ORIGINAL ARTICLE

Increased pulse wave velocity in patients with acute lacunar infarction doubled the risk of future ischemic stroke

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The aim of this study was to determine whether pulse wave velocity (PWV), a marker of vascular endothelial impairment and arteriosclerosis, predicts future ischemic stroke in patients who developed acute lacunar infarction. Patients with a first-ever ischemic stroke due to acute lacunar infarction were enrolled in this study. An oscillometric device (Form PWV/ABI; Omron Colin, Tokyo, Japan) was used to measure brachial–ankle PWV 1 week after stroke onset. Patients were followed for at least 5 years. The main end point of the study was recurrent ischemic stroke. Event-free survival was analyzed using Kaplan–Meier plots and log-rank tests. The risk of recurrent ischemic stroke was estimated using the Cox proportional-hazards model. Of the 156 patients (61% male, mean age: 69.2 ± 11.3 years) assessed in this study, 29 developed recurrent ischemic stroke. The median brachial–ankle PWV value was $20.4 \, \mathrm{m \, s^{-1}}$. Patients with high PWV values had a greater risk of recurrent ischemic stroke than patients with low PWV values (28% vs. 15%, $P = 0.08$). Kaplan–Meier curve analysis showed that patients with high PWV values had a less favorable (that is, free of recurrent ischemic stroke) survival time ($P = 0.015$). A multivariate Cox proportional-hazards model identified high PWV as an independent predictor of recurrent ischemic stroke after adjusting for age, sex and blood pressure (hazard ratio 2.35, 95% confidence interval, 1.02–5.70, $P = 0.044$). In patients with acute lacunar infarction, a high PWV predicts a twofold greater risk of future ischemic stroke, independent of patient age, sex and blood pressure levels.
Hypertension Research (2017) 40, 371–375; doi:10.1038/hr.2016.157; published online 17 November 2016

INTRODUCTION

Arterial stiffness is an independent determinant of cardiovascular and cerebrovascular risks; it is also a marker of vascular endothelial impairment, arteriosclerosis and subclinical organ damage.[1–3] Arterial stiffness has been monitored using pulse wave velocity (PWV) parameters, such as carotid–femoral PWV,[4,5] brachial–ankle PWV[6–9] and cardio-ankle vascular index.[10,11] Although some methodological differences exist between these surrogate markers,[12,13] the significance of PWV assessment has been clarified.[1–3,14–16] Evidence of PWV indicates microvessel arteriosclerosis presenting with vascular endothelial dysfunction and can lead to cardiovascular disease,[1,3,16–20] stroke[2,21] and death.[1,3,22] Furthermore, cerebral small vessel diseases, such as silent lacunar infarction and white matter hyperintensities, pose a risk of cerebrovascular disease by affecting arterial stiffness.[3,14,17,23–25] Specifically, vascular narrowing due to atherosclerosis and worsening vascular stiffness can accelerate pulse waves[14] and may also increase the risk of ischemic stroke.

We have previously demonstrated the cross-sectional relationship between PWV and early neurological outcomes after ischemic stroke in patients who developed acute lacunar infarction, which is attributed to cerebral small vessel disease.[7] Although our findings align with those of previous studies,[5,26] the longitudinal neurological outcome (that is, whether PWV predicts recurrent ischemic stroke) has not been clarified. The aim of this study was to determine whether PWV predicts future ischemic stroke in patients who have developed acute lacunar infarction attributed to cerebral small vessel disease.

METHODS

Patients

Between October 2003 and March 2010, we enrolled consecutive patients with clinical lacunar stroke syndrome (within 48 h after stroke onset) who were admitted to the Department of Neurology, Hyogo Brain and Heart Center at Himeji (HBHC), Himeji, Japan. All patients had experienced a first-ever ischemic stroke owing to acute lacunar infarction. The cross-sectional analysis of these patients is described elsewhere.[7] This longitudinal observational study

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complied with the Declaration of Helsinki, and it was approved by the Institutional Review Board at the HBHC. Informed consent was obtained from all patients. This study is registered with the UMIN Clinical Trials Registry (UMIN000023239).

Baseline assessment

We assessed the following clinical parameters: (1) demographic data, such as age and sex, (2) vascular risk factors, (3) laboratory data, (4) brain imaging, (5) arteriosclerosis assessment, and (6) clinical outcomes. Using an oscillometric device (Form PWV/ABI; Omron Colin, Tokyo, Japan), we measured brachial–ankle PWV 1 week after the onset of stroke.[7] We

measured the common carotid artery intima-media thickness using high-resolution B-mode ultrasonography, with a 7.5-MHz linear array transducer (Aplio XG SSA-790A, Toshiba Medical, Tokyo, Japan).[9,11] Trained neurologists assessed the National Institutes of Health Stroke Scale scores upon patient admission and the modified Rankin Scale scores at discharge. Detailed information is provided in the Supplementary File and described elsewhere.[7]

Longitudinal assessment

Patients were followed for at least 5 years after the onset of stroke at their primary care physician's offices and/or at the HBHC. The study end points were all-cause mortality and recurrent ischemic stroke. Recurrent

Table 1 Characteristics of patients based on their brachial–ankle pulse wave velocity (PWV)

	Brachial–ankle PWV		
	High (⩾20.4 m s⁻¹, n = 78)	Low (<20.4 m s⁻¹, n = 78)	P-value
Demographics			
Female sex, n (%)	40 (51)	21 (27)	0.003
Age, years	76 (69–81)	63 (58–71)	<0.001
Body mass index, kg m^{-2}	22.5 (20.4–24.3)	23.3 (20.9–25.8)	0.141
Physical status			
Systolic blood pressure, mm Hg	162 (150–180)	164 (151–180)	0.989
Diastolic blood pressure, mm Hg	84 (78–97)	90 (80–101)	0.016
Pulse pressure, mm Hg	80 (66–92)	70 (65–86)	0.046
Heart rate, beat per min	72 (64–82)	72 (63–84)	0.681
NIHSS score on admission, points	3 (1–5)	2 (1–4)	0.082
Progressive neurological deficit, n (%)	38 (49)	14 (18)	<0.001
Risk factors			
Hypertension, n (%)	73 (94)	62 (79)	0.017
Diabetes mellitus, n (%)	29 (37)	21 (27)	0.230
Hypercholesterolemia, n (%)	42 (54)	39 (50)	0.749
Ischemic heart disease, n (%)	7 (9)	8 (10)	1.000
Smoking habit, n (%)	23 (29)	45 (58)	<0.001
Chronic kidney disease, n (%)	65 (83)	47 (61)	0.002
Laboratory data			
WBC, mm^3	6250 (5275–7325)	6100 (5200–7125)	0.510
CRP, mg dl^{-1}	0.1 (0–0.23)	0.1 (0–0.20)	0.707
Serum creatinine, mg dl^{-1}	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.831
eGFR, ml min^{-1} 1.73 m^{-2}	43.4 (34.8–50.6)	54.8 (41.1–68.2)	<0.001
Blood glucose, mg dl^{-1}	127 (108–165)	115 (103–150)	0.194
Brain imaging			
Infarct size on DWI ⩾15 mm, n (%)	26 (33)	19 (24)	0.289
Infarct slice number ⩾3, n (%)	49 (63)	31 (40)	0.004
Silent lacunar infarct, n (%)	54 (69)	31 (40)	<0.001
White matter hyperintensities, n (%)	62 (79)	36 (46)	<0.001
Assessment of arteriosclerosis			
CCA-IMT, mm	1.3 (1.1–1.6)	1.2 (1.0–1.5)	0.027
Ankle–brachial index	1.10 (1.04–1.19)	1.13 (1.08–1.17)	0.233
Clinical outcomes			
mRS 0–1 at discharge, n (%)	29 (37)	51 (65)	<0.001
mRS 4–5 at discharge, n (%)	28 (36)	12 (15)	0.006
All-cause mortality, n (%)	18 (23)	10 (13)	0.143
Recurrent ischemic stroke, n (%)	20 (26)	9 (12)	0.038

Abbreviations: CCA-IMT, common carotid artery intima-media thickness; CRP, C-reactive protein; DWI, diffusion-weighted imaging; eGFR, estimated glomerular filtration rate; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; PWV, pulse wave velocity; WBC, white blood cell count.
Data are shown as the median and interquartile range or as the number of patients and percentage.
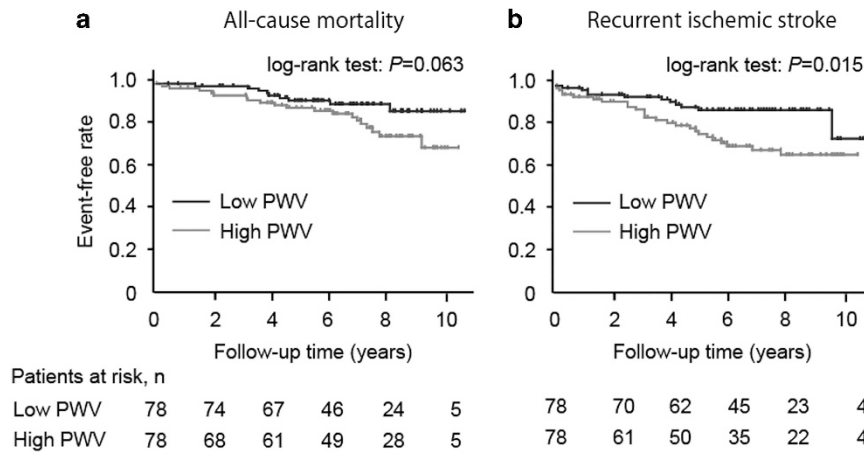
Figure 1 Kaplan–Meier survival curve estimates of the risk of (a) all-cause mortality and (b) recurrent ischemic stroke associated with pulse wave velocity.

ischemic stroke subtypes were categorized as atherothrombotic (large-artery atherosclerosis), cardioembolism, lacunar (small-artery occlusion) and other causes attributed to undetermined etiology or other determined etiology.[27] Patients were thoroughly assessed using multiple concurrent approaches, including reviewing the HBHC hospital medical records, contacting the patients and their families for telephone interviews and contacting their primary care physicians using a standardized interview form. The longitudinal assessment ended in March 2015.

Statistical analysis

Continuous, ordinal and categorical variables were compared using unpaired Student's t-tests, Wilcoxon rank-sum tests and χ^2 tests, respectively. First, we compared the PWV values of the patients who developed recurrent ischemic stroke and those who did not. Second, we divided the patients into two groups, according to their PWV values (high vs. low compared with the median PWV value), and we compared their clinical characteristics. Third, an event-free survival analysis was performed using Kaplan–Meier plots and log-rank tests to compare the two groups. Fourth, a Cox proportional-hazards model was used to estimate the risks of recurrent ischemic stroke and all-cause mortality associated with PWV (unadjusted, adjusted for age, sex, blood pressure and the presence of cerebral small vessel disease). Hazard ratios (HRs) are presented along with 95% confidence intervals (CIs). All comparisons were two-tailed, and a P value < 0.05 was considered to be being statistically significant. All data were analyzed using the JMP 11.0 software package (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Of the 1503 consecutive patients with acute ischemic stroke, we assessed 156 eligible patients (61% males, mean age: 69.2 ± 11.3 years).[7] The median brachial–ankle PWV value was 20.4 m s^{-1}. The end points were reached by 29 recurrent ischemic stroke patients and 28 all-cause mortality patients. The distribution of recurrent ischemic stroke subtypes was as follows: lacunar 16, other causes 7, and atherothrombotic 6. The median follow-up time was 5.9 years.

Recurrent ischemic stroke

Among the patients who developed recurrent ischemic stroke, more than half developed lacunar stroke (16 of the 29 patients). Patients who developed atherothrombotic stroke had higher PWV values, which were measured during the acute phase of first-ever stroke, compared with patients who developed lacunar stroke (median value, 28.2 vs. 21.2 m s^{-1}, $P = 0.036$). Conversely, the patients who did not develop recurrent ischemic stroke had lower PWV values compared with those who did develop recurrent ischemic stroke (median value,

Table 2 Associations of brachial–ankle pulse wave velocity and the study end points evaluated using the Cox proportional-hazards model

	HR	95% CI	P-value
All-cause mortality			
Unadjusted	2.09	0.97–4.86	0.060
Model 1[a]	0.83	0.34–2.16	0.697
Recurrent ischemic stroke			
Unadjusted	2.62	1.32–5.54	0.006
Model 1[a]	2.34	1.06–5.47	0.036
Model 2[b]	2.35	1.02–5.70	0.044
Model 3[c]	2.25	0.96–5.55	0.062
Model 4[d]	2.11	0.90–5.21	0.086
Model 5[e]	2.13	0.89–5.38	0.091

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age and sex.
[b]Adjusted for model 1 and the systolic blood pressure.
[c]Adjusted for model 2 and the presence of silent lacunar infarction.
[d]Adjusted for model 3 and the presence of white matter hyperintensities.
[e]Adjusted for model 4 and the presence of diabetes mellitus, hypercholesterolemia, ischemic heart disease and smoking habits.

19.5 vs. 22.7 m s^{-1}, $P = 0.035$). The PWV cutoff value used to predict recurrent ischemic stroke was 19.9 m s^{-1}, with 72% sensitivity and 52% specificity.

High vs. low PWV

Compared with patients with low PWV values, patients with high PWV values were more likely to be female and older. They were also more likely to have chronic kidney disease, silent lacunar infarct, white matter hyperintensities and a severe neurological deficit upon admission, as well as poor functional outcomes at discharge (Table 1). Patients with high PWV values were more likely to have a high risk of all-cause mortality and recurrent ischemic stroke (23% vs. 13%, $P = 0.143$ and 26% vs. 12%, $P = 0.038$, respectively).

Longitudinal analyses

Kaplan–Meier curve analyses showed that patients with high PWV values had less favorable survival times free of all-cause mortality (log-rank test, $P = 0.063$) and recurrent ischemic stroke (log-rank test, $P = 0.015$) than those with low PWV values (Figure 1). The multivariate Cox proportional-hazards model revealed that high PWV was

an independent predictor of recurrent ischemic stroke, after adjusting for age, sex and systolic blood pressure (Table 2).

DISCUSSION

Our study showed that high PWV doubles the risk of future ischemic stroke in patients who developed acute lacunar infarction, independent of age, sex and blood pressure levels. Measuring PWV during the acute phase of ischemic stroke is useful to assess the risk of future ischemic stroke.

The progressive neurological deficit that develops in patients with acute lacunar infarction[7] might share several multifactorial mechanisms with recurrent ischemic stroke. The vascular endothelial impairment indicated by PWV is associated with blood–brain barrier failure and damages the cerebral parenchyma.[25,28] The related arteriosclerotic microcirculatory impairment may also increase the risk of ischemic stroke.[7] Our hypothesis regarding a possible 'tsunami effect' of high PWV on microcirculatory cerebral parenchyma damage[14] may partially explain this association. Additionally, lacunar stroke was a major subtype of recurrent ischemic stroke in the present study. This finding also supports our hypothesis. Consequently, these multifactorial mechanisms could increase the risk of future ischemic stroke.

The results of this study highlight the utility of measuring PWV to predict future ischemic stroke after the onset of first-ever ischemic stroke. To date, numerous studies have demonstrated the relationships between PWV and mortality,[1,3,22] cardiovascular diseases[1,3,16–20] and cerebrovascular diseases,[2,16,21] including cerebral small vessel diseases,[4,8,9,23] in hypertensive adults. Furthermore, some studies have assessed PWV during the acute phase of stroke.[5–7,15,24,26,29] Although high PWV has been previously shown to predict mortality[6] and functional outcomes[5,7,26] in patients with acute ischemic stroke, the causal relationship between PWV and recurrent ischemic stroke has not been clarified. Our findings extend the clinical significance of PWV to include it as a predictor of the risk of future ischemic stroke in acute ischemic stroke patients.

Our study has several limitations. First, the study sample size was small. A study with a relatively small number of patients may be at risk of being statistically underpowered. Second, we did not assess cerebral microbleeds because T2*-weighted magnetic resonance imaging was only used after the present study had started. Third, cardiovascular events were also not assessed because of the small number of such patients ($n = 9$). A full assessment of the relationship between PWV and recurrent ischemic stroke will require the inclusion of patients with cerebral microbleeds and cardiovascular events. Fourth, we did not thoroughly assess PWV after patient discharge. The PWV changes may provide further information to help understand the pathophysiology associated with predicting future ischemic stroke.

In conclusion, high PWV values in patients who developed acute lacunar infarction double the risk of future ischemic stroke, independent of patient age, sex and blood pressure. Measuring PWV during the acute phase of ischemic stroke is useful to assess the risk of future ischemic stroke in such patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)