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Elevated Brachial-Ankle Pulse Wave Velocity Is Associated with Left Ventricular Hypertrophy in Hypertensive Patients after Stroke

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Brachial-ankle pulse wave velocity (baPWV) is widely used as a marker of arterial stiffness, but there are no data regarding the usefulness of measuring baPWV in hypertensive patients after stroke. The purpose of this study was to examine the clinical significance of baPWV by assessing its correlation with echocardiographic parameters in hypertensive patients after stroke. The study enrolled 61 hypertensives after stroke (24 patients with cerebral infarction and 37 with cerebral hemorrhage) and 61 age-matched hypertensives without stroke. Left ventricular (LV) hypertrophy was evaluated by measuring LV mass index (LVMI) and relative wall thickness (RWT), and LV diastolic function was evaluated by measuring peak early mitral annular velocities (E′) using echocardiography. Concentric LV hypertrophy showing increased RWT (0.50 ± 0.12) was observed in hypertensives after stroke, but not in hypertensives without stroke. In hypertensives after stroke, elevated baPWV correlated with age ($r = 0.60$, $p < 0.001$), systolic blood pressure ($r = 0.56$, $p < 0.001$), increased LVMI ($r = 0.47$, $p < 0.001$), and decreased E′ ($r = -0.40$, $p = 0.002$). Multiple regression analysis showed that age (β coefficient = 0.43, $p < 0.001$), systolic blood pressure (β coefficient = 0.40, $p < 0.001$), and LVMI (β coefficient = 0.25, $p = 0.008$) were independent determinants of elevated baPWV. In conclusion, elevated baPWV is more closely associated with LV hypertrophy than with LV diastolic dysfunction. Elevated baPWV is independently associated with the severity of LV hypertrophy adjusted with systolic blood pressure and age in hypertensive patients after stroke.

Keywords: hypertension; stroke; brachial-ankle pulse wave velocity; echocardiography; left ventricular hypertrophy
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It is well known that increased arterial stiffness is an independent risk factor for cardiovascular diseases, including heart diseases and stroke (Laurent et al. 2001; London and Cohn 2002; Safar et al. 2003). Recently, brachial-ankle pulse wave velocity (baPWV) has become widely used as a marker of arterial stiffness in clinical settings (Yamashina et al. 2002; Liu et al. 2005, 2006). Several studies have demonstrated that elevated baPWV is a clinically useful marker for diagnosing the presence and prognosis of heart diseases, including coronary artery diseases (Tomiyama et al. 2005; Saito et al. 2008; Xu et al. 2008; Meguro et al. 2009). However, there are no data regarding the usefulness of measuring baPWV in cerebrovascular diseases. In particular, the clinical usefulness of baPWV in hypertensive patients after stroke has not been elucidated.

It is well known that left ventricular hypertrophy as well as elevated baPWV is a risk factor for cardiovascular diseases in hypertensive patients (Levy et al. 1990; Verdecchia et al. 1998). However, the relationship between baPWV and left ventricular hypertrophy is still controversial. Previous studies (Masugata et al. 2005; Nakae et al. 2008; Wang et al. 2009) have shown a close correlation between baPWV and left ventricular diastolic function assessed by echocardiography. However, left ventricular hypertrophy did not show a close correlation with baPWV in these studies. The purpose of this study was to elucidate the clinical significance of baPWV by assessing its correlation with clinical and echocardiographic parameters of left

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ventricular hypertrophy and function in hypertensive patients who have had a stroke.

Methods

Subjects and protocol

The present study enrolled 61 hypertensive patients (60 ± 8 years) who had had a stroke and who had visited the outpatient clinic of the Kagawa General Rehabilitation Center between April 2008 and October 2009. The hypertensive patients with stroke consisted of 24 hypertensive patients with cerebral infarction and 37 with cerebral hemorrhage. Although all hypertensive patients with stroke had a history of stroke at least one month prior to the study, their condition with regard to stroke was stable during their participation in the study. The study also included age-matched hypertensive patients who had never had a stroke (hypertensives without stroke group: 60 ± 8 years) for the comparison of echocardiographic findings. Hypertension was defined as having a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. The study subjects visited the outpatient clinic of Kagawa General Rehabilitation Center for rehabilitative treatment for stroke and/or treatment of hypertension, and underwent routine echocardiography for cardiac assessment in order to screen for cardiac diseases. None of the patients were diagnosed with cardiac disease, and no overt heart failure was found. None of the hypertensive patients with stroke had a history of any atherosclerotic cardiovascular diseases except stroke. This study excluded patients with cerebral embolism, which was diagnosed by brain magnetic resonance imaging or clinical findings. This study also excluded patients with atrial fibrillation and/or peripheral arterial disease, which may have affected the exact measurements of baPWV. Blood pressure was determined in the outpatient clinic using the conventional cuff method. Echocardiography and blood sampling were performed in the morning after a 12-hour overnight fast. Plasma total cholesterol, triglyceride, and HbA1c were measured by standard laboratory techniques. After echocardiographic and blood examination, arterial stiffness was assessed by measuring brachial-ankle pulse wave velocity (baPWV). This protocol was approved by the Ethics Committee of Kagawa University. Informed consent was obtained from all participants.

Echocardiographic examination

Two-dimensional and M-mode echocardiography was performed using an echocardiographic instrument (Vivid Seven System; GE, Horten, Norway). We first measured the following left ventricular (LV) structural parameters by M-mode echocardiography: the ventricular septal thickness at the chordae tendineae level (VS), the left ventricular end-diastolic dimension at the chordae tendineae level (LVDd), the left ventricular posterior wall thickness at the chordae tendineae level (PW), the dimensions of the ascending aorta (AO), and the end-systolic dimension of the left atrium (LAD). The LV mass was calculated according to the American Society of Echocardiography conventions (Wallerson and Devereux 1987) using the following equation: LV mass = 0.80 [1.04 × (PW + VS + LVDd)^3 – (LVDd)^3] + 0.6. The LV mass index was calculated as the LV mass divided by the body surface area. The relative wall thickness (RWT) was also calculated in order to assess the morphology of LV hypertrophy using the following equation: RWT = (VS + PW)/LVDd. The left ventricular ejection fraction (LVEF) was estimated by Teichholz's method (Teichholz et al. 1976) and was used as the parameter of left ventricular systolic function.

We next measured the parameters of LV diastolic function by recording the conventional transmitral flow velocity using pulsed Doppler echocardiography (Nishimura and Tajik 1997). The conventional transmitral flow velocity was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. The peak early transmitral flow velocity (E velocity) and the peak late transmitral flow velocity (A velocity) were recorded, and the ratio of E to A (E/A ratio) was calculated. The deceleration time of E velocity (DcT) was measured as the time interval from the E-wave peak to the decline of the velocity to its baseline value.

Pulsed wave tissue Doppler imaging (TDI) was performed by activating the TDI function on the same machine. The sample volume was located at the septal side of the mitral annulus. Peak early (E´) and late (A´) diastolic mitral annulus velocities and the ratio of the early to late peak velocities (E´/A´) were obtained. In addition, the ratio of the E velocity to E´ velocity (E/E´) was calculated. It is well known that the mitral annulus velocity determined by TDI is a relatively preload-independent variable and is superior to conventional transmitral flow velocity for the early diagnosis of many heart diseases (Nikitin and Witte 2004).

Measurement of Pulse Wave Velocity

Brachial-ankle pulse wave velocity (baPWV) was measured using an automatic waveform analyzer (Form/ABI; Omron-Colin Co., Ltd., Komaki, Japan). Details of the methodology have been described elsewhere (Yamashina et al. 2002; Tomiyama et al. 2003). Measurements were taken with subjects lying in a supine position after resting for at least 5 minutes. Electrocardiographic electrodes were placed on both wrists, and cuffs were wrapped on the bilateral brachia and ankles. Pulse volume waveforms at the brachium and ankle were recorded using a semiconductor pressure sensor. The baPWV values on the right and left sides were determined, and the left and right values were averaged for the analysis in this study. It is well known that the baPWV increases with advancing age. Thus, the elevation of baPWV above normal values was assessed by calculating the difference between the measured baPWV of the patients in this study and the mean values of baPWV in age-matched normal subjects. The normal data were provided by a previous study (Tomiyama et al. 2003) of 12,400 normal subjects. The exclusion criteria of the previous study performed by Tomiyama et al. (2003) were same as those of the present study.

Statistical analysis

Data are expressed as the means ± s.d. Statistical analysis was performed with SPSS/Windows, version 11.5J (SPSS, Chicago, IL). Categorical variables were compared by the chi-square test. For the comparison of mean values between the two groups, the unpaired Student's *t*-test was used. Dichotomous data are presented as frequencies for background variables. Linear regression analysis was performed to evaluate the association between the baPWV and other variables. Step-wise multiple regression analysis was performed to determine the correlation between the baPWV and each independent variable. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Clinical and echocardiographic characteristics of subjects

The clinical and echocardiographic parameters of the

Table 1. Clinical and Echocardiographic Characteristics of Subjects.

	Hypertensives without stroke	Hypertensives with stroke
Number (male/female)	61 (49/12)	61 (49/12)
Time from stroke onset (months)	–	59 ± 65
Age (years)	60.1 ± 8.2	60.1 ± 8.2
BMI (kg/m^2)	22.5 ± 2.4	22.6 ± 2.5
Diabetes mellitus (*n* (%))	6 (10 %)	7 (11 %)
Dyslipidemia (*n* (%))	20 (33 %)	19 (31 %)
Antihypertensive drugs		
ARB/ACEI (*n* (%))	45 (74 %)	49 (80 %)
CCB (*n* (%))	47 (77 %)	46 (75 %)
β-blockers (*n* (%))	5 (8 %)	5 (8 %)
Systolic BP (mmHg)	126 ± 15	124 ± 18
Diastolic BP (mmHg)	75 ± 8	76 ± 10
Heart rate (beats/min)	68 ± 10	67 ± 11
Total cholesterol (mg/dL)	189 ± 31	186 ± 29
HDL cholesterol (mg/dL)	55 ± 12	54 ± 11
Triglycerides (mg/dL)	126 ± 59	128 ± 56
HbA1c (%)	5.4 ± 0.7	5.5 ± 0.6
Echocardiographic parameters		
LV structural parameters		
LVMI (g/m^2)	105 ± 19	109 ± 35
RWT	0.44 ± 0.09	0.50 ± 0.12**
LAD (mm)	35.5 ± 3.9	37.0 ± 6.8
AO (mm)	31.8 ± 5.6	33.7 ± 3.5
LV functional parameters		
LVEF (%)	71 ± 6	72 ± 7
E (cm/s)	63 ± 14	48 ± 12***
A (cm/s)	75 ± 15	64 ± 12***
E/A	0.85 ± 0.19	0.77 ± 0.20*
DcT (msec)	199 ± 67	203 ± 43
E´ (cm/s)	7.7 ± 1.6	6.1 ± 1.3***
A´ (cm/s)	10.0 ± 1.5	10.4 ± 1.4
E´/A´	0.78 ± 0.19	0.60 ± 0.14***
E/E´	8.4 ± 2.1	8.0 ± 1.3
baPWV (cm/s)	–	1548 ± 258
Elevation of baPWV above normal values (cm/s)	–	215 ± 211

BMI, body mass index; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blockers; BP, blood pressure; HDL, high-density lipoprotein; LV, left ventricular; LVMI, left ventricular mass index; RWT, relative wall thickness; LAD, left atrial dimension; AO, dimension of ascending aorta; LVEF, left ventricular ejection fraction; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A, the ratio of E to A; DcT, deceleration time of early diastolic transmitral flow; E´, peak early diastolic annular velocity; A´, peak late diastolic annular velocity; E´/A´, the ratio of E´ to A´; E/ E´, the ratio of E to E´; baPWV, brachial-ankle pulse wave velocity. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. hypertensives without stroke.

study subjects are summarized in Table 1. There were no significant differences in age, gender, or body mass index between the patients with and without stroke. There were also no significant differences in the proportion of patients with diabetes or dyslipidemia, or in the results of blood examination between the two groups. Finally, there were no significant differences in heart rate, blood pressure, or the percentage of patients using antihypertensive medication between the groups. The time interval from the stroke onset to the participation in this study was 59 ± 65 months in the hypertensives with stroke. All patients had hypertension, but the mean systolic blood pressure of the subjects

was not particularly high (126 ± 15 and 124 ± 18 mmHg in hypertensive patients without and with stroke, respectively) because the blood pressure of hypertensive patients was well controlled by medication. Although there were no significant differences in LVMI between the two groups, the RWT was significantly larger in hypertensives with stroke (0.50 ± 0.12) than those without stroke (0.44 ± 0.09) ($p < 0.01$). The increased mean RWT indicated the presence of LV concentric hypertrophy in the hypertensives with stroke. In addition, E, E/A, E´, and E´/A´ were significantly lower in hypertensives with stroke (48 ± 12 cm/s, 0.77 ± 0.20, 6.1 ± 1.3 cm/s, and 0.60 ± 0.14, respectively) than those without stroke (63 ± 14 cm/s, 0.85 ± 0.19, 7.7 ± 1.6 cm/s, and 0.78 ± 0.19, respectively) ($p < 0.001$, $p < 0.05$, $p < 0.001$, and $p < 0.001$, respectively). The decreased mean E/A and E´ in hypertensives with stroke indicated LV diastolic dysfunction accompanying the LV concentric hypertrophy. The elevation of baPWV above normal values, i.e., the difference between the measured baPWV of the hypertensives with stroke and the mean value of baPWV in age-matched normal subjects, was considerably high (215 ± 211 cm/s). The measured baPWV of hypertensives (1548 ± 258 cm/s) with stroke was significantly higher than that of age-matched normal subjects (1333 ± 109 cm/s) ($p < 0.001$). There were no significant differences in the measured baPWV between the two types of stroke, which were cerebral infarction (1574 ± 262 cm/s) and hemorrhage (1531 ± 257 cm/s).

Association between baPWV and other variables in hypertensives with stroke

Linear regression analysis was performed to examine the relationship between baPWV and other variables in hypertensives with stroke (Table 2). Elevated baPWV was correlated with age ($r = 0.604$, $p < 0.001$), systolic blood pressure ($r = 0.559$, $p < 0.001$), diastolic blood pressure ($r = 0.282$, $p = 0.028$), LVMI ($r = 0.471$, $p < 0.001$), E ($r = –0.265$, $p = 0.039$), E/A ($r = –0.254$, $p = 0.048$), E´ ($r = –0.396$, $p = 0.002$), and A´ ($r = –0.358$, $p = 0.005$). Among the echocardiographic parameters, the correlation of baPWV to LVMI was closer than those to E, E/A, E´, and A´.

Assessment of the factors related to baPWV in hypertensives with stroke

Stepwise multiple regression analysis was performed to identify which clinical and echocardiographic parameters were independently associated with elevated baPWV in hypertensives with stroke. Stepwise multiple regression analysis was performed for the parameters that showed significant correlation with elevated baPWV in the linear regression analysis in Table 2 and the antihypertensive drugs in Table 1. This analysis indicated that age (β coefficient = 0.432, $p < 0.001$), systolic blood pressure (β coefficient = 0.404, $p < 0.001$), and LVMI (β coefficient = 0.247, $p = 0.008$) were independently associated with baPWV (Table 3). Thus, among the echocardiographic parameters, only LVMI was independently associated with elevated baPWV. The antihypertensive drugs were not selected as independent determinants of baPWV.

Table 2. Correlation Coefficients of Linear Regression Analysis between baPWV and Other Parameters in Hypertensives with Stroke.

	r	*p* value
Age	0.604	< 0.001
Time from stroke onset (months)	0.138	NS
BMI	–0.029	NS
Systolic BP	0.559	< 0.001
Diastolic BP	0.282	0.028
Heart rate	0.060	NS
Total cholesterol	–0.084	NS
HDL cholesterol	–0.101	NS
Triglycerides	–0.112	NS
HbA1c	–0.009	NS
Echocardiographic parameters		
LV structural parameters		
LVMI	0.471	< 0.001
RWT	0.246	NS
LAD	0.073	NS
AO	0.027	NS
LV functional parameters		
LVEF	–0.198	NS
E	–0.265	0.039
A	0.082	NS
E/A	–0.254	0.048
DcT	0.111	NS
E´	–0.396	0.002
A´	–0.358	0.005
E´/A´	–0.105	NS
E/E´	0.100	N

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LV, left ventricular; LVMI, left ventricular mass index; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; AO, dimension of ascending aorta; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A, the ratio of E to A; DcT, deceleration time of early diastolic transmitral flow; E´, peak early diastolic annular velocity; A´, peak late diastolic annular velocity; E´/A´, the ratio of E´ to A´; E/E´, the ratio of E to E´; NS, not significant.

Discussion

The present study presents the data regarding the relationships between elevated baPWV and clinical and echocardiographic parameters in hypertensive patients after stroke. The data led us to the following conclusions: (1) even in well-controlled hypertensive patients after stroke attack, elevated baPWV suggesting increased arterial stiffness was observed; (2) among the echocardiographic

Table 3. Multiple Regression Analysis for baPWV and Related Parameters in Hypertensives with Stroke.

Independent variables	β coefficient	t value	p value
Age	0.432	4.831	< 0.001
Systolic BP	0.404	4.656	< 0.001
LVMI	0.247	2.769	0.008
	F ratio = 28.898	$r^2 = 0.603$	
	($p < 0.001$)		

baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; LVMI, left ventricular mass index.

parameters, the correlation of baPWV to LV mass index, which reflects LV hypertrophy, was closer than those of baPWV to parameters of LV diastolic function; and (3) among the echocardiographic parameters, LV mass index, which reflects LV hypertrophy, was the only independent predictor of baPWV.

The elevated baPWV in hypertensive patients after stroke in this study indicates that increased arterial stiffness persists after stroke in hypertensive patients even if their hypertension is well controlled by antihypertensive treatment. Previous studies (Tomiyama et al. 2003; Hashimoto et al. 2005) have demonstrated that baPWV correlates with age and blood pressure in subjects without cardiovascular diseases. Although the present study also showed that baPWV correlated with age and blood pressure (Table 2), our data provide new information regarding baPWV in hypertensive patients after stroke. The most striking result of our data is that baPWV can predict the severity of LVH adjusted by systolic blood pressure and age in hypertensive patients after stroke. The morphological feature of LV hypertrophy (i.e., concentric LV hypertrophy) observed in hypertensive patients after stroke may have led to the significant association between baPWV and LV hypertrophy in the present study. The elevated baPWV in hypertensive patients after stroke indicates the importance of continuing antihypertensive treatment for improving arterial stiffness in order to prevent the recurrence of stroke. Previous studies (Laurent et al. 2003; Mattace-Raso et al. 2006) have shown that increased arterial stiffness confers a risk of stroke. However, there are no data regarding arterial stiffness assessed by baPWV in stroke patients. Furthermore, there are no studies demonstrating alterations of arterial stiffness during antihypertensive treatment after stroke. In the present study, baPWV did not correlate with the time interval between the stroke onset and the participation in this study (Table 2). However, the present study was a cross-sectional study, and thus could not show the cerebrovascular outcomes after the first attack of stroke. It is important to clarify whether baPWV values independently contribute to the prediction of recurrent stroke. Therefore, a further follow-up study is needed to clarify the effects of anti-hypertensive treatment on arterial stiffness in stroke patients.

In the present study, the correlation of elevated baPWV to LVMI, which reflects LV hypertrophy, was closer than those of baPWV to LV diastolic functional parameters such as E, E/A, E´, and A´. Previous studies (Masugata et al. 2005; Nakae et al. 2008; Wang et al. 2009) have shown a close association between arterial stiffness assessed by baPWV and LV diastolic function assessed by echocardiography. In these studies, LV hypertrophy did not show a close correlation with arterial stiffness assessed by baPWV. We can not determine the precise reason why the data in the present study differed from those of the previous studies (Masugata et al. 2005; Nakae et al. 2008; Wang et al. 2009). One possible explanation is the difference in participants between the present study and previous studies (Masugata et al. 2005; Nakae et al. 2008; Wang et al. 2009). In the present study, concentric LV hypertrophy showing increased RWT was observed in hypertensive patients after stroke, but not in hypertensive patients without stroke. This morphological feature of LV hypertrophy in hypertensives after stroke may have led to the result that baPWV was more significantly associated with LV hypertrophy rather than with LV diastolic dysfunction.

The data in the present study indicate that hypertensive patients who have experienced a stroke and have elevated baPWV may be more likely to have LV hypertrophy. It is well known that LV hypertrophy is a risk factor for cardiovascular events in hypertensive patients (Levy et al. 1990; Verdecchia et al. 1998). Therefore, our data suggest that hypertensive patients who have had a stroke and have elevated baPWV should be carefully examined for LV hypertrophy, and those found to have LV hypertrophy should be intensively treated with antihypertensive drugs. Thus, measuring baPWV in hypertensive patients after stroke is clinically useful for detecting LV hypertrophy. However, a further follow-up study is needed to examine the changes in LV hypertrophy under antihypertensive treatment, since the present study was a cross-sectional study. There were no differences in the measured baPWV between the two types of stroke, i.e., cerebral infarction (1574 ± 262 cm/s) and hemorrhage (1531 ± 257 cm/s). However, the number of study subjects may have been too small to reach a conclusion about the levels of arterial stiffness associated with different types of stroke.

In conclusion, baPWV was more closely associated

with LV hypertrophy than with LV diastolic dysfunction in hypertensive patients who had experienced a stroke. Therefore, measuring baPWV in hypertensive patients after stroke is clinically useful to detect LV hypertrophy. Selecting antihypertensive drugs that reduce LV hypertrophy may be important for hypertensive patients who have had a stroke and show elevated baPWV.

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