生活習慣病　高血圧

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- 高血圧は普遍的な疾患であり，有病率は加齢とともに大きく増加する．
- 高血圧の発症や進展には，遺伝因子と環境要因がともに関与している．
- 高血圧の早期発見と適切な管理は，心血管疾患の予防にきわめて重要である．
- 全成人は定期的な血圧測定を受けるべきで，小児についても血圧測定が望まれる．
- 高血圧の早期発見には検診の充実が重要であるが，それで十分とはいえない．
- 高血圧と仮面高血圧の早期発見には，家庭血圧計による家族全員の血圧測定が望まれる．

Key Words　高血圧，検診，家庭血圧，遺伝子，生活習慣，仮面高血圧

はじめに

高血圧は普遍的な疾患であるが，脳卒中や心筋梗塞など，多くの心血管疾患の主要な危険因子であることは，よく知られている．降圧治療により高血圧患者の心血管予後および生命予後が改善することも，多くの臨床試験により証明されている．したがって，高血圧の予防や早期発見および適切な管理はきわめて重要であり，それにより心血管疾患が減少すれば，利得は非常に大きいと考えられる[1]．高血圧の診断は血圧値によってなされるので，早期発見に血圧測定が必要なことは当然であるが，その対象や時期については，年齢や他の危険因子などを考慮すべきであろう．また，仮面高血圧が注目されている今，高血圧の診断は検診などでの随時血圧測定でよいのであろうか．本稿では，これらの事柄をふまえながら，高血圧の早期発見について述べていきたい．

□ 高血圧の診断と疫学

高血圧の診断基準は，収縮期血圧 140 mmHg 以上あるいは拡張期血圧 90 mmHg 以上であり，国際的な合意が得られている[2~4]．ただし，臨床的に高血圧と診断するには，1 度だけの血圧測定では不十分で，繰り返しの測定を要する．

表 1 に，日本高血圧学会のガイドライン（JSH 2004）における成人の血圧値の分類を示す[4]．高血圧は軽症，中等症，重症に分かれ，また収縮期血圧 140 mmHg 以上で拡張期血圧 90 mmHg 未満は収縮期高血圧となる．正常血圧も至適，正常，正常高値に分かれる．正常高値血圧は 130-139/85-89 mmHg で，正常や至適群に比べて心血管リスクが高く，高血圧に進展しやすいことから，高血圧の早期発見の点からも注意すべき状態と考えられる．米国のガイドライン（JNC 7）は，より低い血圧値を含む 120-139/80-89 mmHg を前高血圧（Prehypertension）と呼び，注意を喚起している[2]．

表 1　成人における血圧値の分類

分類	収縮期血圧		拡張期血圧
至適血圧	＜120	かつ	＜80
正常血圧	＜130	かつ	＜85
正常高値血圧	130～139	または	85～89
軽症高血圧	140～159	または	90～99
中等症高血圧	160～179	または	100～109
重症高血圧	≧180	または	≧110
収縮期高血圧	≧140	かつ	＜90

（高血圧治療ガイドライン 2004[4]より引用）

高血圧は普遍的な疾患であり，わが国における患者数は約 3500 万人といわれている．また，血圧は加齢とともに上昇し，わが国では高齢者の 60% 以上は高血圧である．

図 1 に，2000 年に行われたわが国の第 5 次循環

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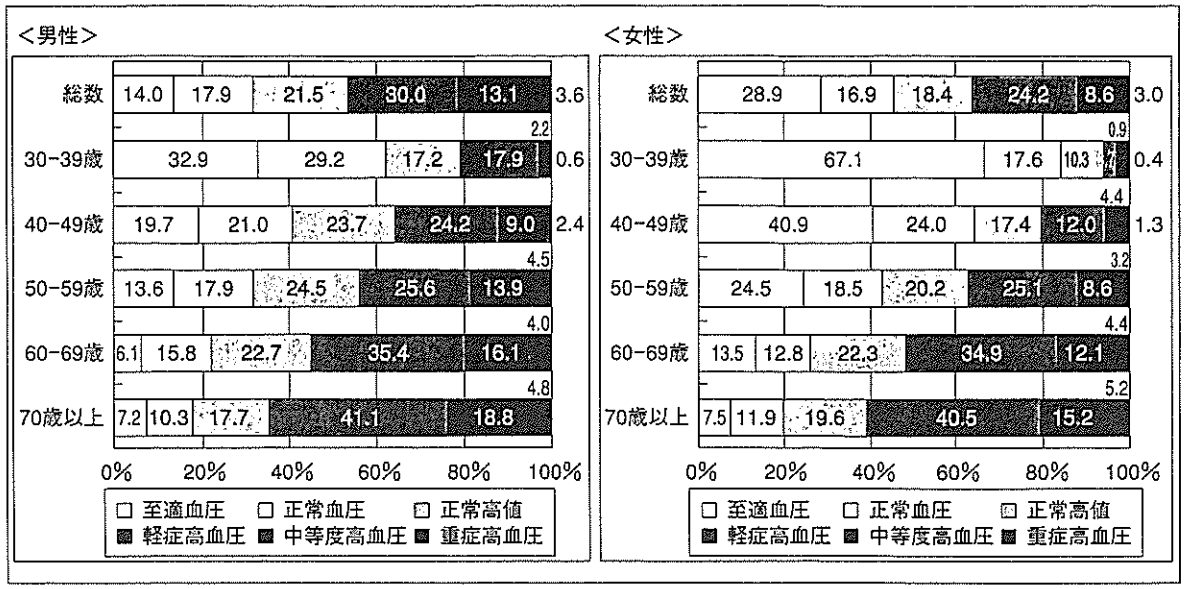

図1　厚生労働省第5次循環器疾患基礎調査（2000年）における性・年齢階級別の血圧区分（2回の平均値による）
（厚生労働省：第5次循環器疾患基礎調査（平成12年）[5]より）

器疾患基礎調査における，性・年齢階級別の血圧区分を示す[5]．2回の測定の平均値が高血圧であった者の頻度は，30歳以上の男性では47%と高く，女性では36%であった．また，その頻度は，男性では30歳代22%，40歳代36%，50歳代44%，60歳代55%，70歳以上65%で，女性はそれぞれ5%，18%，37%，51%，61%であった．この数字は降圧治療中の者の血圧を含んでおり，実際の高血圧者の頻度はさらに高いと考えられる．

このように高血圧の頻度は高く，また年齢とともに上昇する．高血圧の早期発見のためには，全成人における定期的な血圧測定がきわめて重要と考えられる．

□ 遺伝因子と環境要因

高血圧者の大部分を占める本態性高血圧の成因はいまだ特定されてはいないが，遺伝因子と環境要因がともに関与していることは疑いない（図2）．各個人におけるこれらの要因を考慮することは，高血圧の早期発見の面からも重要と考えられる．

遺伝因子が高血圧の発症に役割を持つことは，多くの研究で示されている．特に両親が高血圧の場合には，子供が高血圧になる可能性が高く，定期的な血圧測定が望まれる．

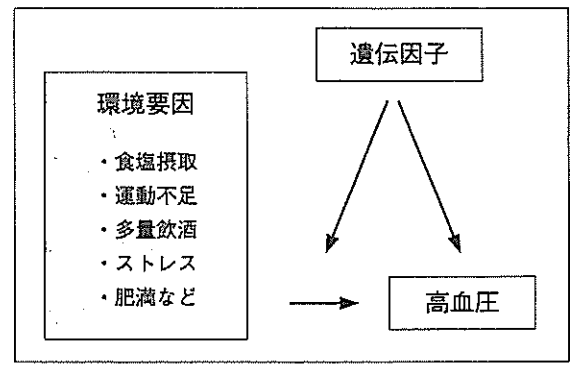

図2　高血圧の成因における遺伝と環境の影響

高血圧の遺伝子研究は急速に進行しており，われわれもミレニアム・ゲノム・プロジェクトにおいて，多くの血圧に関係する遺伝子やSNPを同定した[6,7]．これまでの知見では，一部のまれな二次性高血圧は特定の遺伝子変異によるが，本態性高血圧については，関連する遺伝子は多いものの，大部分の成因を説明できる単一の遺伝子変化はないようである．しかし，遺伝子が高血圧に関与することは明らかであり，生活習慣と高血圧との関係にも遺伝子が影響すると考えられる（図2）．遺伝子診断による高血圧の予知はまだ研究段階であるが，将来は実用化が期待される．

環境要因もまた，高血圧の発症や進展に大きな

表2　未治療の外来血圧正常者における仮面高血圧の頻度

	報告年	雑誌	CBPM 正常血圧基準	非医療環境下血圧		頻度 (%)	平均年齢 (歳)	男性 (%)
				血圧測定法	高血圧基準			
Sega	2001	*Circulation*	<140	HBPM	≧132	10.1*	25～74†	51.0
			<90		≧83	11.4*		
Hozawa	2002	*Hypertens Res*	<140/90	HBPM	≧135/85	11.0	40以上†	32.0
Hond	2002	*Blood Press Monit*	<140/90	HBPM	≧135/85	46.7*	52.8	46.8
Selenta	2000	*Arch Fam Med*	<140	daytime ABPM	≧135	23.0	17～68†	48.3
	2000		<90		≧85	24.0		
Hond	2003	*Blood Press Monit*	<140/90	daytime ABPM	≧135/85	33.3*	52.8	48.8
Bjorklund	2003	*Circulation*	<140/90	daytime ABPM	≧135/85	30.4*	70.0	100
Liu	1999	*Ann Intern Med*	<140/90	daytime ABPM	>134/90	20.7*	30～66†	46.4
Enstrom	1991	*J Hypertens*	<90	24 h ABPM/ at screening	≧85/≧90	14.0	40～64†	100
Imai	1996	*Hypertens Res*	≦140/90	24 h ABPM	≧133/78	13.6*	20～79†	31.4
Sega	2001	*Circulation*	<140	24 h ABPM	≧125	11.6*	25～74†	51-58
			<90		≧79	11.3*		
Hozawa	2002	*Hynertens Res*	<140/90	24 h ABPM	≧135/85	9.0	40以上†	32.0

（小原　拓，他：血圧 11：783-787，2004[14]より引用）

役割を有している．そのほとんどは生活習慣に関するもので，高血圧の危険因子として食塩の過剰摂取，肥満，運動不足，多量飲酒，ミネラルの摂取不足，ストレスなどがあげられる[8]（図2）．また，これらの生活習慣の修正は，高血圧の管理において広く推奨されている[1~4,9]．

生活習慣による血圧変化は，それぞれの項目や個人によって異なるが，食塩摂取は1 g/日あたり1 mmHgほど，体重増加は1 kgあたり1 mmHgほど収縮期血圧を上昇させる[8,9]．したがって，体重が大きく増加した場合などは高血圧を発症するリスクが高く，適切に血圧を測定することが望まれる．

□ 定期検診と家庭血圧測定

高血圧の有病率は高く，年齢とともに増加するので，早期発見には全成人における定期的な血圧測定が重要と考えられる．高血圧はSilent killerといわれるように自覚症状に乏しく，血圧値が診断基準になることから，血圧測定は絶対条件である．男性では30歳以上，女性では40歳以上になると高血圧の頻度が高くなるので，定期検診などの機会に必ず血圧測定を受けるべきであろう．特に正常高値血圧の者は高血圧を発症する可能性が高く，注意深い経過観察を要する．

小児では，高血圧の診断基準は成人とは異なり，その頻度や血圧の平均値はより低い．しかし，小児においても高血圧はまれではなく，また肥満者の増加にともない血圧値が高くなっていることが示されている[10]．血圧が高い者はその後も高いというtracking現象があるので，小児においても入学時などでの検診時に血圧が測定されることが望ましい．

検診や外来で測定される随時血圧は，各個人の通常の血圧を表しているとは限らない．随時血圧は高いが24時間血圧や家庭血圧は正常な白衣高血圧や，その逆の仮面高血圧を呈する者が少なくない[11]．白衣高血圧は，持続性高血圧より臓器障害や予後は良好であり，随時血圧のみで管理されれば過剰な治療を受けることになろう．仮面高血圧は，臓器障害や予後が持続性高血圧と同等であり，注意すべき病態であることが示されている[12,13]．

白衣高血圧や仮面高血圧の頻度は，診断基準などにより異なるが，前者は検診で高血圧とされる者の約20%，後者は正常血圧とされる者の10～20%にのぼる[14]（表2）．わが国における数は，それぞれ約700万人と推計される．このことは，全国民が検診を受けても約1,400万人は誤った管理を受ける可能性を示しており，重要な問題と考えられる．家庭血圧測定のさらなる普及と，それに基づいた管理システムの確立が望まれる．

おわりに

高血圧の早期発見の重要性と，関連する事柄について述べた．わが国では検診システムがかなり整っているが，すべての成人が定期的に血圧測定を受けているわけではない．したがって，高血圧であっても診断されていない者は少なくないと考えられる．高血圧の早期発見には検診のさらなる普及が望まれるが，それだけでは不十分なことは白衣高血圧や仮面高血圧の病態や予後に示されている．家庭血圧計はかなり普及しているが，これが常備され家族全員の血圧が測定できれば，より効果的な高血圧の早期発見と適切な管理が可能となるであろう．

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Masked Hypertension and Target Organ Damage in Treated Hypertensive Patients

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Background: Recent studies have shown that an elevated ambulatory or home blood pressure (BP) in the absence of office BP—a phenomenon called masked hypertension—is associated with poor cardiovascular prognosis. However, it remains to be elucidated how masked hypertension modifies target organ damage in treated hypertensive patients.

Methods: A total of 332 outpatients with chronically treated essential hypertension were enrolled in the present study. Patients were classified into four groups according to office (<140/90 or ≥140/90 mm Hg) and daytime ambulatory (<135/85 or ≥135/85 mm Hg) BP levels; ie, controlled hypertension (low office and ambulatory BP), white-coat hypertension (high office but low ambulatory BP), masked hypertension (low office but high ambulatory BP), and sustained hypertension (high office and ambulatory BP). Left ventricular mass index, carotid maximal intima-media thickness, and urinary albumin levels were determined in all subjects.

Results: Of the patients, 51 (15%), 65 (20%), 74 (22%), and 142 (43%) were identified as having controlled hypertension, white-coat hypertension, masked hypertension, and sustained hypertension, respectively. Left ventricular mass index, maximal intima-media thickness, and urinary albumin level in masked hypertension were significantly higher than in controlled hypertension and white-coat hypertension, and were similar to those in sustained hypertension. Multivariate regression analyses revealed that the presence of masked hypertension was one of the independent determinants of left ventricular hypertrophy, carotid atherosclerosis, and albuminuria.

Conclusions: Our findings indicate that masked hypertension is associated with advanced target organ damage in treated hypertensive patients, comparable to that in cases of sustained hypertension. Am J Hypertens 2006; 19:880–886 © 2006 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, ambulatory, cardiac hypertrophy, atherosclerosis, albuminuria.

Several population-based studies and prospective clinical studies have shown that ambulatory blood pressure (BP) is a significant predictor for cardiovascular morbidity and mortality even after adjustment for conventional BP.[1–3] In fact, left ventricular (LV) hypertrophy and other end-organ damage are more closely associated with average BP levels assessed by 24-h ambulatory monitoring than isolated BP readings taken in the office.[4,5] There is often a discrepancy between office and ambulatory BP, and many studies have evaluated the association between white-coat hypertension, a normal ambulatory but elevated office BP, and cardiovascular risk.[6,7] On the other hand, the converse of white-coat hypertension called "reverse white-coat hypertension," "white-coat normotension," or "isolated ambulatory hypertension," ie, a high ambulatory but normal office BP, has received little attention. This phenomenon is also called "masked hypertension" on the grounds that the hypertension is not detected by routine methods in the clinic.[8] Recent studies indicated that an elevated ambulatory or home BP despite a normal or well-controlled office BP is associated with poor cardiovascular prognosis in both untreated and treated hypertensive patients.[9–11] The present study was conducted to verify

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the possible association between masked hypertension and target organ abnormalities such as LV hypertrophy, carotid arteriosclerosis, and albuminuria in treated hypertensive patients.

Methods

Subjects

A total of 332 outpatients with treated essential hypertension (163 men and 169 women; mean age, 66 ± 10 years) were enrolled in the present study. Patients with secondary hypertension, stroke, ischemic heart disease including myocardial infarction, congestive heart failure, chronic glomerulonephritis, nephrotic syndrome, renal failure (serum creatinine ≥160 μmol/L), or poorly controlled (fasting plasma glucose ≥10.0 mmol/L or hemoglobin A_{1c} ≥8.0%) or insulin-treated diabetes mellitus were excluded from this study. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria, such as a fasting plasma glucose of ≥7.0 mmol/L and/or a plasma glucose level at 2 h after a 75-g oral glucose load of ≥11.1 mmol/L, or when medication was taken for treatment of hyperglycemia. A diagnosis of hyperlipidemia required a serum total cholesterol level of ≥5.69 mmol/L and/or a serum triglyceride level of ≥1.69 mmol/L or the use of lipid-lowering drugs.

All patients had taken antihypertensive drugs for at least 1 year (average, 13 years). Of the patients, 237 patients (71%) were treated with Ca channel blockers, 111 (33%) with angiotensin II receptor blockers, 56 (17%) with angiotensin converting enzyme inhibitors, 106 (32%) with β-blockers, 66 (20%) with diuretics, and 34 (10%) with other classes of agents. Combination drug treatments were used in 188 subjects (57%). All subjects gave their informed consent to participate in the present study. All procedures of the present study were carried out in accordance with institutional and national ethical guidelines for human studies.

Measurement of BP

In each visit, office BP was measured twice by a physician in a hospital outpatient clinic with the patient in a sitting position after ≥20 min of rest, using an appropriate-sized arm cuff and mercury sphygmomanometer. The first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Office BP was determined by averaging six measurements taken on three separate occasions during a 3-month period.

In the same study period, all subjects underwent 24-h ambulatory BP monitoring. BP and heart rate were measured every 30 min during the day and night by the oscillometric method using an automatic monitoring device (TM-2421, A&D Co., Tokyo, Japan).[12] Accuracy and performance of this device have been previously demonstrated.[13] The patients were instructed to continue with their normal daily activities during measurements and to note their activity and location in a diary. According to the diary, daytime and night-time were determined as the waking and sleeping periods of the patient, respectively, and mean values of 24-h, daytime, and night-time BP (systolic and diastolic) were calculated. We also analyzed short-term BP variability and circadian BP variation. Short-term BP variability was calculated as the standard deviation (SD) of daytime and night-time ambulatory BP obtained every 30 min. Circadian BP variation was defined as a nocturnal dipping in BP and calculated as 100 × (daytime BP − night-time BP) / daytime BP.

In the present study, all subjects were classified into four groups based on the levels of office and daytime ambulatory BP, as follows: 1) controlled hypertension (ie, office BP <140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg); 2) white-coat hypertension (ie, isolated uncontrolled office hypertension, office BP ≥140/90 mm Hg, and ambulatory BP <135/85 mm Hg); 3) masked hypertension (ie, isolated uncontrolled ambulatory hypertension, office BP <140/90 mm Hg and ambulatory BP ≥135/85 mm Hg); and 4) sustained hypertension (ie, uncontrolled hypertension, office BP ≥140/90 mm Hg and ambulatory BP ≥135/85 mm Hg).

Echocardiography

A comprehensive two-dimensional echocardiography was performed using a cardiac ultrasound unit (Sonos 5500, Philips Medical Systems, Andover, MA) as previously described.[14] Echocardiographic parameters were measured by the consensus of two experienced investigators who were blinded to the clinical data including office and ambulatory BP of the subjects. Measurements included interventricular septal thickness (IVSTd), posterior wall thickness (PWTd), LV diameter at end-diastole (LVDd), and LV diameter at end-systole (LVDs). The LV mass was estimated using the formula validated by Devereux and Reichek[15]: LV mass (g) = $1.04 \times \{(IVSTd + PWTd + LVDd)^3 - LVDd^3\} - 13.6$. The LV mass was normalized for body surface area and expressed as the LV mass index. The intra- and interobserver coefficients of variation of LV mass index were 6.7% and 9.8%, respectively.

Carotid Ultrasonography

Ultrasound examinations of both carotid arteries were performed using a high resolution Duplex scanner (model SSA-390A, Toshiba, Tokyo, Japan) with the probe at a frequency of 7.5 MHz for the B-scan, as previously described.[16] All measurements were performed by two trained sonographers who were unaware of the subjects' clinical data. The carotid arteries were carefully examined with regard to wall changes from different longitudinal and transverse views. The common carotid artery, the carotid bulb, and the internal and external carotid arteries were studied in all subjects. Each ultrasound image was taken at the end-diastolic phase. We assessed carotid intima-media thickness (IMT) and plaques by measuring generally used

parameters such as conventional IMT and maximal IMT.[16] Conventional IMT was defined as an average of six IMT approximately 15 mm proximal to the carotid bulb in the right and left common carotid arteries avoiding discrete plaques. Maximal IMT was defined as the maximal thickness of intima-media including plaques. Maximal IMT was assessed from the region branching off from the brachiocephalic artery (right) or aorta (left) to the bifurcation of the common carotid artery. The intra- and inter-observer coefficients of variation of maximal IMT were 4.2% and 7.9%, respectively.

Biochemical Measurements

Blood samples were obtained in the morning after an overnight fast. Total cholesterol, triglycerides, fasting plasma glucose, hemoglobin A_{1c}, fasting insulin, and serum creatinine levels were determined by standard laboratory measurements. The homeostasis model assessment (HOMA) index, a parameter of insulin resistance, was calculated as fasting plasma glucose × fasting insulin/22.5. Creatinine clearance was calculated from the Cockcroft-Gault formula.[17] The urinary albumin (U-Alb) level was measured as the ratio of albumin to creatinine excretion in the urine and expressed as $\log_{10}$ mg/g Cr.

Statistical Analysis

Statistical analysis was performed using StatView Version 5 Software (Abacus Concepts, Berkeley, CA). Values are expressed as the mean ± SD. The significance of differences among the four groups with controlled, white-coat, masked, and sustained hypertension was evaluated by unpaired ANOVA with subsequent Fisher's multiple comparison test. A stepwise multiple regression analysis was performed to identify independent determinants of target organ damage (LV mass index, maximal IMT, and U-Alb levels). A value of $P < .05$ was accepted as statistically significant.

Results

General characteristics of the four subject groups classified according to certain levels of office BP (<140/90 or ≥140/90 mm Hg) and daytime ambulatory BP (<135/85 or ≥135/85 mm Hg) are summarized in Table 1. Of the patients, 51 (15%), 65 (20%), 74 (22%), and 142 (43%) were identified as having controlled hypertension, white-coat hypertension, masked hypertension, and sustained hypertension, respectively. Age was youngest and the proportion of men was highest in subjects with masked hypertension. The rate of habitual drinkers was significantly

Table 1. Clinical characteristics and antihypertensive treatment of study patients

Characteristic	Controlled hypertension (n = 51)	White-coat hypertension (n = 65)	Masked hypertension (n = 74)	Sustained hypertension (n = 142)
Age (y)	67 ± 8	67 ± 7	63 ± 11*†	67 ± 10‡
Sex (male/female)	24/27	23/42	48/26*†	68/74‡
Body mass index (kg/m^2)	24 ± 3	24 ± 3	25 ± 4	24 ± 3
Duration of hypertension (y)	19 ± 11	20 ± 11	17 ± 10	18 ± 11
Diabetes mellitus (%)	14	23	20	21
Hyperlipidemia (%)	59	72	70	67
Current smoking (%)	16	17	20	18
Habitual drinking (%)	51	46	66†	52
Total cholesterol (mmol/L)	5.1 ± 0.6	5.3 ± 0.8	5.3 ± 0.8	5.3 ± 0.7
Triglycerides (mmol/L)	1.4 ± 0.6	1.3 ± 0.8	1.6 ± 0.9†	1.5 ± 0.9
Fasting plasma glucose (mmol/L)	5.7 ± 1.6	5.7 ± 1.2	5.7 ± 1.0	5.8 ± 1.0
Hemoglobin A_{1c} (%)	5.5 ± 0.7	5.7 ± 0.9	5.5 ± 0.6	5.7 ± 0.8
Fasting insulin (mU/L)	6.0 ± 2.6	6.7 ± 4.3	7.4 ± 4.5	7.7 ± 11.7
HOMA index	1.5 ± 0.9	1.8 ± 1.5	1.9 ± 1.2	2.0 ± 3.1
Creatinine clearance (mL/min)	81 ± 26	81 ± 23	89 ± 36	80 ± 26
Antihypertensive treatment				
Period of medication (y)	13 ± 9	14 ± 10	11 ± 9†	13 ± 9
Ca channel blockers (%)	57	74*	76*	73*
AII receptor blockers (%)	41	28	38	31
ACE inhibitors (%)	18	12	15	20
β-Blockers (%)	31	45	31	27†
Diuretics (%)	20	23	27	15‡
Others (%)	16	5	8	12
Combination treatment (%)	55	62	68	49‡
Total number of classes	1.8 ± 1.0	1.9 ± 0.8	1.9 ± 0.8	1.8 ± 1.0

ACE = angiotensin-converting enzyme; AII = angiotensin II; HOMA = homeostasis model assessment.
Values are mean ± SD or percentage.
* $P < .05$ *v* controlled hypertension; † $P < .05$ *v* white-coat hypertension; ‡ $P < .05$ *v* masked hypertension.

increased in masked hypertension compared with white-coat hypertension. Body mass index, duration of hypertension, the prevalence of diabetes mellitus and hyperlipidemia, and the rate of current smokers did not differ among the four groups. In addition, there were no intergroup differences in metabolic parameters and renal function, except that triglyceride level was somewhat increased in masked hypertension.

As for antihypertensive treatment, the period of medication was significantly shorter in masked hypertension than in white-coat hypertension, probably reflecting that the mean age of the group with masked hypertension was lowest. The percentage of the use of Ca channel blockers was significantly higher in white-coat hypertension, masked hypertension, and sustained hypertension than in controlled hypertension. The percentage of treatment with β-blockers or diuretics and that of combination treatment were lower in sustained hypertension than in white-coat hypertension or masked hypertension. The use of angiotensin II receptor antagonists or angiotensin-converting enzyme inhibitors and total number of classes of antihypertensive drugs did not differ among the four groups.

As shown in Table 2, clear differences in office and ambulatory BP levels were observed among the groups with controlled, white-coat, masked, and sustained hypertension. The standard deviations of ambulatory daytime and night-time BP values were significantly increased in masked hypertension compared with controlled hypertension or white-coat hypertension. The degree of nocturnal dipping in systolic BP was significantly larger in masked hypertension than in controlled and white-coat hypertension.

The LV and carotid arterial structural changes and U-Alb levels in the four groups are shown in Fig. 1. The LV mass index (g/m^2) was significantly increased in masked hypertension (134 ± 29) than in controlled hypertension (115 ± 34) and white-coat hypertension (119 ± 32). Its level in sustained hypertension (126 ± 32) was significantly higher only compared with that in controlled hypertension. There was no difference in conventional IMT among the four groups (data not shown). However, maximal IMT (mm), which more sensitively reflects the severity of carotid atherosclerosis than conventional IMT,[16] was significantly greater in masked hypertension (1.93 ± 1.07) than in controlled hypertension (1.61 ± 0.67) and white-coat hypertension (1.60 ± 0.82). The level in sustained hypertension (1.69 ± 0.92) was not significantly higher compared with those in controlled and white-coat hypertension. The patients with masked hypertension tended to have more increased LV mass index and maximal IMT than those with sustained hypertension ($P < .10$, respectively). The U-Alb levels (log_{10} mg/g Cr) were significantly higher in masked (1.43 ± 0.62) and sustained hypertension (1.42 ± 0.55) than in controlled (1.12 ± 0.43) and white-coat hypertension (1.22 ± 0.47), and the

Table 2. Office and ambulatory blood pressure (BP), heart rate, and BP variability in study patients

Characteristic	Controlled hypertension ($n = 51$)	White-coat hypertension ($n = 65$)	Masked hypertension ($n = 74$)	Sustained hypertension ($n = 142$)
Office BP (mm Hg)				
Systolic	130 ± 6	152 ± 16*	130 ± 6†	155 ± 15*‡
Diastolic	75 ± 8	86 ± 12*	77 ± 7†	88 ± 11*‡
Ambulatory BP (mm Hg)				
24-h Systolic	125 ± 7	128 ± 9	137 ± 8*†	144 ± 13*†‡
24-h Diastolic	72 ± 7	74 ± 7	82 ± 8*†	83 ± 10*†
Daytime systolic	127 ± 6	129 ± 6	142 ± 7*†	147 ± 14*†‡
Daytime diastolic	73 ± 6	76 ± 7	85 ± 9*†	86 ± 11*†
Night time systolic	120 ± 11	121 ± 12	129 ± 13*†	137 ± 16*†‡
Night time diastolic	68 ± 8	70 ± 9	77 ± 9*†	78 ± 11*†
Heart rate (beats/min)				
Office	67 ± 10	69 ± 9	68 ± 9	70 ± 9*
24-h	64 ± 9	63 ± 11	68 ± 9*†	68 ± 10*†
Daytime	67 ± 10	66 ± 10	70 ± 10†	70 ± 11*†
Night time	58 ± 8	59 ± 9	62 ± 9*†	62 ± 9*†
SD of ambulatory BP (mm Hg)				
Daytime systolic	14.2 ± 3.5	13.7 ± 2.8	15.0 ± 3.8†	14.7 ± 4.6
Daytime diastolic	9.9 ± 3.1	9.5 ± 2.7	10.8 ± 3.4*†	10.1 ± 2.9
Night time systolic	11.6 ± 3.4	10.8 ± 3.7	12.0 ± 3.9†	11.4 ± 3.3
Night time diastolic	8.6 ± 2.3	7.9 ± 2.8	9.0 ± 2.5†	8.5 ± 2.4
Nocturnal BP dipping (%)				
Systolic	5.6 ± 8.1	5.6 ± 8.3	8.7 ± 7.7*†	6.7 ± 8.6
Diastolic	7.0 ± 8.6	7.6 ± 8.4	9.9 ± 7.7	8.4 ± 8.7

Values are mean ± SD.
* $P < .05$ *v* controlled hypertension; † $P < .05$ *v* white-coat hypertension; ‡ $P < .05$ *v* masked hypertension.

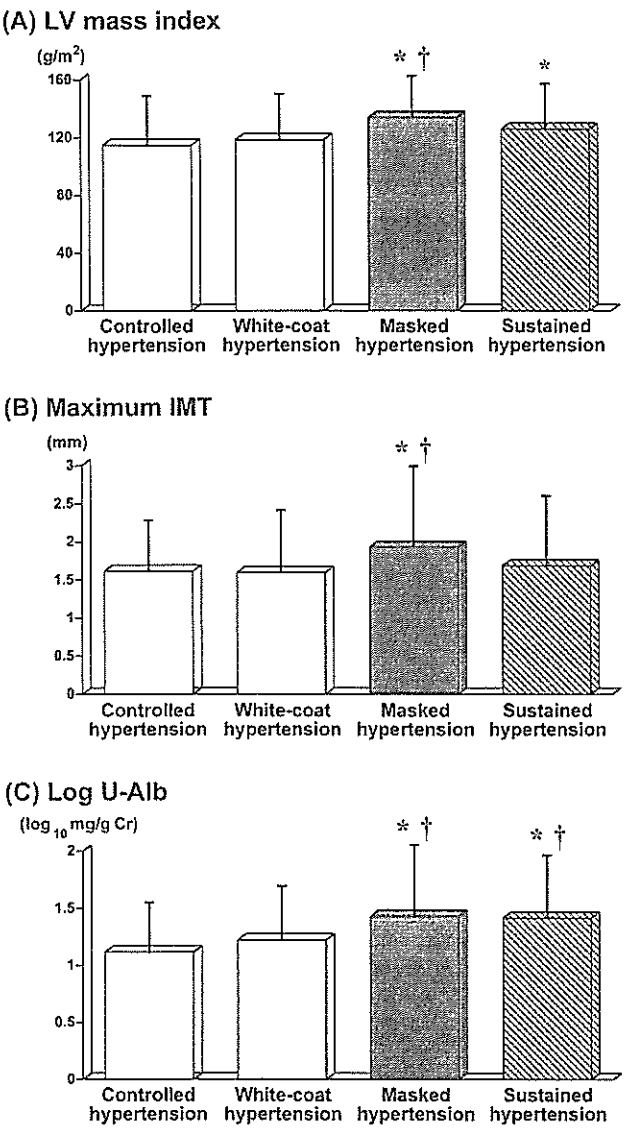

FIG. 1. Left ventricular (LV) mass index (**A**), maximal intima-media thickness (IMT) (**B**), and urinary albumin (U-Alb) (log scale, C) in the four study groups, divided by office and daytime ambulatory blood pressure levels. Values are given as mean ± SD. *$P < .05$ *v* controlled hypertension; †$P < .05$ *v* white-coat hypertension.

levels in masked hypertension and sustained hypertension were almost the same.

To identify independent predictors for target organ changes, we investigated possible determination factors using a stepwise multiple regression analysis in all subjects. Although daytime systolic BP was a strong predictor for LV mass index, maximal IMT, and U-Alb levels, the presence of masked hypertension was found to be one of the independent determinants of these end-organ changes (Table 3).

Discussion

There have been a few studies reporting the possible association between masked hypertension and cardiac and carotid arterial structural changes in the general population. In a cross-sectional study, Liu et al[18] found that LV mass and carotid wall thickness in patients with masked hypertension were significantly greater than those in true normotensive subjects and similar to those in patients with sustained hypertension. The data from the Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) Study also showed that LV mass index was increased in untreated subjects with isolated ambulatory hypertension and sustained hypertension than in those with true normotension.[19] The present findings were broadly consistent with these previous observations. Therefore, our study suggests that a higher level of ambulatory BP largely affects target organ damage in treated hypertensive patients as well as in untreated subjects. In the present study, however, the average levels of 24-h, daytime, and night-time ambulatory BP in the masked hypertension group were somewhat lower than those in the sustained hypertension group. In addition, the presence of masked hypertension was a significant predictor for end-organ changes, independent of average daytime BP levels. Thus factors other than a higher ambulatory BP could contribute to target organ damage in masked hypertension. A shorter period of antihypertensive medication might partially explain the advanced target organ changes in patients with masked hypertension.

In the present study, 22% of subjects were identified as having masked hypertension, which was associated with a higher proportion of men and younger age. These characteristics observed in our study are in agreement with those of masked hypertension described in other studies.[20,21] Increased physical and mental activities in younger men are likely to induce the augmentation of daytime BP variability, which might promote cardiac, carotid arterial, and renal damage in masked hypertension, because several studies have shown that short-term BP variability, apart from average ambulatory BP values, is associated with target organ damage in hypertensive patients.[22–25]

Two recent large-scale prospective studies revealed that a high ambulatory or home BP is a powerful predictor for cardiovascular morbidity in patients with treated hypertension even when their office BP is well controlled. One study by Clement et al[10] showed that the relative risk of cardiovascular events associated with a high 24-h ambulatory systolic BP (≥135 mm Hg) as compared with a low 24-h systolic BP (<135 mm Hg) was 3.19 (unadjusted) or 2.80 (after adjustment) among patients with an office systolic BP of <140 mm Hg. In another cohort study by Bobrie et al,[11] the incidences of cardiovascular events in patients with controlled hypertension (office BP <140/90 mm Hg and home BP <135/85 mm Hg), elevated BP in the office but not at home (ie, white-coat hypertension), elevated BP at home but not in the office (ie, masked hypertension), and uncontrolled hypertension (ie, sustained hypertension) were 11.1, 12.1, 30.6, and 25.6 cases per 1000 patient-years, respectively. The hazard ratio of cardiovascular events in the group with masked hyperten-

Table 3. Independent predictors for target organ damage by multivariate regression analysis

Characteristic	β-Coefficient	F value	P value
LV mass index			
Daytime systolic BP	0.270	25.64	<.0001
Sex (male)	0.190	13.53	.0002
Presence of masked hypertension	0.136	6.56	.0101
Daytime heart rate	−0.135	6.25	.0112
Duration of hypertension	0.119	5.69	.0164
Body mass index	0.110	5.22	.0268
SD of daytime systolic BP	0.102	4.76	.0476
	$R^2 = 0.240$, $F = 14.37$, $P < .0001$		
Maximum IMT			
Age	0.342	37.47	<.0001
Daytime systolic BP	0.233	14.91	.0001
Daytime diastolic BP	−0.252	12.51	.0006
Sex (male)	0.184	11.38	.0008
Presence of masked hypertension	0.157	10.04	.0025
Current smoking	0.120	6.09	.0225
	$R^2 = 0.275$, $F = 12.42$, $P < .0001$		
Log U-Alb			
Daytime systolic BP	0.237	18.38	<.0001
Use of Ca channel blocker	0.166	8.84	.0035
Creatinine clearance	−0.168	8.82	.0030
Period of antihypertensive medication	0.159	7.16	.0067
Presence of diabetes mellitus	0.126	5.08	.0232
Presence of masked hypertension	0.114	4.02	.0421
	$R^2 = 0.205$, $F = 11.77$, $P < .0001$		

BP = blood pressure; Ca = calcium; IMT = intima-media thickness; LV = left ventricular; SD = standard deviation; U-Alb = urinary albumin.
The stepwise regression model included age, sex, body mass index, duration of hypertension, diabetes mellitus, hyperlipidemia, current smoking, habitual drinking, creatinine clearance, period of antihypertensive medication, use of each class of antihypertensive drug (Ca channel blocker, angiotensin II receptor blocker, angiotensin converting enzyme inhibitor, β-blocker, or diuretic), daytime systolic BP, daytime diastolic BP, daytime heart rate, SD of daytime systolic BP, SD of daytime diastolic BP, white-coat hypertension, masked hypertension, and sustained hypertension, as possible independent variables.

sion was shown to be greatest among the four subgroups by an analysis with the multivariable Cox model. Interestingly, our present findings were consistent with these observations examining the prognostic significance of masked hypertension in treated hypertensive subjects. Therefore, the progression of end-organ damage induced by masked hypertension may lead to the high incidence of cardiovascular events in such patients.

There were some limitations in our study. The sample size of our subjects might be relatively small to evaluate properly the differences in target organ damage among the four groups of patients. In addition, the present findings were derived from cross-sectional data on the basis of one-time examination of ambulatory BP monitoring, cardiac and carotid ultrasonography, and urinalysis. Thus a prospective study using larger population of hypertensive subjects will be required to confirm the influence of masked hypertension on target organ damage.

All patients in the present study had received antihypertensive medication. As another limitation of this study, we must therefore consider the possibility that different classes of antihypertensive drugs may have differently affected the development of target organ damage, partly independently of their BP-lowering effects. Renin-angiotensin system inhibitors, above all, have been known to have BP fall–independent protective effects on hypertensive target organ, although the percentage of patients treated with angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors did not differ among the four study groups. Our multivariate analysis showed that the association of masked hypertension with target organ damage was independent of the use of any class of antihypertensive agent. However, approximately 60% of the present subjects were under combination drug treatments. In those cases, the possible specific effect of one or another class of antihypertensive drug could hardly be account for.

In conclusion, the present study shows that masked hypertension is associated with increased LV mass, carotid IMT, and albuminuria in patients with treated essential hypertension, and that the impact of masked hypertension on such end-organ changes is greater than that of controlled hypertension or white-coat hypertension and comparable to that of sustained hypertension. Masked hypertension as well as uncontrolled hypertension is a significant risk for target organ damage in treated hypertensive patients and ambulatory BP monitoring seems to be necessary to unmask this latent risk that is not detectable by routine BP measuring in the office.

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B-Type Natriuretic Peptide Strongly Reflects Diastolic Wall Stress in Patients With Chronic Heart Failure

Comparison Between Systolic and Diastolic Heart Failure

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OBJECTIVES We explored the stimulus for B-type natriuretic peptide (BNP) secretion in the clinical setting of heart failure (HF).

BACKGROUND Increasingly, plasma BNP levels are being incorporated into the clinical assessment and management of systolic heart failure (SHF) as well as diastolic heart failure (DHF). However, heterogeneity in BNP levels among individuals with HF can cause some confusion in interpreting results.

METHODS In 160 consecutive patients presenting with HF, we measured plasma BNP levels and performed echocardiography and cardiac catheterization. Systolic and diastolic meridional wall stress was calculated from echocardiographic and hemodynamic data.

RESULTS Although plasma BNP had a significant correlation (r^2 = 0.296 [$p < 0.001$]) with left ventricular end-diastolic pressure (EDP) as previously reported, the correlation between plasma BNP and end-diastolic wall stress (EDWS) (r^2 = 0.887 [$p < 0.001$]) was more robust. In a subanalysis of 62 patients with DHF, a similar result was obtained (r^2 = 0.143 for EDP and r^2 = 0.704 for EDWS). In a comparison between SHF and DHF, the BNP level was significantly higher in SHF ($p < 0.001$). Although EDP did not show any difference, EDWS was significantly higher in SHF than in DHF ($p < 0.001$).

CONCLUSIONS The present study shows that plasma BNP levels reflect left ventricular EDWS more than any other parameter previously reported, not only in patients with SHF, but also in patients with DHF. The relationship of left ventricular EDWS to plasma BNP may provide a better fundamental understanding of the interindividual heterogeneity in BNP levels and their clinical utility in the diagnosis and management of HF. (J Am Coll Cardiol 2006;47:742–8)

Plasma B-type natriuretic peptide (BNP) levels are reported not only to be a strong marker of left ventricular (LV) dysfunction, but also a marker to predict morbidity and mortality accurately in patients with chronic heart failure (HF) (1,2). Recently, BNP-guided therapy for chronic HF has been suggested. Troughton et al. (3) demonstrated that pharmacotherapy guided by BNP levels reduces cardiovascular events and delays time to first cardiovascular event compared with intensive clinically guided therapy. Recent reports also demonstrated the contribution of LV diastolic function to plasma BNP levels and the usefulness of BNP in the diagnosis of diastolic HF (4).

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However, heterogeneity in BNP levels among individuals with HF has been recognized, and it has caused some confusion in interpreting results (5). Previous human studies have suggested correlations between BNP levels and cardiac functional or dimensional indexes such as end-diastolic pressure (EDP), ejection fraction (EF), pulmonary capillary wedge pressure, and LV volume, none of which sufficiently explain the heterogeneity (6–9). Therefore, it is essential to determine the stimulus for BNP secretion in the clinical setting of HF. In vitro studies have clarified the mechanism of secretion and regulation of BNP precisely (10). Stretch of cardiomyocytes is reported to be the most important stimulus of BNP regulation (11). It is also believed that BNP in humans may be released from the heart in response to increased wall stress. However, there have been few human studies exploring a direct relationship between wall stress and BNP regulation (12). Vanderheyden et al. (13) have very recently demonstrated, for the first time, in 40 patients with aortic stenosis (AS), a significant correlation of BNP with LV end-diastolic wall stress (EDWS). In their study, however, subjects were limited to patients with AS. Hence, there now is a need for the same assessment in patients

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Abbreviations and Acronyms

AS	= aortic stenosis
BNP	= B-type natriuretic peptide
CHF	= congestive heart failure
DHF	= diastolic heart failure
EDP	= end-diastolic pressure
EDWS	= end-diastolic wall stress
EF	= ejection fraction
HF	= heart failure
LV	= left ventricle/ventricular
LVEDVI	= left ventricular end-diastolic volume index
LVMI	= left ventricular mass index
SHF	= systolic heart failure
SWS	= systolic wall stress

with HF of various etiologies. Accordingly, in the present study, we evaluated plasma BNP levels in 160 consecutive patients presenting with HF of various etiologies including diastolic HF.

METHODS

Patients. Among the patients referred to our National Cardiovascular Center Hospital between October 2003 and December 2004, we included in this study those admitted with congestive heart failure (CHF) consecutively. Patients who did not undergo LV catheterization or had renal dysfunction (serum creatinine >2.0 mg/dl) were excluded. A sample of 160 patients was obtained. For all participants, cardiac catheterization and echocardiograms were performed at a compensated CHF stage (before discharge), and plasma BNP was measured on the day before cardiac catheterization. The clinical characteristics of these patients are listed in Table 1.

BNP assay. Blood was collected into tubes containing EDTA, and plasma BNP was measured using a validated and commercially available immunoassay kit (Tosoh Co. Ltd., Japan).

Cardiac catheterization. Left ventricular pressure was recorded with a 5-F pigtail catheter connected to a fluid-filled transducer. Left ventricular volume and EF were determined with left ventriculography with contrast medium using Kennedy's formula.

Echocardiography. Echocardiographic examinations were performed with a Sonos 5500 machine equipped with a 2.5-MHz probe. M-mode images were obtained to measure left atrial and ventricular dimensions (14). The left ventricular mass index (LVMI) was estimated from the formula of Devereux et al. (15). The severity of mitral regurgitation was quantified on a semicontinuous scale from none (0) to moderately severe (3+). In patients with sinus rhythm, the pulsed Doppler transmitral flow velocity was recorded to measure a ratio of peak mitral E-wave velocity to peak mitral A-wave velocity (E/A ratio) and the deceleration time of the mitral E-wave velocity.

On the basis of hemodynamic and echocardiographic data, end-diastolic and systolic meridional wall stresses (WS) were calculated. These were obtained by using the formula: $WS = 0.334 \times P(LVID)/WT(1 + WT/LVID)$, where P = LV pressure (i.e., peak systolic pressure or EDP, which was obtained during cardiac catheterization), LVID = left ventricular internal dimension, and WT = wall thickness (16). In the present study, the posterior wall thickness was used to assess WT regardless of regional wall motion abnormalities. In the analysis of the interobserver reproducibility of the posterior wall thickness measurement in 48 patients with CHF, a high degree of the reproducibility was

Table 1. Patient Characteristics

	Total	SHF	DHF	p Value
n	160	98	62	
Women	31	25	40	0.052
Age, yrs	66.8 ± 1.0	66.3 ± 1.3	67.7 ± 1.6	0.485
BMI, kg/m^2	22.9 ± 0.3	22.8 ± 0.4	23.1 ± 0.4	0.684
NYHA functional class ≥2	32	37	24	0.138
HT	71	61	87	0.001
DM	35	36	34	0.946
HLP	53	49	58	0.338
AF	18	17	19	0.912
Etiology				
DCM	18	30	0	
ISCM or OMI	29	44	6	
HHD	26	9	53	
VHD	26	17	40	
Medications				
ACEI or ARB	70	77	57	0.013
Beta-blocker	51	54	46	0.397
Diuretics	60	71	42	0.001
BNP, pg/ml	282 ± 23	379 ± 33	129 ± 13	<0.001

Values are mean ± SEM or %.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; DCM = dilated cardiomyopathy; DHF = diastolic heart failure; DM = diabetes mellitus; HHD = hypertensive heart disease; HLP = hyperlipidemia; HT = hypertension; ISCM = ischemic cardiomyopathy; NYHA = New York Heart Association; OMI = old myocardial infarction; SHF = systolic heart failure; VHD = valvular heart disease.

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Table 2. Echocardiographic and Hemodynamic Parameters

	Total (n = 160)	SHF (n = 98)	DHF (n = 62)	p Value
FS, %	27 ± 1	20 ± 1	38 ± 1	<0.001
LVEDD, mm	57 ± 1	61 ± 1	50 ± 1	<0.001
LVMI, g/m^2	166 ± 4	179 ± 5	145 ± 6	<0.001
LAD, mm	45 ± 1	45 ± 1	44 ± 1	0.779
E/A	1.3 ± 0.1	1.5 ± 0.2	1.0 ± 0.1	0.024
EF, %	41.5 ± 1.1	32.0 ± 0.9	56.4 ± 0.5	<0.001
LVEDVI, ml/m^2	106 ± 4	125 ± 15	76 ± 2	<0.001
LVSP, mm Hg	134 ± 3	124 ± 3	151 ± 4	<0.001
LVEDP, mm Hg	14.9 ± 0.4	15.0 ± 0.6	14.8 ± 0.5	0.829

Values are mean ± SEM.

EF = ejection fraction; E/A = ratio of peak mitral E-wave velocity to peak mitral A-wave velocity; FS = fractional shortening; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular mass index; LVSP = left ventricular peak systolic pressure. Other abbreviations as in Table 1.

found with an intraclass correlation coefficient value 0.830 (95% confidence interval 0.609 to 0.925), and absolute difference was small (mean ± SD; 0.01 ± 1.16 mm). Also, adequate M-mode images were not available in three patients, and they were excluded in the present study.

Statistical analysis. Comparisons between groups were made using chi-square analysis for proportions and unpaired Student *t* tests for continuous variables. Linearity of a relationship between two variables was assessed by linear regression analysis; $p < 0.05$ was considered significant. Results were expressed as mean ± SEM.

RESULTS

Patient characteristics. Clinical characteristics of the group of 160 patients are summarized in Table 1. Mean age was 66.8 ± 1.0 years (range 20 to 87 years), and 31% of the patients were women. In all, 98 patients had HF symptoms with an LV EF of ≤50%. These comprised the systolic heart failure group (SHF). The diastolic heart failure group (DHF) was comprised of 62 patients with preserved systolic function (LV EF >50%). Mean age and body mass index did not differ significantly between SHF and DHF groups, while there was a trend of more female patients in DHF. A history of hypertension and etiologies of dilated cardiomyopathy and ischemic cardiomyopathy/old myocardial infarction were more prevalent in SHF. Patients with SHF were more likely to be taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and diuretics.

Geometric and functional parameters obtained by echocardiography or cardiac catheterization are shown in Table 2. In total patients, mean EF was 41.5 ± 1.1% (range 13% to 66%), and mean LVMI and LV end-diastolic volume index (LVEDVI) were 166 ± 4 g/m^2 and 106 ± 4 ml/m^2, respectively.

Correlations of plasma BNP to echocardiographic and hemodynamic parameters. Scatter plots of plasma BNP levels (dependent variable) against some echocardiographic and hemodynamic parameters (independent) are shown in Figure 1. There were strong correlations between LV EF, LVEDVI or LV end-systolic volume index, or LV EDP and plasma BNP (coefficient of correlation; $r^2 = 0.325$, 0.343, 0.421, and 0.328, respectively). There were weak correlations with parameters of transmitral Doppler flow $r^2 = 0.201$ and 0.101 for E/A and deceleration time, respectively. In contrast, LVMI and left atrial diameter did not show significant correlations with BNP levels. Although LV systolic wall stress (SWS) calculated by echocardiographic and hemodynamic parameters showed a modest correlation ($r^2 = 0.277$), a correlation of BNP with LV EDWS was much more robust ($r^2 = 0.887$).

Although age, gender, and atrial fibrillation were not significantly associated, body mass index (BMI) and New York Heart Association functional class ≥II were associated with BNP levels ($p < 0.001$ in both).

Comparison between SHF and DHF. Plasma BNP levels were significantly higher in SHF than in DHF (median [interquartile range]; 267 [136 to 583] and 105 [64 to 146] pg/ml, respectively, $p < 0.001$); however, EDP levels did not show any differences as shown in Figure 2 and Table 2. Other parameters such as SWS, EDWS, LV end-diastolic dimension, LVMI, LVEDVI, and LV peak systolic pressure were significantly higher in SHF than in DHF ($p < 0.001$). Scatter plots in patients with SHF and DHF are demonstrated in Figures 3A and 3B and Figures 3C and 3D, respectively. End-diastolic wall stress showed a better correlation with BNP ($r^2 = 0.704$) than EDP ($r^2 = 0.143$) in DHF as well as in SHF.

Subanalysis in patients without local wall motion abnormality. It is conceivable that this estimation of wall stress did not accurately reflect the entire non-uniform LV wall stress in patients with regional asynergy in LV wall motion or with variation in segmental LV wall thickness. In the present study, 83% of patients with ischemic cardiomyopathy or old myocardial infarction and 28% with dilated cardiomyopathy had regional wall motion abnormalities. Therefore, a subanalysis was performed for patients without local wall motion abnormality (n = 105). As a result, an even stronger correlation was obtained as shown ($r^2 = 0.919$). A correlation in patients with regional wall motion abnormality (n = 55) was still strong ($r^2 = 0.820$).

DISCUSSION

Heterogeneity of BNP levels among individuals with HF can cause some confusion in interpreting results. It has been unclear why some patients with LV EF <35% have BNP levels in the normal range whereas others exhibit extremely elevated levels, and why some patients with isolated diastolic dysfunction (i.e., with normal EF) show a similar increase of plasma BNP as do the patients with severe systolic dysfunction. One of the answers to the question has been the change of EDP levels in the LV (6). Another recent report has demonstrated that heterogeneity of BNP levels in patients with systolic HF reflects the severity of diastolic abnormality, right ventricular function, and mitral regurgi-

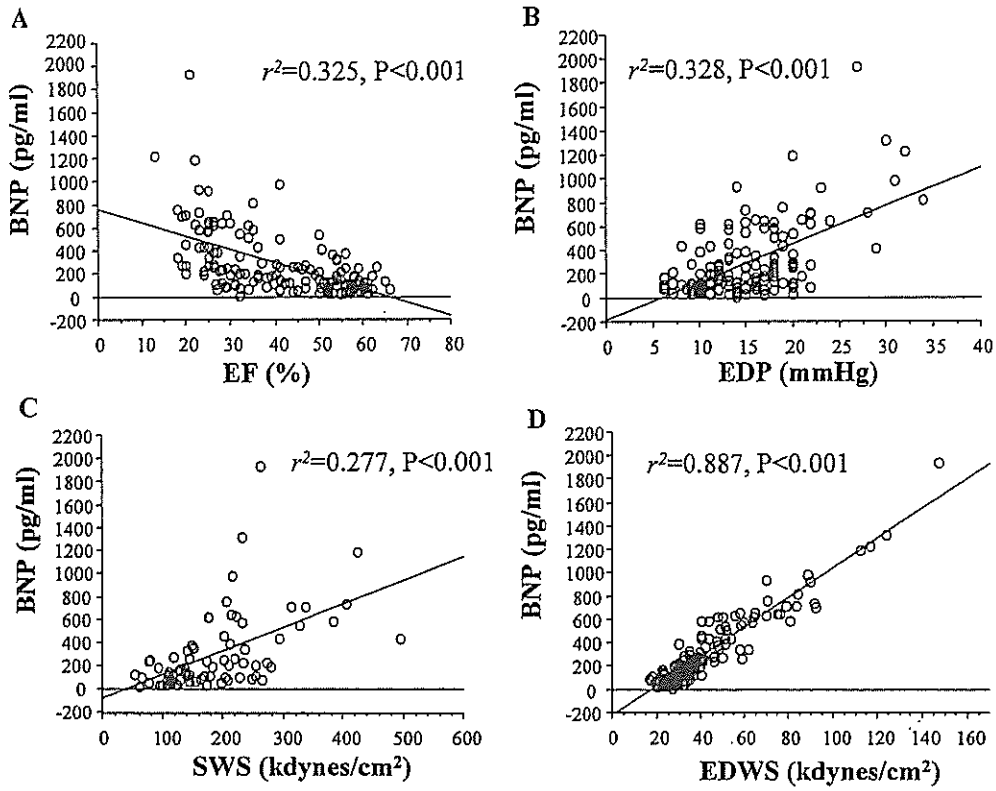

Figure 1. Correlation between B-type natriuretic peptide (BNP) and left ventricular functional parameters in all 160 patients. (A) Left ventricular ejection fraction (EF) (%). (B) End-diastolic pressure (EDP) (mm Hg). (C) End-systolic wall stress (SWS) (kdynes/cm²). (D) End-diastolic wall stress (EDWS) (kdynes/cm²).

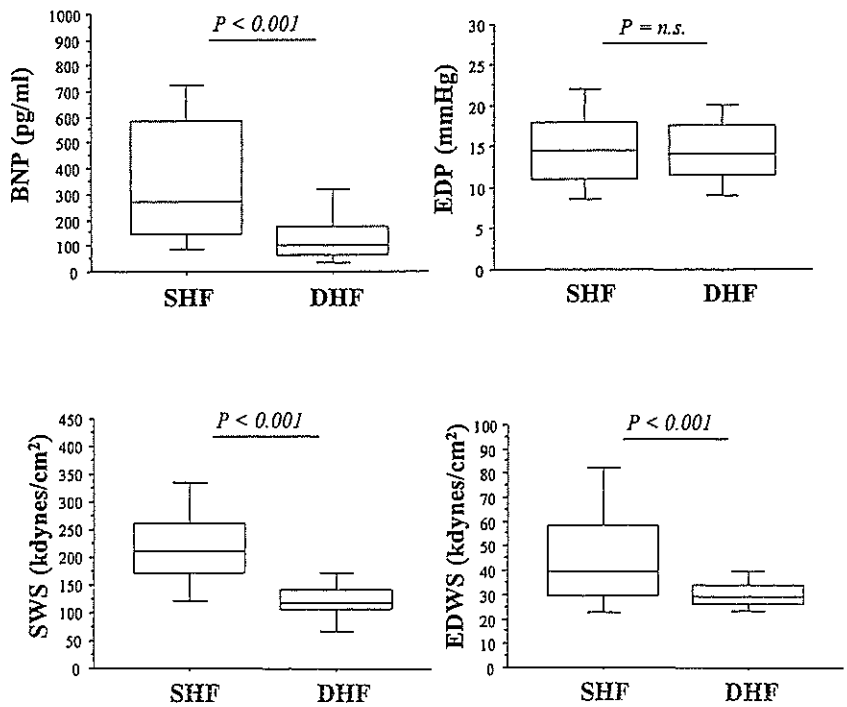

Figure 2. Differences of B-type natriuretic peptide (BNP) and left ventricular functional parameters between systolic heart failure (SHF) (n = 98) and diastolic heart failure (DHF) (n = 62). The box defines the interquartile range with the median indicated by the crossbar. The error bars indicate the 10th and 90th percentiles. EDP = end-diastolic pressure (mm Hg); EDVI = end-diastolic volume index (ml/m²); EDWS = end-diastolic wall stress (kdynes/cm²); SWS = end-systolic wall stress (kdynes/cm²).

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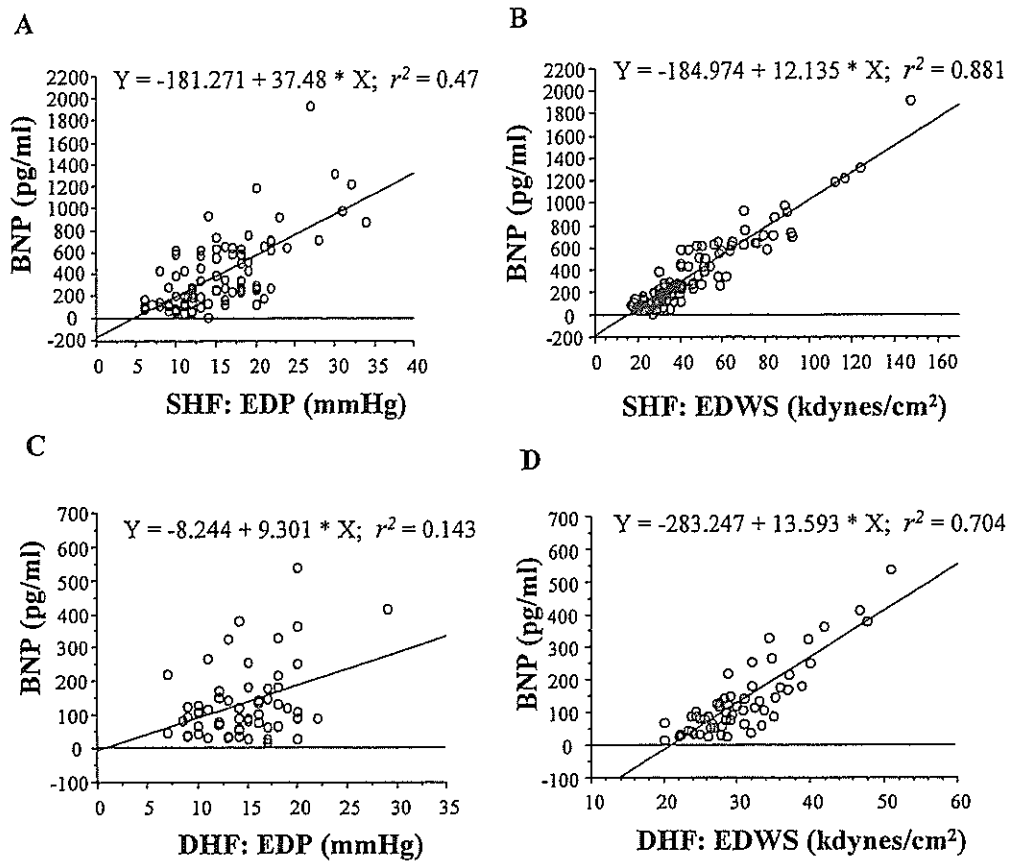

Figure 3. Correlation between B-type natriuretic peptide (BNP) and left ventricular functional parameters in 98 patients with systolic heart failure (SHF) (A and B) and in 62 patients with diastolic heart failure (DHF) (C and D); (A and C) end-diastolic pressure (EDP) (mm Hg) and (B and D) end-diastolic wall stress (EDWS) (kdynes/cm²).

tation in addition to LV EF, age, and renal function (7). The present study demonstrates the significance of LV EDWS in the regulation of BNP in patients with HF in general. This was true not only in patients with SHF but also with DHF. Although correlation analysis suggested a relationship between other parameters of LV geometry and function including EDP and plasma BNP levels, the correlation between LV EDWS and BNP was the most robust (r^2 = 0.887). Many studies including ours have shown that BNP levels correlate well with changes in filling pressures during tailored therapy (6,17), while O'Neill et al. (18) recently reported that plasma BNP might not correlate closely with changes in intracardiac filling pressures. In any case, plasma BNP levels are not uniform across different patients with the same LVEDP (i.e., interindividual heterogeneity), and this may be because BNP is determined more by EDWS than by filling pressure. Left ventricular EDWS might account for the wide variations that they observed in patients with HF.

The present result suggests that LV EDWS may regulate BNP secretion in humans. Indeed, experiments using cultured neonatal rat ventricular cells showed that cardiac myocytes are able to respond to mechanical stretch by increasing BNP secretion and gene expression (11). Wiese et al. (19), using isolated human myocardium, have also demonstrated that, while the isometric contraction mode did not have any influence on BNP expression, diastolic overstretch increased BNP gene expression in a time-dependent manner. This implies that diastolic stretch (i.e., preload rather than afterload) seems to be the mechanical factor responsible for the induction of BNP expression and may be the reason that in the present study LV EDWS shows a better correlation with the plasma BNP levels than does LV SWS. Furthermore, in vitro studies have implicated the contributions of local paracrine and autocrine factors in the stretch-induced BNP activation (11). Local angiotensin II was shown to play a critical role in the development of stretch-induced cardiac hypertrophy and to at least partly regulate mechanical load-induced BNP expression. Recently, in addition to stimuli such as myocyte stretching and neurohumoral activation, acute myocardial hypoxia has been reported to increase cardiac BNP gene transcription and raise the plasma proBNP concentration in an animal study (20). This mechanism may explain the increase in plasma BNP in patients with acute coronary syndromes and myocardial infarction (21). In the present study, because such patients with acute ischemia were not included, the correlation between LV EDWS and plasma BNP might actually be stronger.

Myocardial wall stress is one of the primary determinants of myocardial oxygen consumption (22). Cardiac decompensation is thought to result when the feedback loop that normalizes wall stress to abnormal loading of the heart dysfunctions. The increased wall stress may act directly or indirectly via cellular mediators such as angiotensin, endothelin, inflammatory cytokines, reactive oxygen species, and matrix metalloproteinase to orchestrate a variety of molecular and cellular remodeling events determining the structural and functional properties of the myocardium and, ultimately, the rate of disease progression (23–27). Therefore, usefulness of plasma BNP levels in predicting morbidity and mortality accurately in patients with chronic HF may be explained by the relationship between the LV EDWS and BNP. Many other factors, such as age, gender, body mass, genetics, etc., are also known to affect plasma BNP levels. However, the demonstration of the link between the hemodynamics (LV EDWS) and neurohormonal factor (BNP) may support the usefulness of BNP-guided treatment of HF. Although more randomized studies are needed, pharmacotherapy guided by BNP levels is intriguing and promising (3).

There are several methods to estimate the wall stress, and we used a formula based on M-mode echocardiographic variables (16). This method may have several limitations. For example, when there is regional asynergy in LV wall motion and variation in local LV wall thickness, the estimate may not reflect the entire non-uniform LV wall stress correctly. To test this possibility, we analyzed the data of the patients without LV asynergy demonstrated by echocardiogram and LV ventriculography. We obtained an even better correlation. Interestingly, a correlation in patients with a local wall motion abnormality was still strong ($r^2 = 0.820$). There are several other limitations to our study. Echocardiography and blood sampling were typically performed the day before cardiac catheterization. This time lag could have influenced the results. A further limitation is that the study population was composed of the patients who were in stable condition and could tolerate LV cardiac catheterization; thus, patients who could not bear cardiac catheterization (e.g., patients with New York Heart Association functional class IV HF) were excluded.

In the present study, we demonstrated that plasma BNP levels strongly reflect EDWS in the LV more than any other parameter previously reported. In addition, EDWS accurately accounts for the increase in plasma BNP levels even in patients with diastolic HF. The relationship of LV EDWS to plasma BNP may give a better understanding to the interindividual heterogeneity of plasma BNP levels and its clinical utility in the diagnosis and management of HF.

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Intensive treatment of risk factors in patients with type-2 diabetes mellitus is associated with improvement of endothelial function coupled with a reduction in the levels of plasma asymmetric dimethylarginine and endogenous inhibitor of nitric oxide synthase

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KEYWORDS
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Aims Vascular endothelium is a major organ involved in hyperglycaemia and is affected by plasma asymmetric dimethylarginine (ADMA). ADMA is an endogenous, competitive inhibitor of nitric oxide synthase and is induced by inflammatory cytokines of tumour necrosis factor (TNF)-α *in vitro*. We hypothesized that a tight glycaemic control may restore endothelial function in patients with type-2 diabetes mellitus (DM), in association with modulation of TNF-α and/or reduction of ADMA level.

Methods and results In 24 patients with type-2 DM, the flow-mediated, endothelium-dependent dilation (FMD: %) of brachial arteries during reactive hyperaemia was determined by a high-resolution ultrasound method. Blood samples for glucose, cholesterol, TNF-α, and ADMA analyses were also collected from these patients after fasting. No significant glycaemic or FMD changes were observed in 10 patients receiving the conventional therapy. In 14 patients who were hospitalized and intensively treated, there was a significant decrease in glucose level after the treatment [from 190 ± 55 to 117 ± 21 (mean ± SD) mg/dL, $P < 0.01$]. After the intensive control of glucose level, FMD increased significantly (from 2.5 ± 0.9 to 7.2 ± 3.0%), accompanied by a significant ($P < 0.01$) decrease in TNF-α (from 29 ± 16 to 11 ± 9 pg/dL) and ADMA (from 4.8 ± 1.5 to 3.5 ± 1.1 μM/L) levels. The changes in FMD after treatment correlated inversely with those in TNF-α ($R = -0.711$, $P < 0.01$) and ADMA ($R = -0.717$, $P < 0.01$) levels.

Conclusion The intensive correction of hyperglycaemia is associated with the improvement of endothelial function, which is coupled with the decrease in the levels of reduction of plasma TNF-α and ADMA in patients with type-2 DM. A strict glycaemic control may exert anti-cytokine and anti-atherogenic effects and may therefore be pathophysiologically important.

Introduction

Cardiovascular disease is the major cause of morbidity and mortality in patients with type-2 diabetes mellitus (DM),[1] in whom hyperglycaemia is one of the main metabolic abnormalities.[2] Blood glucose control occupies the centre stage in DM management.[3] A recent controlled trial, i.e. the United Kingdom Prospective Diabetes Study (UKPDS), suggested that an intensive glucose-lowering treatment decreases the occurrence of macrovascular complications.[4] However, the exact roles of hyperglycaemia and glycaemic control in cardiovascular complications remain to be determined in patients with type-2 DM.

Previous studies demonstrated that acute hyperglycaemia impairs endothelium-dependent vasodilation in healthy subjects[5,6] and further depresses it in patients with type-2 DM.[6] These findings indicate a possible link between glucose level and endothelial function in humans. Endothelial dysfunction is an important phenomenon in the pathogenesis of atherosclerosis[7] and is related to the derangements of nitric oxide (NO) synthase in the vessel wall.[8] Asymmetric dimethylarginine (ADMA) is an endogenous, competitive inhibitor of NO synthase.[9] Its concentration is increased by tumour necrosis

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factor-α (TNF-α),[10] which is implicated as an important factor in the pathogenesis of type-2 DM.[11]

Thus, the present study was designed to investigate whether an intensive therapy of hyperglycaemia may improve endothelial function in association with the modulation of the cytokines and/or decrease in plasma ADMA level in patients with type-2 DM.

Methods

Study patients

The study protocol was approved by the Institutional Review board, and all these patients gave their written informed consent to participate in the study. Type-2 DM was defined according to the criteria of the Diagnosis and Classification of Diabetes Mellitus.[12] Between May 1999 and June 2000, type-2 DM patients with poor glycaemic control [fasting blood glucose >200 mg/dL and/or haemoglobin A-1C (Hb A-1C) >9%] were recruited for intensive treatment of hyperglycaemia during hospitalization. Twenty-four patients were initially assessed for inclusion in the study. Among them, 14 patients [nine men and five women, mean age 61 ± 12 (SD) years] gave their consent and were admitted to the Hospital of the National Cardiovascular Center (intensive treatment group). The remaining 10 patients [seven men and three women, mean age 63 ± 15 (SD) years], who refused to be hospitalized and were obliged to keep conventional (non-intensive) diabetes treatment, served as the control group in the present study.

All the patients underwent history screening, physical examination, and laboratory analysis, including a complete blood count: the levels of plasma electrolyte, glucose, insulin, Hb A-1C, blood urea nitrogen, creatinine, transaminases and urinary protein levels, and lipid profile. Moreover, the patients were assessed for the presence of diabetic complication, i.e. retinopathy, neuropathy, nephropathy, a history of myocardial infarction, and the presence of angina pectoris and arteriosclerosis obliterans. Patients with nephrotic-range proteinuria, thyroid disease, apparent infections, or haematologic, hepatic, or renal disease were excluded from the study. Before admission, five patients had been receiving angiotensin-converting enzyme inhibitors for hypertension and five patients receiving statin for hyperlipidaemia for over 6 months. These medications were not changed throughout the study period. In addition, no new drugs other than insulin or oral hypoglycaemic agents were administered to any of these patients.

Study design

On admission, following an overnight fasting, a non-invasive assessment of brachial arterial vasoreactivity in response to reactive hyperaemia or nitroglycerin was performed with blood sampling for the determination of the levels of glucose, insulin, Hb A-1C, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, TNF-α, and ADMA in the plasma. We also measured plasma hepatocyte growth factor (HGF) level. The HGF may protect against endothelial dysfunction, and its production is suppressed by high glucose levels.[13] Body mass index (BMI) was calculated using the formula BMI = weight (kg)/height^2 (m^2). All measurements were repeated after ~1 month of intensive treatment for hyperglycaemia.

The intensive therapy was aimed at maintaining normal fasting glucose (80–115 mg/dL) and pre-prandial blood glucose (< 130 mg/dL) levels. Throughout the study, the patients followed a 1200–1300 Kcal diet regimen of 60–65 g of protein, 30–35 g of fat, and 160–170 g of carbohydrates. The level of dietary cholesterol was 350 g/day. The dose of oral anti-diabetic drugs was adjusted accordingly and/or insulin therapy was administered to improve glycaemic control. The patients were examined once or twice a week over a 4–5-week period of blood glucose monitoring. None of the patients experienced a hypoglycaemic reaction during the study.

Brachial artery ultrasound

Flow-mediated, endothelium-dependent vasodilation (FMD) following reactive hyperaemia and endothelium-independent nitroglycerin-induced vasodilation of the brachial artery were assessed using a high-resolution ultrasound machine (System Five, General Electronics) equipped with a 7.5 MHz linear array transducer.[6] After a 10 min rest in a temperature-controlled room (22–23 C), the diameter of the right brachial artery and baseline forearm flow velocity were measured. Increased forearm blood flow was induced by the inflation of a blood pressure cuff placed around the forearm to 200 mmHg or to a pressure of 50 mmHg greater than the systolic blood pressure. This was followed by deflation (RD2 Cuff Deflator, Hokanson Inc., Bellevue, WA, USA) after 5 min. Repeated blood flow scans were obtained to measure the diameter of the brachial artery. After 15 min of vessel recuperation, a repeated measurement of the diameter of the resting brachial artery and repeated blood flow scans were obtained. Sublingual nitroglycerin (0.4 mg) was administered, and then final scans were obtained after 3 min. Throughout the study, a single lead electrocardiogram was obtained, and blood pressure was measured in the left arm every 2 min by an automated blood pressure recorder.

Ultrasound images were recorded on an S-VHS videocassette recorder. Depth and gain settings were used to optimize the images of the lumen–arterial wall interface. Vessel diameter was measured in triplicate at end diastole, from the anterior to the posterior interface between the media and the adventitia. Flow-mediated vasodilation was calculated as the ratio of brachial artery diameter after reactive hyperaemia to baseline diameter and expressed as a per cent increase. Nitroglycerin-mediated vasodilation was calculated in an analogous manner. Volumetric flow rate was calculated by multiplying the time velocity integral of the angle (~70°)-corrected Doppler flow signal by the heart rate and the vessel cross-sectional area. Changes in blood flow were expressed as the percentages of the resting flow measurements. All measurements were performed with the observers blind to patient information and study date. Using this methodology and analysis, the intra- and inter-observer variabilities in brachial artery diameter were 0.03 ± 0.02 (mean ± SD) and 0.06 ± 0.02 mm, respectively, and the variability in FMD performed on two different days was 1.4 ± 0.5%.

Laboratory measurements

Fasting plasma glucose level was measured by the glucose oxidase method and Hb A-1C level was measured by automated high-performance liquid chromatography. Insulin level was measured by the conventional radioimmunoassay. To assess insulin resistance, we used the following homeostasis model assessment (HOMA) parameters: HOMA-R = [fasting blood glucose (mg/dL) × fasting insulin (μU/mL)]/405.[14]

Total cholesterol, triglyceride, and HDL cholesterol levels were determined as described previously.[15] LDL cholesterol level was calculated using the Friedewald equation.[16]

TNF-α and HGF levels were determined by enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co., Tokushima, Japan). The detection limits of these methods are 2 pg/mL for TNF-α and 0.1 ng/mL for HGF. The intra- and inter-assay coefficients of variation were both ~7% for the enzyme-linked immunosorbent assay.

Plasma ADMA concentration was measured using high-performance liquid chromatography with pre-column derivatization, as previously described.[17] In brief, equilibrated CBA columns