

Conclusions: Our findings suggest that low HDL cholesterol may unfavorably modify LV structure and diastolic function in patients with treated essential hypertension. Am J Hypertens 2003;16:938–944 © 2003 American Journal of Hypertension, Ltd.

Key Words: Lipoproteins, cholesterol, hypertrophy, ventricular function, hypertension.

Left ventricular (LV) hypertrophy and LV diastolic dysfunction, which are common cardiac consequences of hypertension, are both independent risk factors for cardiovascular morbidity and mortality.[1–4] Although LV hypertrophy is primarily considered as an adaptation to the increased afterload, this structural adaptation of LV in hypertension is modified by several nonhemodynamic factors such as genetic, neurohumoral, and metabolic factors.[5–7] The LV diastolic dysfunction (abnormal relaxation) in hypertensive patients results from an increase in afterload (systemic arterial pressure) and LV hypertrophy, especially concentric hypertrophy.[8] However, diastolic dysfunction also may be affected by some factor other than blood pressure (BP) or cardiac hypertrophy in treated hypertension, as it was shown that diastolic impairments of LV function persisted despite effective control of BP in treated hypertensive patients and that these impairments were independent of LV hypertrophy.[9] In fact, abnormalities in glucose and insulin metabolism have been shown to accelerate the deterioration of LV diastolic function in essential hypertension.[10–12]

Dyslipidemia is another of the metabolic abnormalities observed most frequently in hypertensive patients. However, the influence of serum lipids on ischemia-independent cardiac structural and functional changes has not been fully elucidated.[13–15] A positive association between total and low-density lipoprotein (LDL) cholesterol and coronary heart disease is well established, and low high-density lipoprotein (HDL) cholesterol and elevated triglycerides are also known to be risk factors for coronary events.[16,17] Despite the growing evidence concerning the impact of these lipid disorders on coronary heart disease, little is known about whether dyslipidemia plays a part in hypertensive heart disease. Thus, the major aim of the present study was to clarify the relationship of dyslipidemia, especially of low HDL cholesterol, to LV hypertro-

Received December 12, 2002. First decision February 5, 2003. Accepted June 11, 2003.

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0895-7061/03/$30.00
doi:10.1016/S0895-7061(03)01015-X

phy and diastolic function in patients with essential hypertension.

Methods

Patients

A total of 274 patients with essential hypertension (144 men and 130 women; mean age (± SD), 61 ± 13 years) were enrolled in our study. Patients with secondary hypertension, coronary heart disease, valvular heart disease, atrial fibrillation, congestive heart failure, renal failure (serum creatinine ≥ 133 μmol/L (1.5 mg/dL)), overt diabetes mellitus, or unsatisfactory B-mode and Doppler echocardiograms were excluded from this study. Individuals treated with lipid-lowering drugs or participants whose serum triglycerides were ≥4.52 mmol/L (≥400 mg/dL) were also excluded from the study. Hypertension was defined as a systolic BP of ≥140 mm Hg and/or a diastolic BP of ≥90 mm Hg by repeated measurements or when medication was taken for treatment of hypertension. Among the 274 patients, 235 (86%) were receiving antihypertensive drugs, including combination therapy in some cases. A total of 175 patients (64%) were treated with calcium channel blockers, 107 (39%) with renin angiotensin system inhibitors, 80 (29%) with β-blockers, 37 (14%) with diuretics, and 31 (11%) with other classes of agents. In all, 39 patients (14%) were treated with diet or exercise therapy, or both, without antihypertensive medication. All subjects gave their informed consent to participate in the present study.

Glucose and Lipid Measurement

Blood samples were obtained in the morning after an overnight (≥12 h) fast. Fasting plasma glucose and serum concentrations of total cholesterol, HDL cholesterol, and triglycerides were determined by standard laboratory measurements; LDL cholesterol was calculated using the Friedewald formula.[18]

Echocardiographic Examination

On the same day or within 1 week of the blood sampling, comprehensive two-dimensional echocardiography was performed using a cardiac ultrasound unit (Sonos 5500; Hewlett Packard, Andover, MA) as previously described.[19] Echocardiographic parameters were measured by the consensus of two experienced investigators who were blinded to the metabolic data of the subjects. Measurements included interventricular septal thickness at end-diastole (IVSTd), posterior wall thickness at end-diastole (PWTd), and LV diameter at end-diastole (LVDd). The LV relative wall thickness was calculated as (IVSTd+PWTd)/LVDd. LV mass was estimated using the formula validated by Devereux and Reichek[20]: LV mass (g) = $1.04 \times \{(IVSTd+PWTd+LVDd)^3 - LVDd^3\} - 13.6$. The LV mass index was obtained traditionally by dividing the LV mass by body surface area (LVMI(a), g/m^2). The LV mass was also indexed by height to the 2.7 power (LVMI(h), g/m$^{2.7}$), to take into account the influence of obesity that is partly overlooked when indexing for body surface area.[21]

To assess LV diastolic function, the diastolic filling of LV (LV inflow) 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.[22] 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 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.

Statistical Analysis

Values are expressed as mean ± SD. Unpaired t test was used for comparison between the two groups. The significance of differences among more than two groups was evaluated by an unpaired analysis of variance with subsequent use of Fisher's multiple comparison test. Relationships between variables were assessed using univariate linear regression analyses and Pearson's correlation coefficient. Stepwise multiple regression analyses were performed to identify independent predictors of LV mass and LV diastolic function. Age, gender, body mass index, systolic and diastolic BP, fasting plasma glucose, and total LDL, and HDL cholesterol, triglycerides, as well as use of each type of antihypertensive drug (calcium channel blocker, renin angiotensin system inhibitor, β-blocker, or diuretic) were included as potential independent variables. LVMI(a), LVMI(h), relative wall thickness, and heart rate were added as independent variables in the analysis for diastolic function. A value of $P < .05$ was accepted as statistically significant.

Results

Clinical and echocardiographic characteristics of the study subjects are shown in Table 1. There were no significant differences in age, body mass index, systolic BP, diastolic BP, or fasting plasma glucose between men and women. Heart rate was somewhat increased in women. However, no gender differences were found in the percentage of patients treated with any type of antihypertensive drug (data not shown). Serum levels of total cholesterol and HDL cholesterol were higher, and that of triglycerides was lower, in women than in men. LVMI(a), LV mass normalized for body surface area, in addition to IVSTd, PWTd, and LVDd were significantly increased in men compared with women, but LVMI(h), LV mass normalized for height$^{2.7}$, did not differ between genders. The A/E ratio

Table 1. Clinical and echocardiographic characteristics of the study subjects

	All (n = 274)	Men (n = 144)	Women (n = 130)
Age, y	61 ± 13	60 ± 13	62 ± 11
Body mass index, kg/m^2	24.3 ± 3.3	24.5 ± 2.8	24.0 ± 3.8
Systolic blood pressure, mm Hg	143 ± 14	143 ± 13	142 ± 15
Diastolic blood pressure, mm Hg	83 ± 9	84 ± 9	82 ± 10
Heart rate, beats/min	66 ± 10	64 ± 10	68 ± 10*
Fasting plasma glucose, mmol/L	5.50 ± 0.81	5.55 ± 0.82	5.46 ± 0.80
Total cholesterol, mmol/L	5.23 ± 0.73	5.11 ± 0.73	5.37 ± 0.70†
LDL cholesterol, mmol/L	3.25 ± 0.66	3.19 ± 0.64	3.31 ± 0.68
HDL cholesterol, mmol/L	1.37 ± 0.41	1.24 ± 0.29	1.52 ± 0.46†
Triglycerides, mmol/L	1.33 ± 0.67	1.47 ± 0.74	1.17 ± 0.53†
IVSTd, mm	10.7 ± 1.7	11.1 ± 1.7	10.3 ± 1.7†
PWTd, mm	10.7 ± 1.6	11.1 ± 1.5	10.2 ± 1.5†
LVDd, mm	45.5 ± 4.5	47.1 ± 3.8	43.8 ± 4.7†
LVMI(a), g/m^2	124 ± 30	130 ± 29	116 ± 30†
LVMI(h), g/m$^{2.7}$	57.6 ± 15.0	58.5 ± 14.3	56.5 ± 15.7
Relative wall thickness	0.48 ± 0.09	0.48 ± 0.08	0.47 ± 0.10
E wave velocity, m/sec	0.70 ± 0.16	0.69 ± 0.17	0.71 ± 0.16
A wave velocity, m/sec	0.79 ± 0.17	0.77 ± 0.18	0.82 ± 0.16*
A/E ratio	1.19 ± 0.34	1.18 ± 0.34	1.20 ± 0.34
Deceleration time, msec	226 ± 45	227 ± 43	226 ± 48

IVSTd = interventricular septal thickness at end-diastole; LVDd = left ventricular diameter at end-diastole; LVMI(a) = left ventricular mass indexed by body surface area; LVMI(h) = left ventricular mass indexed by height$^{2.7}$; PWTd = posterior wall thickness at end-diastole. Values are mean ± SD.

* $P < .05$ and † $P < .01$ *v* men.

and deceleration time, indices of LV diastolic function, also did not differ by gender.

We examined the association of lipid levels with echocardiographic parameters of LV hypertrophy and diastolic function, in all subjects or separately in men and women. No significant correlation was found between total or LDL cholesterol and LV mass or diastolic function without regard to gender (Table 2). In contrast, HDL cholesterol showed significant negative correlations with all parameters of LV hypertrophy, ie, LVMI(a) and LVMI(h), and diastolic dysfunction (A/E and deceleration time) in the overall subject group. The association of HDL cholesterol with LV diastolic function was observed in both men and women. However, its association with LV mass was gender-dependent; ie, HDL cholesterol was inversely associated with LVMI(a) and LVMI(h) in women only. Triglycerides showed a positive correlation with LV mass in all subjects and in women and a weak correlation with the A/E ratio only in men.

We found that HDL cholesterol and triglycerides were also correlated with body mass index (HDL cholesterol, $r = -0.31$, $P < .001$; triglycerides, $r = 0.26$, $P < .001$) and with fasting plasma glucose (HDL cholesterol, $r = -0.20$, $P = .001$; triglycerides, $r = 0.25$, $P < .001$) in all subjects. These two lipid levels showed no association with age, BP, or heart rate (data not shown).

Next, we subdivided each study group (men and women) by gender-specific tertiles of HDL cholesterol and triglycerides. We then examined the influence of the lowest HDL cholesterol tertile (men, <1.14 mmol/L [44 mg/dL]; women, <1.27 mmol/L [49 mg/dL]) or the highest triglyceride tertile (men, ≥ 1.56 mmol/L [138 mg/dL]; women, ≥ 1.32 mmol/L [117 mg/dL]) on LV mass and diastolic function. All subjects were divided by these lipid levels into four groups; subjects without the lowest HDL cholesterol or the highest triglyceride tertile (group 1, n = 133), with the highest triglyceride tertile alone (group 2, n = 47), with the lowest HDL cholesterol tertile alone

Table 2. Correlation between lipid levels and indices of LV hypertrophy and diastolic function

	LVMI(a)	LVMI(h)	A/E	DcT
Total Cholesterol				
All	−0.07	−0.02	0.03	0.05
Men	−0.06	−0.04	0.06	0.06
Women	0.00	0.02	−0.01	0.04
LDL Cholesterol				
All	0.00	0.05	0.07	0.12
Men	−0.06	−0.03	0.06	0.10
Women	0.10	0.14	0.08	0.14
HDL Cholesterol				
All	−0.21†	−0.22†	−0.15*	−0.18†
Men	−0.02	−0.05	−0.19*	−0.17*
Women	−0.24†	−0.31†	−0.17*	−0.20*
Triglycerides				
All	0.13*	0.14*	0.12	0.09
Men	−0.01	0.03	0.17*	0.08
Women	0.21*	0.21†	0.06	0.10

DcT = deceleration time of the E wave. Values are correlation coefficients. * $P < .05$; † $P < .01$.

Table 3. Comparison of clinical findings among the four groups divided by HDL cholesterol and triglyceride levels

	Group 1 (n = 133)	Group 2 (n = 47)	Group 3 (n = 49)	Group 4 (n = 45)
Age, y	60 ± 12	59 ± 11	62 ± 15	63 ± 11
Gender (men), %	50.4	59.6	59.2	44.4
Body mass index, kg/m^2	23.3 ± 3.3	25.0 ± 2.6*	25.0 ± 3.4*	25.5 ± 3.1*
Systolic blood pressure, mm Hg	142 ± 14	142 ± 17	144 ± 13	143 ± 13
Diastolic blood pressure, mm Hg	84 ± 9	84 ± 11	83 ± 8	83 ± 9
Heart rate, beats/min	66 ± 10	66 ± 10	65 ± 10	68 ± 9
Fasting plasma glucose, mmol/L	5.38 ± 0.75	5.59 ± 0.68	5.43 ± 0.92	5.85 ± 0.92*‡
Total cholesterol, mmol/L	5.22 ± 0.70	5.59 ± 0.58*	4.92 ± 0.68*†	5.22 ± 0.82†‡
LDL cholesterol, mmol/L	3.18 ± 0.64	3.22 ± 0.56	3.42 ± 0.61*	3.28 ± 0.83
HDL cholesterol, mmol/L	1.62 ± 0.38	1.45 ± 0.27*	1.00 ± 0.14*†	1.00 ± 0.14*†
Triglycerides, mmol/L	0.92 ± 0.27	2.02 ± 0.71*	1.10 ± 0.24*†	2.08 ± 0.55*‡

Values are mean ± SD or percentage.
* $P < .05$ *v* group 1. † $P < .05$ *v* group 2. ‡ $P < .05$ *v* group 3.

(group 3, n = 49), and with both the lowest HDL cholesterol and the highest triglyceride tertiles (group 4, n = 45). There were no significant differences in age, gender (percentage of men), BP, or heart rate among the four study groups (Table 3). Body mass index was higher in groups 2, 3, and 4 than in group 1. The fasting plasma glucose level in group 4 was higher than that in groups 1 and 3. All lipid parameters had group-specific differences as shown in Table 3. LVMI(h), but not LVMI(a), was slightly but significantly increased in group 4 compared with group 1 (Figs. 1A, 1B). The A/E ratio in groups 3 and 4 (ie, those subjects who were in the lowest tertile of HDL choles-

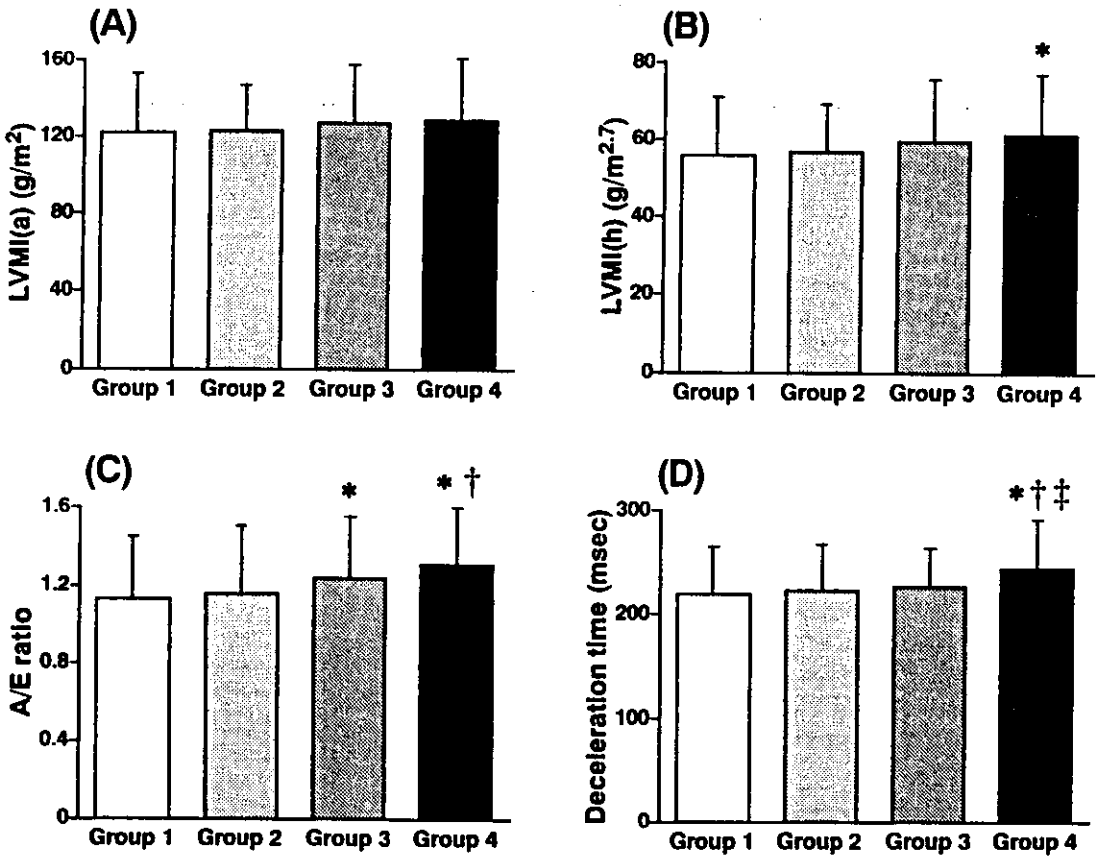

FIG. 1. Comparison of LVMI(a) (**A**), LVMI(h) (**B**), A to E ratio (**C**), and deceleration time of the E wave (**D**) among the four groups divided by HDL cholesterol and triglyceride levels. Values are given as mean ± SD. *$P < .05$ compared with group 1; †$P < .05$ compared with group 2; ‡$P < .05$ compared with group 3.

Table 4. Independent predictors for LV mass and diastolic dysfunction by stepwise regression analysis

	Standardized Regression Coefficient	*F* Value	*P* Value
LVMI(a)			
Systolic blood pressure	0.236	18.65	
Use of β-blockers	0.220	16.12	
Gender (male)	0.213	13.36	
Age	0.182	10.37	
HDL cholesterol	−0.180	9.30	< .0001
LVMI(h)			
Body mass index	0.291	26.52	
Systolic blood pressure	0.233	19.17	
Age	0.234	18.03	
Use of β-blockers	0.215	16.40	
HDL cholesterol	−0.160	7.92	< .0001
A/E ratio			
Age	0.484	89.88	
Relative wall thickness	0.166	10.54	
HDL cholesterol	−0.139	7.53	
Heart rate	0.130	6.64	< .0001
Deceleration time			
Age	0.273	23.26	
Use of diuretics	0.169	9.04	
HDL cholesterol	−0.164	8.66	
Relative wall thickness	0.138	5.94	< .0001

terol) was significantly higher than in the other groups, and group 4 had the highest A/E ratio (1.31 ± 0.29) among the four study groups (Fig. 1C). The deceleration time in group 4 (245 ± 48 msec) was also prolonged significantly in comparison with the other three groups (Fig. 1D).

To confirm whether the effect of low HDL cholesterol on LV hypertrophy was independent of other factors (especially high triglycerides, glucose levels, obesity, gender, and use of specific types of antihypertensive drugs) and whether its effect on LV diastolic function was independent of LV hypertrophy, we investigated possible predictive factors for LVMI(a), LVMI(h), A/E ratio, and deceleration time using a stepwise regression analysis in all subjects. As a result, low HDL cholesterol as well as age, male gender, body mass index, systolic BP, and use of β-blockers was an independent determinant of LV mass, both LVMI(a) and LVMI(h) (Table 4). When the analysis was performed separately in men and women, the independent relation of low HDL cholesterol to LV mass was observed in women only (data not shown). As for the association with LV diastolic function, low HDL cholesterol was a significant predictor of both A/E ratio and deceleration time, independent of other predictive factors such as age, relative wall thickness, heart rate, and use of diuretics. A high level of triglycerides in addition to total and LDL cholesterol could not be adopted as an independent determinant of LV mass or diastolic dysfunction.

Discussion

The relationship between LV hypertrophy and HDL cholesterol levels in hypertensive patients or population-based samples has been reported in previous studies, with conflicting results.[14,15,23–27] Among these studies, only one report by Schillaci et al[14] has revealed an independent relationship of low HDL cholesterol to LV mass in male and female hypertensive patients. The present observations concerning the associations between several lipid levels and LV mass are broadly consistent with their findings. In our study, however, the significant association of HDL cholesterol with LV mass by univariate and multivariate regression analyses was observed only in women. Although the exact reason for the inconsistent findings in men among these studies is unclear, the gender (women)-specific influence of HDL cholesterol on LV mass was also reported from the Framingham Heart Study.[23] Furthermore, LV hypertrophy has a greater impact on total and cardiac mortality in women than in men.[28] These findings suggest that the contribution of low HDL cholesterol to hypertensive heart disease is possibly stronger in women than in men, as low HDL cholesterol appears to raise the risk for coronary heart disease more potently in women compared with men.[29]

Impaired LV diastolic relaxation is another common cardiac change observed in hypertensive patients; this diastolic dysfunction has a prognostic significance, independent of BP and LV mass.[4] Nonetheless, the relationship of serum lipids to LV diastolic function in essential hypertension has never been investigated until now. Only one recent study showed in a limited population of postmenopausal women that total, LDL, and HDL cholesterol were correlated with an abnormal LV diastolic filling pattern. In the present study, we first demonstrated that

HDL cholesterol, but not total or LDL cholesterol, had a significant association with impairments of LV diastolic relaxation in both men and women with essential hypertension, and that the association between the two was independent of traditional determinants of impaired LV relaxation such as age and LV concentric hypertrophy. Therefore, our findings suggest that low HDL cholesterol may exert an adverse effect on LV diastolic function in hypertensive subjects regardless of gender, BP level, or LV structure.

In the present study, triglyceride levels showed a small correlation with LV mass and diastolic function, although total or LDL cholesterol was not associated with these echocardiographic indices at all. In addition, LV hypertrophy and LV diastolic dysfunction were most advanced in a subgroup with both low HDL cholesterol and high triglycerides. Individuals in this group were also accompanied with increased body mass index and elevated plasma glucose level, and so they appeared to belong to a cluster of multiple interrelated abnormalities in lipid and glucose metabolism along with hypertension and obesity, called the metabolic syndrome.[30,31] Insulin resistance with compensatory hyperinsulinemia is considered to be a primary pathophysiologic basis of the syndrome in hypertensive subjects.[30,31] As a possible explanation for the effects of low HDL cholesterol on cardiac structural and functional alterations, therefore, the involvement of insulin resistance and hyperinsulinemia could be included. In fact, serum levels of HDL cholesterol are inversely correlated with serum insulin levels,[32] and some studies have reported that hyperinsulinemia or insulin resistance is related to LV hypertrophy and diastolic dysfunction in hypertensive patients.[12,33] However, other studies have shown that such abnormalities in insulin metabolism per se are not associated with either increased LV mass or impaired LV diastolic function.[10,27,34,35] Our multiple regression study also showed that the associations of low HDL cholesterol with these cardiac changes were independent of the other components of the metabolic syndrome such as BP, body mass index, plasma glucose, and serum triglyceride levels. However, the independent relationship of HDL cholesterol to LV structure and function may have reflected a relationship to other, unmeasurable variables that were more directly implicated in the pathogenesis of the association, as we did not determine the plasma insulin concentration or insulin resistance index in the present cohort. Further investigations are needed to clarify whether insulin resistance is really involved in the relationship between low HDL cholesterol and LV hypertrophy and diastolic dysfunction.

A limitation of the present study may be that the majority of patients in this study were administered antihypertensive drugs. Therefore, we must consider the possibility that some types of antihypertensive agents may have affected cardiac structure and function and lipid levels.[12,36] In particular, β-blockers and diuretics unfavorably affect serum lipid profiles[36] and also may influence LV dimension and diastolic filling patterns. However, our multivariate analysis proved that the associations of low HDL cholesterol with LV mass and LV diastolic function were independent of the use of these types of antihypertensive drugs.

In conclusion, the present study has demonstrated that low serum level of HDL cholesterol is one of the independent determinants of LV mass in patients with essential hypertension and that low HDL cholesterol is also related to the deterioration of LV diastolic function, independent of that exerted by LV hypertrophy. These findings observed in patients with chronically treated hypertension suggest that such a metabolic factor as low HDL cholesterol modifies the growth and diastolic properties of LV in these patients, even if antihypertensive treatments suppress the elevation of BP. Low HDL cholesterol may be a risk factor not only for coronary heart disease but also for hypertensive heart disease.

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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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Received June 23, 2003; Accepted in revised form September 18, 2003.

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