Original Article

Comparison of Arterial Functional Evaluations as a Predictor of Cardiovascular Events in Hypertensive Patients: The Non-Invasive Atherosclerotic Evaluation in Hypertension (NOAH) Study

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Increased arterial stiffness and impaired vasodilator response have been associated with cardiovascular events in high-risk patients. However, whether arterial changes predict the occurrence of hypertensive complications is still unclear. Therefore, we designed a hospital-based cohort study to examine the prognostic impact of arterial functional changes on stroke and cardiovascular diseases in hypertensive patients. The study employed 676 patients with essential hypertension. At baseline, we evaluated second-derived photoplethysmography, carotid-femoral pulse wave velocity (PWV), and forearm reactive hyperemia. We classified subjects into quartile groups according to the baseline measurements of these evaluations and assessed the ability of each measure to predict stroke and cardiovascular diseases (CVD). During a mean follow-up period of 57 months, 52 strokes, 40 CVD, and 22 deaths were recorded. Kaplan-Meier analysis revealed that patients in the highest quartile of PWV showed a higher frequency of stroke and CVD ($p<0.0001$) and total mortality ($p=0.0016$), and those in the highest quartile of reactive hyperemia showed a lower frequency of stroke and CVD ($p=0.0415$). A Cox hazard model identified that classification in the highest quartile of PWV (relative risk=2.717) and reactive hyperemia (0.416) were predictive of stroke and CVD after adjustment for other risk factors. In subjects who did not experience stroke or CVD before the study period ($n=558$), only PWV was related with the occurrence of stroke and CVD based on the Cox hazard model. In conclusion, increased aortic stiffness evaluated by PWV is more prognostic of cardiovascular events in hypertensive patients than several non-invasive atherosclerotic evaluations. (*Hypertens Res* 2008; 31: 1135–1145)

***Key Words*: arterial stiffness, prognosis, stroke, cardiovascular disease, pulse wave velocity**

Introduction

Multi-center trials have revealed that lowering blood pressure leads to reduction of cardiovascular mortality and morbidity (*1*). However, the ability to identify hypertensive patients destined to suffer a fatal complication in the long presymptomatic phase of this condition is limited by the weak relationship between blood pressure level and the occurrence of complications. Arterial functional changes, such as arterial compliance and stiffness, are systemic complications caused by hypertension, and several methods to evaluate these changes have

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been reported. Recent epidemiologic and clinical studies have shown that aortic pulse wave velocity (PWV), a measure of arterial stiffness, is accelerated (*2*) and is a predictor of cardiovascular mortality in patients with end-stage renal disease (*3*), hypertension (*4*), and diabetes mellitus (*5*), and in older individuals (*6*), independently of confounding factors such as age, blood pressure, and cardiac mass. These results support the hypothesis that monitoring of arterial stiffness under different medications could help both in risk assessment and risk reduction strategies. Thus, arterial stiffness measurements could serve as an important tool in clinical practice in hypertensive patients.

Second-derived photoplethysmography (SD-PTG) is also an established procedure to evaluate arterial functional change (*7*). Takazawa *et al*. suggested that the b/a index, which was one of the parameters produced by SD-PTG might, reflect large arterial stiffness and that the d/a index indicates peripheral reflection (*7*). Therefore, we analyzed the b/a and d/a ratios as representative parameters for SD-PTG. The vasoreactivity is also one of the arterial functional changes. Evaluating endothelial function is very complicated; however, forearm reactive hyperemia after upper arm ischemia partially represents endothelial function, and vasoreactivity evaluated by reactive hyperemia has been reported to be implicated in the pathogenesis of hypertensive complications (*8*).

As described above, several methods for evaluating arterial functional change exist, and each evaluation is clinically important; however, the clinical usefulness of each method in hypertensive patients is still unclear. Therefore, we designed a hospital-based cohort study to evaluate the clinical importance of PWV, SD-PTG, and reactive hyperemia as predictors of cardiovascular events in hypertensive patients participating in the Non-invasive Atherosclerotic Evaluations in Hypertension (NOAH) study.

Methods

Study Population and Study Design

Figure 1 shows a flow chart of the selection process of the study cohort. In our hospital, a total of 813 serial outpatients who had been diagnosed with essential hypertension were recruited between January 1998 and June 2004. Based on routine physical and laboratory examinations, we excluded from this study hypertensive patients with malignant diseases ($n=6$) and arterial fibrillation ($n=29$). Blinded specialists performed PWV, SD-PTG, and reactive hyperemia for every patient at the same time after 20 min of rest ($n=778$); however, there was not sufficient PWV data for 13 patients; SD-PTG data were insufficient for 15 patients; and data for reactive hyperemia were lacking for 32 patients, leaving 718 hypertensive patients who were enrolled in this study. After performing a clinical survey for each patient as described below, we could not obtain sufficient information about cardiovascular events and/or mortality in 42 patients, and thus a final of 676 patients were investigated.

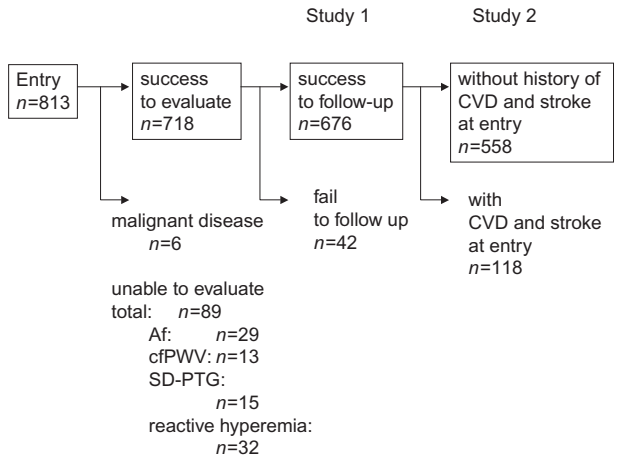

Fig. 1. *Derivation of the study cohort. Af, afrial fibrillation; PWV, carotid-femoral pulse wave velocity; SD-PTG, second-derived photoplethysmography; CVD, cardiovascular disease.*

The characteristics for the 676 hypertensive patients are shown in Table 1. As shown in Fig. 1, two separate studies were performed in this work. In Study 1, we examined the prognostic impact of atherosclerotic evaluations in all participants, and in Study 2, we examined in patients who did not have history of stroke or cardiovascular disease (CVD). The 118 participants included in Study 1 had a history of cardiovascular events and atherosclerotic diseases defined as World Health Organization (WHO) grade 3 in 1999. To clarify the efficacy of each procedure (*i.e.*, PWV, SD-PTG, and reactive hyperemia) in predicting cardiovascular events, we excluded patients who had a history of cardiovascular events, leaving 558 patients for the investigation in Study 2. The study protocol was approved by the hospital ethics committee, and written informed consent was obtained from all participants. A total of 293 patients were not treated with any antihypertensive drugs, and 383 patients were treated with one or more antihypertensive drugs: 244 patients with a calcium antagonist, 150 patients with an angiotensin II receptor blocker (ARB), 125 patients with an angiotensin converting enzyme (ACE) inhibitor, 76 patients with a β-blocker, 46 patients with a diuretic, and 27 patients with an α-blocker. An additional 180 patients were also treated with a statin.

Follow-Up Evaluation

Clinical follow-up was conducted by clinical visits, mailed questionnaires, and telephone contact every September from 2003. The questionnaire included the events of hypertensive complications described below and cause of death. We also confirmed responses in detail by comparing them against

Table 1. Baseline Characteristics in Each Study

	Study 1	Study 2
Number	676	558
Sex (male:female)	372:304	294:264
Age (years old)	62±12	61±12
DM (*n* (%))	148 (21.9)	103 (18.5)
HL (*n* (%))	374 (55.3)	308 (55.3)
WHO classification		
Grade 1 (*n* (%))	372 (55.0)	372 (66.7)
Grade 2 (*n* (%))	186 (27.5)	186 (33.3)
Grade 3 (*n* (%))	118 (17.5)	—
Medication		
Antihypertensive drug (*n* (%))	383 (56.7)	294 (52.7)
ACE inhibitor (*n* (%))	125 (18.5)	95 (17.0)
ARB (*n* (%))	150 (22.2)	114 (20.4)
α-Blocker (*n* (%))	27 (4.0)	24 (4.3)
β-Blocker (*n* (%))	76 (11.2)	56 (10.0)
CCB (*n* (%))	244 (36.1)	181 (32.4)
Diuretics (*n* (%))	46 (6.8)	31 (5.6)
Statin (*n* (%))	180 (26.6)	148 (26.5)
Cardiovascular event		
Total (*n* (%))	88 (13.0)	53 (9.5)
Stroke (*n* (%))	52 (7.7)	36 (6.5)
Cardiovascular disease (*n* (%))	40 (5.9)	21 (3.8)
Total mortality (*n* (%))	22 (3.3)	8 (1.4)

DM, diabetes mellitus; HL, hyperlipidemia; WHO, World Health Organization; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

patient medical sheets. The primary endpoint of this study was new onset of stroke or CVD, such as a new onset of angina pectoris, myocardial infarction, or heart failure, or a rupture of an aortic aneurysm. Specialists diagnosed stroke by neurological disturbance for at least 24 h and evidence of infarction or bleeding using computed tomography or magnetic resource imaging, angina by typical chest pain without creatinine kinase release and positive ST change of stress electrocardiogram, and myocardial infarction by typical chest pain with a more than two-fold normal amount of creatinine kinase release and positive ST change of electrocardiogram. Heart failure was diagnosed by American Heart Association criteria and diagnosis of rupture of an aortic aneurysm was defined by computed tomography and clinical findings. The follow-up duration was considered to encompass the interval from the initial evaluation to the time of event onset or September 2006. The average follow-up period was 57.0±23.7 months.

Second-Derived Photoplethysmography

Measurements were performed in the morning with each patient in the supine position. Blood pressure was measured in the right upper arm after a 5-min rest using an automatic blood pressure meter (HEM-609; OMRON Healthcare Co., Kyoto, Japan). Three measurements taken 2 min apart were averaged. Blood pressure determination, SD-PTG, carotid-femoral PWV (cfPWV), and forearm blood flow measurements were performed in a controlled environment at 22±2°C, respectively. SD-PTG was performed by a Fukuda FCP-4731 with a model IB-70, as described previously (*7*, *9*). Briefly, the IB-70 device was a photoplethysmogram, equipped with double differentiation circuits, and the sensor was positioned on the cuticle of the index finger of the left hand. Photoplethysmography measures the changing absorption of light by hemoglobin, which is related to blood flow volume. The IB-70 performs automatic analysis of each second derivative of the photoplethysmographic waveform, which we called SD-PTG. The SD-PTG waveform consists of four waves in systole (a, b, c, and d) and one in diastole (e). We measured the height of each wave from the baseline, with the values above baseline being considered positive and those under it negative. The b/a ratio was defined as the ratio of the height of the b-wave to that of the a-wave, and the d/a ratio as the height of the d-wave to that of the a-wave.

Determination of Pulse Wave Velocity

We evaluated PWV with the patient in a supine position after 20 min of rest. We determined PWV using a "FCP-4731" device (Fukuda Denshi Co., Tokyo, Japan), which allowed online pulse wave recording and automatic calculation. The pulse waveforms of the right carotid and femoral arteries were recorded non-invasively using a TY-306-Fukuda pressure-sensitive transducer (Fukuda Denshi Co.), and heart sounds were recorded at the same time. A preprocessor automatically analyzed the gain in each waveform and adjusted it for equality of the two signals. This procedure has been published in detail elsewhere (*10*).

Determination of Reactive Hyperemia by Strain Gauge Plethysmography

We measured forearm blood flow by strain-gauge plethysmography (EC5R; D.E. Hokanson Inc., Bellevue, USA) as described by Komai *et al*. (*10*). Briefly, with the subject in a supine position after a 5-min rest, a strain-gauge was applied to the area with the maximal forearm diameter. A venous occlusion cuff was wrapped around the upper arm, and 1% calibration waves were recorded. Then, the venous occlusion cuff was compressed at 40 mmHg. Immediately after compression, the blood flow began to elevate and reached a plateau 1–2 min after compression. This was regarded as the basic blood flow (vol%/min). The cuff pressure was then increased to 200 mmHg for a 5-min compression, and rapidly deflated to 40 mmHg. Antebrachial arterial blood flow (vol%/min) at reactive hyperemia was calculated.

Table 2. Classification of Quartiles in Each Group

	Study 1 (n=676)			Study 2 (n=588)		
	N	Mean±SD	Range (min, max)	*N*	Mean±SD	Range (min, max)
b/a						
1st quartile	170	−0.63±0.09	−0.90, −0.53	138	−0.63±0.09	−0.90, −0.53
2nd quartile	160	−0.47±0.03	−0.52, −0.43	134	−0.47±0.03	−0.52, −0.43
3rd quartile	175	−0.38±0.03	−0.42, −0.34	149	−0.38±0.03	−0.42, −0.34
4th quartile	171	−0.27±0.06	−0.03, 0.04	137	−0.26±0.06	−0.33, −0.04
d/a						
1st quartile	170	−0.57±0.07	−0.90, −0.49	142	−0.56±0.07	−0.90, −0.49
2nd quartile	168	−0.43±0.03	−0.48, −0.40	138	−0.43±0.03	−0.48, −0.40
3rd quartile	166	−0.35±0.03	−0.40, −0.31	140	−0.35±0.03	−0.40, −0.31
4th quartile	172	−0.23±0.07	−0.30, 0.06	138	−0.23±0.07	−0.30, 0.06
Reactive hyperemia (vol%/min)						
1st quartile	169	3.28±0.96	1.02, 4.66	140	3.37±0.96	1.02, 4.67
2nd quartile	169	5.88±0.72	4.67, 7.06	139	5.94±0.71	4.76, 7.14
3rd quartile	170	8.72±0.97	7.12, 10.44	141	8.73±0.94	7.18, 10.43
4th quartile	168	14.44±4.85	10.52, 45.28	138	14.19±4.88	10.44, 45.28
cfPWV (m/s)						
1st quartile	169	6.99±0.63	4.60, 7.70	139	6.92±0.61	4.60, 7.62
2nd quartile	173	8.29±0.33	7.78, 8.80	138	8.12±0.29	7.65, 8.66
3rd quartile	164	9.37±0.33	8.84, 10.04	138	9.13±0.29	8.70, 9.77
4th quartile	170	11.24±1.05	10.05, 16.00	143	10.95±1.12	9.80, 16.00

cfPWV, carotid-femoral pulse wave velocity.

Statistical Analysis

We classified subjects into four groups by quartile in ascending order for each evaluation. The values summarized in Tables 1–3 are presented as the mean±SD. Statistical analysis was performed using ANOVA by post-hoc test adjusted with Bonferroni/Dunn correction. An event-free curve was estimated *via* the Kaplan-Meier method. Patients were stratified according to quartiles of SD-PTG, PWV, or reactive hyperemia for the analysis of event-free rates. The log-rank test was used to compare the differences of event-free rates among these patient groups. To clarify the statistical significance between each quartile, we used a log-rank test for each two quartiles and non-adjusted Cox proportional hazard model to evaluate the relative risk and 95% confidence interval (CI). Baseline clinical variables for these patients were analyzed with the Cox proportional hazard model after adjusting for other common risk factors, such as gender, age, current smoking, presence of diabetes and hyperlipidemia, systolic and diastolic blood pressure and serum creatinine, and the hazard ratio with 95% confidence interval was given for each factor. Analyses were performed with commercially available software (Dr. SPSS II; SPSS Inc., Chicago, USA). Findings of $p<0.05$ were considered significant.

Results

Patient Characteristics

Baseline clinical characteristics for each study are summarized in Table 1. In Study 1, 55% of patients showed no complication, defined as grade 1 in the 1999 WHO classification (*11*). A total of 56.7% of patients (n=383 of 676) in Study 1 were treated with antihypertensive drugs; there were complications of diabetes mellitus in 21.9% (n=148 of 676) and hyperlipidemia in 55.3% (n=374 of 676). The patients with associated clinical complications defined as WHO grade 3 were excluded from Study 2. The mean and range of four evaluations, *i.e.*, b/a, d/a, reactive hyperemia, and PWV, are shown in Table 2. The baseline characteristics for each evaluation in Study 1 are summarized in Table 3. Each evaluation was associated with common risk factors; most notably, every evaluation was influenced by age and systolic blood pressure.

Results of Study 1

By the time of the follow-up survey, 52 of the 676 patients had suffered from stroke, 40 of the 676 patients had suffered from CVD, and 22 of the 676 patients had died. Figure 2A shows the results of the Kaplan-Meier analysis for occurrence of stroke and CVD. The event-free survival of PWV was significantly distributed by log-rank test ($p<0.0001$), and that in

Table 3. Baseline Characteristics of Participants by Each Evaluation in Study 1

	b/a					d/a				
	Quartile				*p* value	Quartile				*p* value
	1st	2nd	3rd	4th		1st	2nd	3rd	4th	
Number	170	160	175	171		170	168	166	172	
Sex (% male)	77.1	65.0	40.0	38.0	<0.0001	51.8	42.9	57.2	66.3	0.0004
Age (years old)	54±14$^{\#\#,\dagger\dagger}$	62±10**	64±9**	67±9**$^{,\#\#,\dagger\dagger}$	<0.0001	63±10	64±10†	61±12$^{\#}$	58±14**$^{,\#\#,\dagger}$	<0.0001
DM (*n* (%))	48 (28)	40 (25)	40 (23)	21 (12)	0.0033	29 (17)	37 (22)	33 (20)	48 (28)	n.s.
HL (*n* (%))	99 (58)	80 (50)	96 (55)	101 (59)	n.s.	92 (54)	99 (59)	83 (50)	100 (58)	n.s.
SBP (mmHg)	135±17$^{\#,\dagger\dagger}$	139±17*	141±18**	145±18**$^{,\#\#,\dagger}$	<0.0001	145±18†	142±17	140±20*	134±16**$^{,\#\#,\dagger\dagger}$	<0.0001
DBP (mmHg)	83±13	83±11	83±11	82±12	n.s.	85±11	83±11	83±13	80±11**$^{,\#,\dagger}$	0.0007
HR (mmHg)	71±11†	70±11	68±9*	63±11**$^{,\#\#,\dagger\dagger}$	<0.0001	66±12	68±11	67±10	70±11**,†	0.0088
TC (mol/L)	5.4±0.93	5.2±0.80	5.4±0.93	5.4±0.88	n.s.	5.3±0.88	5.4±0.85	5.4±0.85	5.3±0.97	n.s.
TG (mol/L)	4.2±2.5††	4.0±3.1††	3.4±2.1**$^{,\#\#}$	3.4±1.9**$^{,\#\#}$	0.0082	3.3±1.8†	3.7±2.6	3.9±2.7*	4.1±2.4**	0.043
HDL-C (mol/L)	1.4±0.47†	1.4±0.40††	1.6±0.52*$^{,\#\#}$	1.5±0.40	0.0188	1.5±0.41	1.6±0.51	1.4±0.37	1.5±0.49	n.s.
HbA1c (%)	6.9±1.1	6.4±1.0	5.5±1.1	5.4±1.0	n.s.	5.6±1.2	6.5±1.1	6.3±1.0	5.8±1.6	n.s.
Crn (mg/dL)	0.96±0.90†	0.85±0.26†	0.78±0.31*$^{,\#}$	0.80±0.28*	0.0117	0.83±0.28	0.79±0.29	0.90±0.83	0.87±0.47	n.s.
UA (mg/dL)	5.8±1.3$^{\#,\dagger\dagger}$	5.4±1.4*	5.3±1.3**	5.2±1.3**	0.0042	5.4±1.3	5.4±1.4	5.4±1.3	5.6±1.4	n.s.
BMI (kg/m^2)	25.0±3.8$^{\#,\dagger\dagger}$	24.2±3.4*	24.0±3.2**	23.7±3.1**	0.0025	23.7±2.8†	23.7±3.2†	24.5±3.3*$^{,\#}$	24.9±4.0**$^{,\#\#}$	0.0011

	Reactive hyperemia					PWV				
	Quartile				*p* value	Quartile				*p* value
	1st	2nd	3rd	4th		1st	2nd	3rd	4th	
Number	169	169	170	168		169	173	164	170	
Sex (% male)	49.1	49.1	61.2	60.1	n.s.	59.8	50.9	50.0	58.8	n.s.
Age (years old)	65±12$^{\#,\dagger\dagger}$	61±12*	60±12**	61±12*	0.0140	54±13$^{\#\#,\dagger\dagger}$	60±10**,††	65±10**$^{,\#\#}$	68±9**$^{,\#\#,\dagger\dagger}$	<0.0001
DM (*n* (%))	34 (20)	41 (24)	37 (22)	27 (16)	n.s.	28 (17)	42 (24)	36 (22)	42 (25)	n.s.
HL (*n* (%))	90 (53)	94 (59)	105 (62)	89 (53)	n.s.	90 (53)	101 (58)	98 (60)	85 (50)	n.s.
SBP (mmHg)	143±18	140±18	140±18	138±17*	<0.0001	136±14$^{\#,\dagger}$	140±16*	140±18*	144±21**,†	0.0004
DBP (mmHg)	83±12	83±12	83±12	82±10	n.s.	84±10††	84±12†	81±12*$^{,\#}$	83±12	0.0456
HR (mmHg)	67±11	65±13	67±10	70±12*$^{,\#\#,\dagger}$	0.0122	69±10	68±13	66±11	68±10	n.s.
TC (mol/L)	5.3±0.94	5.4±0.96	5.4±0.86	5.1±0.85*$^{,\#\#,\dagger}$	0.0120	5.4±0.93	5.3±0.88	5.4±0.87	5.3±0.86	n.s.
TG (mol/L)	4.1±2.5	3.5±1.9	3.6±1.9	3.9±3.0	n.s.	4.0±2.9	3.7±2.1	3.6±2.4	3.7±2.3	n.s.
HDL-C (mol/L)	1.4±0.41	1.5±0.40	1.5±0.53	1.5±0.47	n.s.	1.6±0.51	1.5±0.42	1.5±0.40	1.4±0.44	n.s.
HbA1c (%)	5.6±1.1	5.6±1.4	6.7±1.1	6.7±1.2	n.s.	6.4±1.0	6.5±1.0	5.6±1.2	5.8±1.5	n.s.
Crn (mg/dL)	0.82±0.30	0.81±0.32	0.84±0.35	0.88±0.44	n.s.	0.78±0.20	0.85±0.84	0.84±0.44	0.91±0.31	n.s.
UA (mg/dL)	5.5±1.4	5.4±1.4	5.6±1.3	5.4±1.3	n.s.	5.4±1.2	5.5±1.4	5.4±1.4	5.5±1.4	n.s.
BMI (kg/m^2)	24.3±3.4	24.4±3.3	24.6±3.2	23.6±3.6	n.s.	24.1±3.7	24.4±3.4	24.5±3.0	23.8±3.5	n.s.

*p<0.05, **p<0.01 *vs*. 1st; $^{\#}p$<0.05, $^{\#\#}p$<0.01 *vs*. 2nd; $^{\dagger}p$<0.05, $^{\dagger\dagger}p$<0.01 *vs*. 3rd. DM, diabetes mellitus; HL, hyperlipidemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; HbA1c, hemoglobin A1c; Crn, serum creatinine; UA, uric acid; BMI, body mass index; PWV, pulse wave velocity.

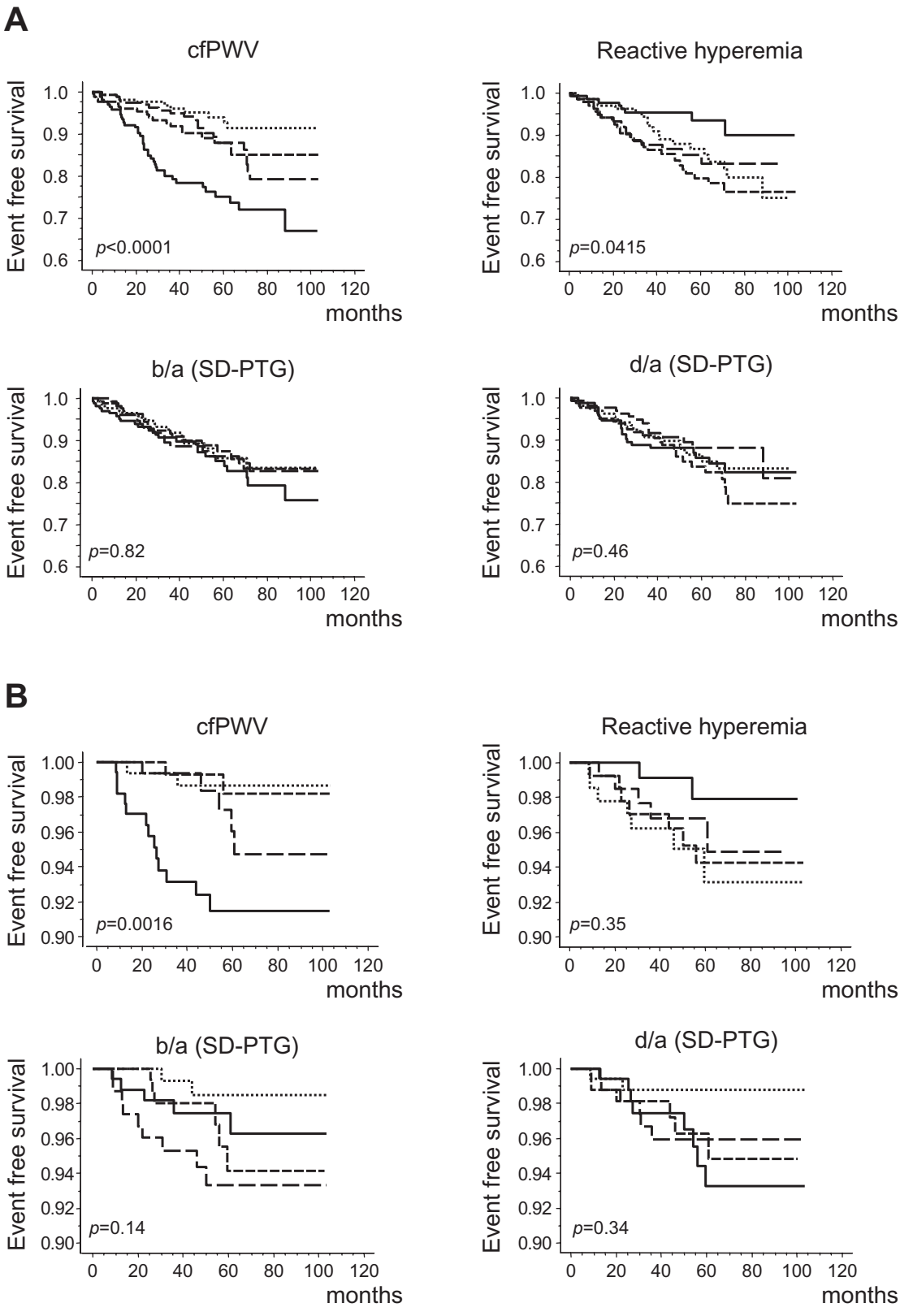

Fig. 2. *Results of Study 1. A: Kaplan-Meier analysis for stroke and cardiovascular diseases. B: Kaplan-Meier analysis for total mortality. ..... , 1st quartile; - - - - - , 2nd quartile; — — — , 3rd quartile; ——— , 4th quartile.*

Table 4. Cox Proportional Hazard Analysis Confounding with Common Risk Factors in Study 1

	b/a			d/a		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Gender (F)	1.100	0.659–1.835	0.7152	1.096	0.665–1.805	0.7192
Age (/10 years)	1.570	1.229–2.007	0.0003	1.575	1.244–1.993	0.0002
DM	1.357	0.804–2.290	0.2523	1.276	0.765–2.128	0.3508
HL	1.296	0.809–2.077	0.2807	1.348	0.845–2.150	0.2107
Current smoking	1.924	1.155–3.206	0.0120	2.003	1.209–3.319	0.0070
Crn (/mg/dL)	1.734	1.351–2.224	<0.0001	1.728	1.348–2.215	<0.0001
SBP (/mmHg)	1.013	0.997–1.029	0.1218	1.015	0.990–1.032	0.0641
DBP (/mmHg)	0.993	0.966–1.021	0.6180	0.989	0.962–1.017	0.4354
Evaluation			0.9441			0.3576
2nd quartile	0.827	0.448–1.528	0.5445	0.821	0.429–1.572	0.5522
3rd quartile	0.942	0.497–1.786	0.8558	0.572	0.284–1.154	0.1188
4th quartile	0.947	0.460–1.949	0.8815	0.976	0.534–1.784	0.9366

	Reactive hyperemia			PWV		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Gender (F)	1.235	0.693–2.202	0.4737	1.133	0.689–1.863	0.6218
Age (/10 years)	1.430	1.104–1.851	0.0067	1.361	1.056–1.755	0.0174
DM	1.424	0.816–2.485	0.2132	1.267	0.767–2.092	0.3556
HL	1.220	0.738–2.017	0.4388	1.417	0.885–2.269	0.1464
Current smoking	1.877	1.071–3.291	0.0278	1.776	1.067–2.954	0.0270
Crn (/mg/dL)	1.368	0.723–2.588	0.3354	1.730	1.353–2.212	<0.0001
SBP (/mmHg)	1.008	0.990–1.026	0.3854	1.009	0.994–1.025	0.2448
DBP (/mmHg)	0.996	0.967–1.026	0.8077	0.997	0.970–1.024	0.8168
Evaluation			0.1457			0.0742
2nd quartile	1.030	0.552–1.924	0.9250	1.751	0.747–4.106	0.1976
3rd quartile	0.968	0.518–1.810	0.9187	1.571	0.666–3.706	0.3022
4th quartile	0.416	0.184–0.942	0.0354	2.717	1.174–6.289	0.0196

F, female; RR, relative risk; CI, confidence interval; DM, diabetes mellitus; HL, hyperlipidemia; Crn, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity.

patients in the highest quartile of PWV was significantly lower than that in patients in the 1st quartile ($p<0.0001$; relative risk=4.477; 95% CI: 2.234–8.973), 2nd quartile ($p=0.0031$; relative risk=2.261; 95% CI: 1.306–3.913) and 3rd quartile ($p=0.0023$; relative risk=2.236; 95% CI: 1.303–3.836). The event-free survival of reactive hyperemia was significantly distributed ($p=0.0415$) and that in patients in the highest quartile of reactive hyperemia was significantly higher than that in patients in the 1st quartile ($p=0.0037$; relative risk=0.429; 95% CI: 0.189–0.976), 2nd quartile ($p=0.0322$; relative risk=0.329; 95% CI: 0.149–0.724) and 3rd quartile ($p=0.0456$; relative risk=0.413; 95% CI: 0.181–0.943); however, there was no difference among quartiles in b/a and d/a.

Figure 2B shows the results of the Kaplan-Meier analysis for total mortality. The event-free survival of PWV was significantly distributed by log-rank test ($p=0.0016$), and that in patients with the highest quartile of PWV was significantly lower than that in patients in the 1st quartile ($p=0.0042$; relative risk=6.675; 95% CI: 1.506–29.584) and 2nd quartile ($p=0.0038$; relative risk=2.564; 95% CI: 2.234–8.973); however, there was no difference in reactive hyperemia or b/a and d/a.

We also performed Cox proportional hazards model analysis for stroke and CVD after adjusting for common risk factors, such as gender, age, current smoking, presence of diabetes and hyperlipidemia, systolic and diastolic blood pressure and serum creatinine (Table 4). In the non-invasive evaluations of arterial functional changes, the fourth quartile value of PWV (relative risk=2.717; 95% CI: 1.174–6.289; $p=0.0196$) emerged as an independent risk factor along with age (per 10 years) (relative risk=1.361; 95% CI: 1.056–1.755; $p=0.0174$), current smoking (relative risk=1.776; 95% CI: 1.067–2.954; $p=0.0270$) and serum creatinine (relative risk=1.730; 95% CI: 1.353–2.212; $p<0.0001$). Moreover, the fourth quartile value of reactive hyperemia (relative risk=0.416; 95% CI: 0.184–0.942; $p=0.0354$) emerged as an independent risk factor along with age (per 10 years) (relative

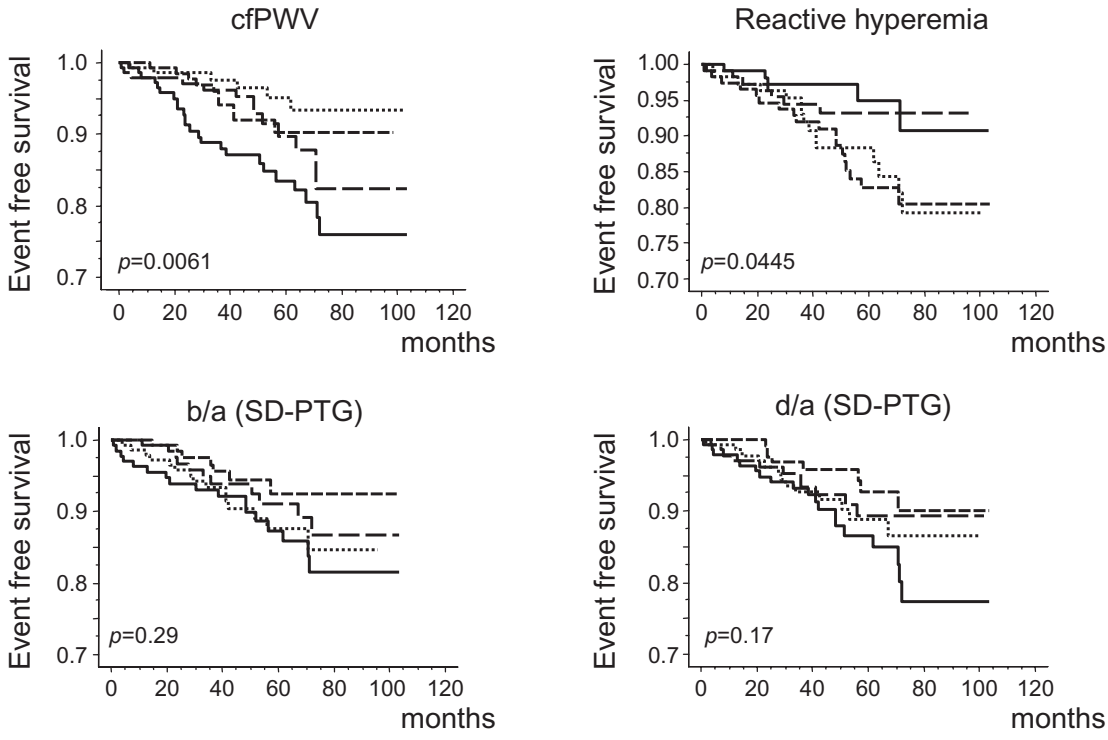

Fig. 3. *Results of Study 2. Kaplan-Meier analysis for stroke and cardiovascular diseases. ..... , 1st quartile; _ _ _ _ _ , 2nd quartile; _ _ _ , 3rd quartile; ____ , 4th quartile.*

risk=1.430; 95% CI: 1.104–1.851; $p=0.0067$) and current smoking (relative risk=1.877; 95% CI: 1.071–3.291; $p=0.0278$).

Results of Study 2

To clarify the influence of each arterial evaluation on adverse events in hypertensive patients, we excluded patients with a history of stroke and/or CVD (Fig. 1). By the time of the follow-up survey, 36 of the 558 patients had suffered from stroke, 21 of the 558 patients had suffered from CVD, and 8 of the 558 patients had died. Figure 3 shows the results of the Kaplan-Meier analysis for occurrence of stroke and CVD. The event-free survival of PWV was significantly distributed by log-rank test ($p=0.0061$), and that in patients with the highest quartile of PWV was significantly lower than that in patients in the 1st quartile ($p=0.0001$; relative risk=4.665; 95% CI: 1.991–10.928), 2nd quartile ($p=0.0074$; relative risk=2.526; 95% CI: 1.250–5.105) and 3rd quartile ($p=0.0061$; relative risk=2.563; 95% CI: 1.267–5.181). The event-free survival of reactive hyperemia was significantly distributed ($p=0.0445$) and that in patients with the highest quartile of reactive hyperemia was significantly higher than that in patients in the 1st quartile ($p=0.0221$; relative risk=0.321; 95% CI: 0.117–0.885) and 3rd quartile ($p=0.0233$; relative risk=0.324; 95% CI: 0.119–0.879). There was no difference in the distribution in b/a and d/a; however, the event-free survival in patients in only the highest quartile of d/a was significantly lower than that in patients in the 1st quartile ($p=0.0317$; relative risk=2.412; 95% CI: 1.056–5.510). By the Kaplan-Meier analysis for total mortality, we could not find any significant distribution (data not shown).

We also performed Cox proportional hazards model analysis for stroke and CVD after adjusting for common risk factors, such as gender, age, current smoking, presence of diabetes and hyperlipidemia, systolic and diastolic blood pressure and serum creatinine (Table 5). In the non-invasive evaluations of arterial functional changes, only the highest quartile value of PWV (relative risk=4.152; 95% CI: 1.341–7.075; $p=0.0080$) emerged as independent risk factors along with age (per 10 years) (relative risk=1.407; 95% CI: 1.027–1.927; $p=0.0337$) and presence of hyperlipidemia (relative risk=1.975; 95% CI: 1.054–3.702; $p=0.0337$).

Discussion

In the present study, we demonstrated that increased arterial stiffness as assessed by PWV contributes to increased incidence of stroke and CVD, and increased reactive hyperemia as evaluated by strain-gauge plethysmography contributes to decreased incidence of stroke and CVD in patients with essential hypertension independent of blood pressure and age.

The concept of using aortic stiffness to predict outcomes of

Table 5. Cox Proportional Hazard Analysis Confounding with Common Risk Factors in Study 2

	b/a			d/a		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Gender (F)	1.018	0.488–2.123	0.9616	1.022	0.495–2.110	0.9523
Age (/10 years)	1.568	1.140–2.157	0.0023	1.660	1.224–2.252	0.0011
DM	1.244	0.589–2.989	0.5667	1.126	0.538–2.356	0.7521
HL	1.601	0.858–2.989	0.1392	1.721	0.929–3.188	0.0845
Current smoking	1.928	0.972–3.823	0.0601	1.981	1.011–3.882	0.0465
Crn (/mg/dL)	1.369	0.389–4.820	0.6246	1.179	0.334–4.169	0.7977
SBP (/mmHg)	1.007	0.984–1.030	0.5567	1.009	0.986–1.033	0.4321
DBP (/mmHg)	1.018	0.979–1.059	0.3631	1.009	0.986–1.033	0.5025
Evaluation			0.7502			0.4257
2nd quartile	0.624	0.224–1.733	0.3652	1.790	0.738–4.342	0.1978
3rd quartile	0.672	0.287–1.575	0.3602	1.029	0.381–2.779	0.9556
4th quartile	0.839	0.405–1.738	0.6364	1.425	0.549–3.696	0.4669

	Reactive hyperemia			PWV		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Gender (F)	1.169	0.521–2.624	0.7050	1.093	0.535–2.234	0.8073
Age (/10 years)	1.500	1.085–2.074	0.0141	1.407	1.027–1.927	0.0337
DM	1.335	0.607–2.935	0.4724	1.111	0.548–2.251	0.7708
HL	1.599	0.836–3.058	0.1562	1.975	1.054–3.702	0.0337
Current smoking	1.835	0.874–3.852	0.1084	1.789	0.923–3.468	0.0849
Crn (/mg/dL)	0.867	0.215–3.495	0.8405	1.222	0.359–4.164	0.7484
SBP (/mmHg)	1.005	0.980–1.030	0.7058	1.002	0.981–1.025	0.8237
DBP (/mmHg)	1.016	0.976–1.058	0.4387	1.024	0.986–1.063	0.2168
Evaluation			0.0978			0.0492
2nd quartile	0.768	0.317–1.860	0.5583	2.010	0.689–5.860	0.2011
3rd quartile	1.490	0.694–3.197	0.3058	1.761	0.595–5.214	0.3067
4th quartile	0.422	0.151–1.182	0.1006	3.826	1.322–11.069	0.0133

F, female; RR, relative risk; CI, confidence interval; DM, diabetes mellitus; HL, hyperlipidemia; Crn, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity.

hypertensive patients is still evolving. Previous cohort studies for hypertensive patients have been performed in France (*4*, *12*). These reports suggested that increased arterial stiffness as measured by PWV showed a prognostic impact on CVD in treated hypertensive patients. In the Japanese population, PWV was reported to be an independent risk factor for CVD in patients with end-stage renal dysfunction (*13*). In the present study, we followed these results in Japanese hypertensive patients; moreover, we directly compared the prognostic impact of arterial functional changes evaluated by PWV, SDPTG, and reactive hyperemia in a cohort study. As there have been no clinical trials to directly assess the usefulness of atherosclerotic evaluations, there is still disagreement regarding the optimal methods for assessing arterial functional changes. Our data suggested that increased arterial stiffness measured by PWV showed strong predictive effects on total mortality and morbidity of stroke and CVD in Japanese hypertensive patients.

In addition, it was a risk factor for occurrence of stroke and CVD with higher reactive hyperemia and age, as analyzed by the Cox hazard model. Several reports evaluating the general population have indicated that decreased endothelially mediated vasodilatation of arteries has a prognostic impact on cardiovascular morbidity and mortality (*14*). Furthermore, a previous cross-sectional study indicated that increased aortic stiffness was associated with endothelial dysfunction. In the present study, reactive hyperemia values in the highest quartile of hypertensive patients improved the prognosis of stroke and CVD. We considered reactive hyperemia measured by strain-gauge plethysmography could not strictly evaluate "endothelial function," because this device evaluates vasodilator response to post-ischemic reactive hyperemia. Although the methodology differs from that in previous studies (*14*, *15*), the results from prior work support our data, indicating that reactive hyperemia also might be an independent prognostic factor for the occurrence of stroke and CVD. Recently, a number of different methods and devices for evaluating the biomechanical properties of the aorta and other large arteries

have become available. These methods may provide a more accurate and integrated picture of arterial stiffness. Therefore, to confirm the present results, further studies using a combination of techniques such as large and small artery compliance, stroke volume/pulse pressure, systemic arterial compliance, stiffness index, and augmentation index are needed (*16*).

Although several parameters measured by SD-PTG were related with aortic stiffness and peripheral reflections (*7*) and improved by antihypertensive therapy (*9*), the present study was the first to evaluate the predictive effects of the parameters b/a and d/a. We found that only the highest quartile of d/a was a significantly higher risk compared with the lowest quartile; however, we could not find any differences in b/a. Takazawa *et al*. (*7*) suggested that SD-PTG was reflected by peripheral arterial reaction, and b/a and d/a were significantly correlated with aging in a population study. We suspected that SD-PTG was not useful for predicting the effect on CVD in hypertensive patients, but that it might prove useful in a general population following a large cohort study in the future.

The present study suggested that PWV was more effective for predicting the risk of stroke and CVD in hypertensive patients than were SD-PTG and reactive hyperemia. Although we were unable to find a previous report establishing an upper or lower limit for PWV in a Japanese hypertensive population, a previous cohort study with a hypertensive population reported that the relative risk of developing CVD predicted by 1 SD of PWV (3.5 m/s) was 1.42 ($p<0.01$) (*17*), and that PWV in subjects who developed CVD events was 12.8±3.3 m/s, which was 1.3 m/s higher than that in subjects without CVD events. A French cohort study also revealed that the presence of a PWV of >13 m/s, taken alone, appeared to be a strong predictor of cardiovascular mortality with high performance values (*18*). According to our results, the mean value in the highest quartile of PWV was 11.24±1.05 m/s (range=10.05–16.00 m/s). Therefore, we suspected that a PWV of around 10.0 to 11.0 m/s constituted the lower limit for increased risk of strok and CVD.

Study Limitations

The present study had several limitations. First, this cohort study was hospital-based but not a multi-center study. To avoid study bias and confirm the present results, a larger cohort and multi-center trials are needed. Second, patients who enrolled in this study received many kinds of antihypertensive treatment, and some patients received statin therapy. Recent reports indicate that treatment with ACE inhibitors (*10*, *19*), ARBs (*20*) or statins (*21*) improves arterial stiffness. As a result, taking these medications could contribute to better effects on survival. Because these medications would affect the prognosis in hypertensive patients, further studies according to the type of medications are needed. For this reason, the ability to generalize the present results to patients with untreated hypertension may be limited. Third, patients with PWV values in the highest quartile were older and had higher systolic blood pressure in the present study. The previous study reported that age and the presence of high blood pressure were the determinants of accelerated progression of aortic stiffness in treated hypertensive subjects (*12*). These determinants would accelerate the progression of aortic stiffness during the follow-up period, resulting in a worse outcome. This limitation, however, does not concern the present conclusions, because PWV and age were accepted as independent risk factors, as shown by the Cox hazard model.

Conclusions

In patients with essential hypertension, higher arterial stiffness estimated by PWV was a better predictor of adverse outcome, whereas higher reactive hyperemia showed a weak correlation with a better outcome. These data support the desirability of increased use of PWV in the management of hypertensive patients in clinical practice; however, brachial-ankle PWV is widely used in Japan and is also an effective procedure. A a multi-center trial called the Japanese Trial on the Prognostic Implication of Pulse Wave Velocity (*22*) will begin soon, and may provide further data to support clinical PWV use in hypertensives. Furthermore, our results indicate that a reduction in arterial stiffness may be a desirable goal of hypertension management and that the stratification of hypertensive patients based on arterial stiffness level can improve hypertension treatment. Further research is needed to clarify the biologic basis of these observations.

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