Pulsatility of middle cerebral arteries is better correlated with white matter hyperintensities than aortic stiffening

Sang-Hwa Lee[1], Yerim Kim[2], Yeongbae Lee[3], and Ju-Hun Lee[2]

[1]Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea
[2]Department of Neurology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea
[3]Department of Neurology, Gachon University Gil Medical Center, Incheon, Korea

Correspondence to
Ju-Hun Lee
Department of Neurology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, 150 Seongan-ro, Gangdong-gu, Seoul 05355, Korea
Tel: +82-2-2224-2206
Fax: +82-2-2224-2114
E-mail: leejuhun@hallym.or.kr

Background: Pulsatility of cerebral arteries and aortic stiffness have been associated with white matter hyperintensities (WMH). We explored which is better correlated with the severity of WMH in a population with acute lacunar infarct.

Methods: We included patients with acute small subcortical infarcts who underwent transcranial Doppler (TCD) and brachial ankle pulse wave velocity (baPWV). Exclusion criteria were any stenosis or occlusion on major cerebral arteries on magnetic resonance angiography; poor temporal insonation windows; ankle brachial index < 0.9; and atrial fibrillation. We assessed the performance of the pulsatility index of bilateral middle cerebral arteries (PI-MCA) and baPWV for predicting moderate-to-severe WMH, defined as an Age Related White Matter Changes score > 5, and then sought to find independent predictors using binary logistic regression analysis.

Results: Eighty-three patients (56 males, mean age 61.5 ± 11.4) participated in the study. Univariate analysis showed old age and high PI-MCA were significantly correlated with moderate-to-severe WMH. However, baPWV was not associated with the severity of WMH. Multivariate analysis revealed old age (odds ratio per 1-year increase, 1.068; $p = 0.044$) and upper tertile of PI-MCA (odds ratio, 5.138; $p = 0.049$) were independently associated with moderate-to-severe WMH. Receiver-operating characteristics showed PI-MCA differentiated those with and without moderate-to-severe WMH with an area under the curve of 0.719.

Conclusions: PI-MCA derived from TCD was better correlated with the severity of WMH than baPWV in a population with lacunar infarction. Pulsatility of cerebral arteries may better predict cerebral small vessel disease than the aortic stiffness index.

Key words: Pulsatility index; Aortic stiffness; Transcranial Doppler ultrasonography

INTRODUCTION

Pulse wave velocity (PWV) is known as an index to quantify arterial stiffness.[1] More specifically, aortic PWV, calculated on the basis of pulse transit time and the distance between carotid and femoral arteries, is a well-known predictor of cardiovascular mortality and morbidity.[2,3] However, aortic PWV measurement may not be practical in the clinical setting due to the difficulty in applying pressure transducers on target arteries and the reluctance of some patients in exposing the inguinal area. Brachial-ankle PWV (baPWV) may provide qualitatively similar information to aortic PWV, although some portions of baPWV may be influenced by peripheral arterial stiffness.[4] Therefore, baPWV is widely used in clinical practice for the assessment of central arterial stiffness.

Transcranial Doppler (TCD) is a useful and safe way to obtain valuable hemodynamic data in cerebrovascular disease. The pulsatility index (PI), derived from TCD, has long been proposed to reflect small vessel vascular resistance.[5,6]

Both pulsatility of cerebral arteries obtained from TCD[7-10] and central arterial stiffness derived from PWV[8,11,12] are known to be associated with cerebral small vessel disease (SVD). However, it remains unclear whether PI obtained from TCD or baPWV better correlates with cerebral SVD. We explored whether PI derived from TCD or baPWV better correlates with the severity of white matter hyperintensities (WMH) in a population with lacunar infarction.

MATERIALS AND METHODS

Subjects

This is a retrospective hospital-based study. We reviewed consecutive patients with acute cerebral infarction who were admitted to two training hospitals in Korea between January 2014 and June 2015. We found 180 patients with lacunar infarct without any stenotic lesions in major cerebral arteries (anterior cerebral arteries, middle cerebral arteries, posterior cerebral arteries, basilar artery, vertebral arteries, and internal cerebral arteries) on magnetic resonance angiography (MRA). We defined lacunar infarct as a small infarct (less than 2 cm on diffusion weighted image) in the territory of perforating arteries. Among them, we included 154 patients who underwent both TCD and baPWV examinations

(Fig. 1). We excluded the patients with any of the following: 1) poor temporal insonation windows (n = 37); 2) ankle-brachial index < 0.9 (n = 17); 3) atrial fibrillation documented on electrocardiography (n = 23).

TCD and baPWV examination

TCD examination was performed by experienced ultrasonographers in each hospital. Middle cerebral arteries (MCAs) were examined at a depth of 50-60 mm through both temporal windows. Pulsatility index (PI) was automatically calculated for each vessel using the formula: PI = (peak systolic velocity-end-diastolic velocity) / mean velocity. We measured PI at least two points in each MCA (proximal and distal points of MCA stem). We defined the PI of bilateral middle cerebral arteries (PI-MCA) as the mean of all measured PI values in both MCAs.

BaPWV was measured using the Form PWV/ABI device (VP 2000; Colin Medical Technology, Komaki, Japan). Patients were examined in the supine position after being at rest for at least 10 minutes. Waveform data and time intervals between the waves were automatically obtained from volume plethysmography cuff sensors on the right brachium and both ankles. The distance between the brachium and the ankle for baPWV was calculated according to patient height. We used the average value of the baPWVs obtained on both sides.
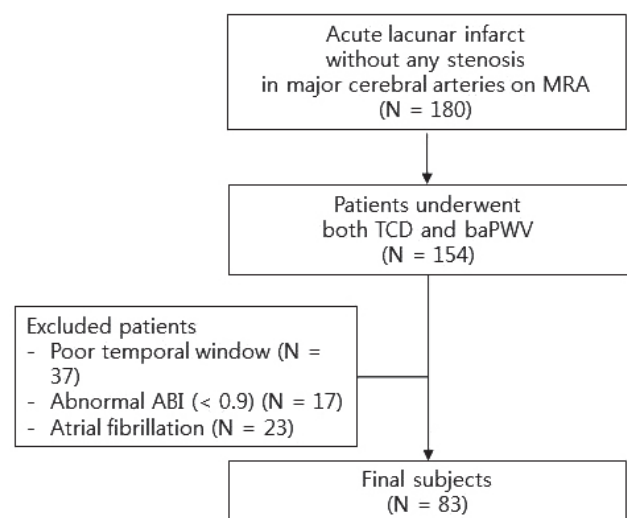
Fig. 1. Flow diagram for study subjects. MRA, magnetic resonance angiography; TCD, transcranial Doppler; baPWV, brachial ankle pulse wave velocity; ABI, ankle-brachial index.

Sang-Hwa Lee, et al. Pulsatility index, aortic stiffening, and WMH

ANNALS OF
CLINICAL
NEUROPHYSIOLOGY

Rating of white matter hyperintensities

We scored the severity of WMH using the Age Related White Matter Changes (ARWMC) scale according to operational definitions suggested by Xiong et al.[13] for improving reliability of the ARWMC scale. We classified the severity of WMH as follows: absent (score 0), mild (1-5), moderate (6-10), and severe (11-15). The scoring was done independently by one neurologist blinded to TCD and baPWV findings as well as clinical features of patients.

Risk factors and confounding variables

We collected information on the patients' age, sex, cardiovascular risk factors, and National Institutes of Health Stroke Scale (NIHSS) at the time of hospitalization. History of stroke included all hemorrhagic or ischemic strokes. Hypertensive patients were defined as individuals previously diagnosed

with hypertension or individuals with a blood pressure of > 140/90 mmHg in repeated measurements at rest after acute phase. Diabetes patients were defined as individuals previously diagnosed with diabetes or individuals with fasting blood glucose > 126 mg/dL or glycated hemoglobin (HbA1c) > 6.5%. Hyperlipidemic patients were defined as individuals diagnosed with hyperlipidemia or individuals with fasting low-density lipoprotein > 130 mg/dL or total cholesterol > 200 mg/dL, which is the cutoff value of borderline high cholesterol according to NCEP III guidelines.[14] Smokers were defined as current smokers.

Statistical analysis

We investigated the association between the severity of WMH and PI-MCA, and between the severity of WMH and baPWV. Values of PI-MCA and baPWV were split into tertiles. We used chi-square tests to compare categorical variables and t-test (or Mann-Whitney test as appropriate) to analyze factors associated with moderate-to-severe WMH. To search for independent predictors of moderate-to-severe WMH, binary logistic regression analysis was used, with age, sex, and cardiovascular risk factors (hypertension, previous stroke, diabetes, hyperlipidemia, and smoking) as covariates. Significance level was set at $p < 0.05$ for all statistical analyses. The moderate-to-severe WMH predicting capability of PI-MCA and baPWV was evaluated through a receiver-operating characteristic curve.

Table 1. Baseline characteristics

Parameters	N = 83
Age, years, mean (SD)	61.5 (11.4)
Sex, women, n (%)	27 (32.5)
Previous stroke, n (%)	16 (19.3)
Hypertension, n (%)	50 (60.2)
Diabetes, n (%)	23 (27.7)
Hyperlipidemia, n (%)	18 (21.7)
Current smoker, n (%)	38 (45.8)
Baseline median NIHSS (IQR)	2.0 (1.0-3.0)
White matter hyperintensities	
Absent, n (%)	1 (1.2)
Mild, n (%)	38 (45.8)
Moderate, n (%)	37 (44.6)
Severe, n (%)	7 (8.4)
baPWV	
Low, cm/s, mean (SD)	1,451 (129)
Intermediate, cm/s, mean (SD)	1,804 (94)
High, cm/s, mean (SD)	2,877 (1,797)
PI-MCA	
Low, PI, mean (SD)	0.74 (0.07)
Intermediate, PI, mean (SD)	0.90 (0.04)
High, PI, mean (SD)	1.11 (0.11)

NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; baPWV, brachial ankle pulse wave velocity; PI-MCA, pulsatility index of bilateral middle cerebral arteries; PI, pulsatility index.

RESULTS

Eighty-three patients (56 male, 67.5%, mean age 61.5 ± 11.4) participated in the study. Patients' baseline median NIHSS score was 2.0 (interquartile range 1.0-3.0). Detailed baseline characteristics are described in Table 1.

In univariate analysis (Table 2), old age was significantly associated with moderate-to-severe WMH ($p < 0.001$). PI-MCA was also significantly associated with moderate-to-severe WMH ($p < 0.001$, linear-by-linear association Chi-square tests). baPWV tended to associate with the severity of WMH, but this association was not statistically significant ($p = 0.082$, linear-by-linear association tests).

We conducted multivariate binary logistic analysis using baPWV (Model 1, Table 3) and using PI-MCA (Model 2, Table 3).

Table 2. Factors associated with white matter hyperintensities in univariate analysis

	White matter hyperintensity		p-value[a]
	Absent or mild (N = 39)	Moderate or severe (N = 44)	
Age, years, mean (SD)	56.5 (11.4)	65.9 (9.5)	< 0.001
Sex, women, n (%)	10 (37.0)	17 (63.0)	0.207
Previous stroke, n (%)	34 (50.7)	33 (49.3)	0.16
Hypertension, n (%)	18 (54.5)	15 (45.5)	0.262
Diabetes, n (%)	28 (46.7)	32 (53.3)	0.925
Hyperlipidemia, n (%)	29 (44.6)	36 (55.4)	0.411
Current smoker, n (%)	20 (44.4)	25 (55.6)	0.613
Baseline mean NIHSS (SD)	2.1 (1.5)	2.7 (2.1)	0.175
baPWV			0.082
Low, n (%)	16 (59.3)	11 (40.7)	
Intermediate, n (%)	13 (46.4)	15 (53.6)	
High, n (%)	10 (35.7)	18 (64.3)	
PI-MCA			< 0.001
Low, n (%)	20 (74.1)	7 (25.9)	
Intermediate, n (%)	12 (42.9)	16 (57.1)	
High, n (%)	7 (25.0)	21 (75.0)	

NIHSS, National Institutes of Health Stroke Scale; WMH, white matter hyperintensities; baPWV, brachial ankle pulse wave velocity; PI-MCA, pulsatility index of bilateral middle cerebral arteries.
[a]Chi-square test, t-test, Mann-Whitney test as appropriate.

Table 3. Predicting facotrs for moderate-to-severe white matter hyperintensities in multivariate analysis

	Model 1				Model 2			
	p-value[a]	HR	95% CI		p-value[a]	HR	95% CI	
Age	0.001	1.108	1.044	1.175	0.044	1.068	1.002	1.138
Sex (women)	0.994	0.995	0.275	3.599	0.894	0.916	0.252	3.325
Previous stroke	0.858	1.129	0.298	4.275	0.497	1.637	0.395	6.791
Hypertension	0.115	2.44	0.805	7.4	0.119	2.473	0.793	7.709
Diabetes	0.463	0.64	0.195	2.106	0.779	0.848	0.268	2.684
Hyperlipidemia	0.292	0.517	0.152	1.765	0.326	0.523	0.144	1.905
Current smoker	0.237	2.17	0.601	7.835	0.116	2.827	0.774	10.324
baPWV								
Low	Ref.							
Intermediate	0.222	2.215	0.619	7.934				
High	0.385	1.805	0.476	6.842				
PI-MCA								
Low					Ref.			
Intermediate					0.136	2.677	0.733	9.775
High					0.049	5.138	1.01	26.15

HR, heart rate; CI, confidence interval; baPWV, brachial ankle pulse wave velocity; Ref., reference; PI-MCA, pulsatility index of bilateral middle cerebral arteries; PI, pulsatility index.
[a]Binary logistic regression analysis.

Sang-Hwa Lee, et al. Pulsatility index, aortic stiffening, and WMH

ANNALS OF
CLINICAL
NEUROPHYSIOLOGY

In multivariate analysis, old age and upper tertile of PI-MCA were independently associated with moderate-to-severe WMH ($p = 0.044$ and 0.049, respectively).

In the receiver-operating characteristics (Fig. 2), PI-MCA differentiated those with and without moderate-to-severe WMH with an area under the curve of 0.719 (95% confidence interval [CI], 0.65-0.832). However, the performance of baPWV for predicting moderate-to-severe WMH was low, with an area under the curve of 0.625 (95% CI, 0.505-0.745).

DISCUSSION

Our data showed that PI-MCA derived from TCD was significantly associated with the severity of WMH. The ability to predict moderate-to-severe WMH was better for PI-MCA than for baPWV.

Aortic stiffness derived from PWV is known to be associated with cerebral SVD.[8,11,12] Our data showed that baPWV tended to be associated with the severity of WMH in univariate analysis although this association was not statistically significant. Aortic stiffening with advancing age increases the transfer of excessive, potentially harmful pulsatile energy

Fig. 2. In the receiver-operator characteristics, PI-MCA differentiated those with and without moderate-to-severe WMH with area under curve of 0.719 (95% CI, 0.65-0.832). However, the performance of baP-WV for predicting moderate-to-severe WMH was low, with area under curve of 0.625 (95% CI, 0.505-0.745). PI-MCA, pulsatility index of bilateral middle cerebral arteries; WMH, white matter hyperintensities; baPWV, brachial ankle pulse wave velocity; CI, confidence interval.

into the peripheral vessels. As a result, increased transmission of pulsatile energy into smaller arteries may lead to reactive changes in vessel resistance, increasing peripheral resistance. In the long term, persistent reactive changes in vessel resistance may lead to remodeling of wall components and permanent vessel changes, which may be the underlying mechanism of the association between aortic PWV and cerebral small vessel disease.[15]

Like aortic stiffness, PI-MCA is known to be well correlated with cerebral small vessel disease.[5,6] These two measurements may be associated with cerebral small vessel disease through a complex function of various hemodynamic factors. For example, PI derived from TCD may be not dependent solely on cerebrovascular resistance, but may describe cerebral perfusion pressure in a more accurate manner.[16] High PI was significantly associated with low cerebral perfusion pressure. Cerebral blood flow is determined by cerebral perfusion pressure as well as cerebral vascular resistance. Therefore, low cerebral perfusion pressure (CPP) and high cerebrovascular resistance (CVR) in patients with high PI may cause chronic ischemic damage to the brain. The mechanism behind the better predictive ability of PI-MCA when compared to baPWV is not easily understandable and warrants further research. A previous study also showed a significantly stronger association of leukoaraiosis with PI-MCA than with any other physiological measure.[17] We think PI-MCA reflects cerebral blood flow more accurately through interplay with CPP and CVR than other physiological measures such as aortic stiffness.

Our study has some limitations. First, it was a small cross-sectional and observational study and therefore there may be unmeasured confounders potentially associated with WMH. The association between baPWV and WMH was not statistically significant in our study. The statistical significance between PI-MCA and WMH also diminished in the multivariate analysis. We think that age may be relatively a strong predictor compared with baPWV or PI-MCA. Relatively weak predictors might be obscured probably due to small sample size. Second, we did not assess other hemodynamic measures such as heart rate and blood pressure, and blood viscosity parameters such as hematocrit, which influence PI. We could not adjust the time of examination after acute ischemic stroke. In addition, we did not adjust drugs such as cilostazol or statin which can influence on PI. However,
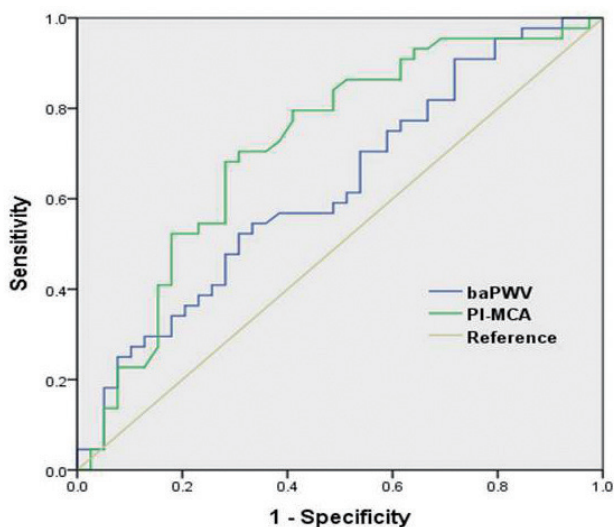
we minimized the influence of irregular heart rate on PI through exclusion of patients with atrial fibrillation. Furthermore, it was a strength of this study that we excluded any stenosis of proximal cerebral arteries on MRA. When there is a significant stenosis on the internal cerebral artery, PI-MCA becomes low and therefore inaccurately reflects cerebral small vessel disease. Therefore, exclusion of any stenosis in proximal cerebral arteries is a strong point of this study as it allows for the accurate assessment of small vessel disease.

PI-MCA derived from TCD was better correlated with the severity of WMH than baPWV in this study's lacunar infarction population. Pulsatility of cerebral arteries may be more predictive of cerebral small vessel disease than the aortic stiffness index.

Acknowledgements

REFERENCES

1. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 2002;15:426-444.

2. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434-2439.

3. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236-1241.

4. Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, et al. Brachial-ankle pulse wave velocity: an index of central arterial stiffness? J Hum Hypertens 2005;19:401-406.

5. Legarth J, Thorup E. Characteristics of doppler blood-velocity waveforms in a cardiovascular in vitro model. i. the model and the influence of pulse rate. Scand J Clin Lab Invest 1989;49:451-457.

6. Giller CA, Hodges K, Batjer HH. Transcranial doppler pulsatility in vasodilation and stenosis. J Neurosurg 1990;72:901-906.

7. Heliopoulos I, Artemis D, Vadikolias K, Tripsianis G, Piperidou C, Tsivgoulis G. Association of ultrasonographic parameters with subclinical white-matter hyperintensities in hypertensive patients. Cardiovasc Psychiatry Neurol 2012;2012:616572.

8. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the age, gene/environment susceptibility--Reykjavik study. Brain 2011;134(Pt 11):3398-3407.

9. Kidwell CS, el-Saden S, Livshits Z, Martin NA, Glenn TC, Saver JL. Transcranial doppler pulsatility indices as a measure of diffuse small-vessel disease. J Neuroimaging 2001;11:229-235.

10. Mok V, Ding D, Fu J, Xiong Y, Chu WW, Wang D, et al. Transcranial doppler ultrasound for screening cerebral small vessel disease: a community study. Stroke 2012;43:2791-2793.

11. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, et al. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension 2008;52:1120-1126.

12. Kim DH, Choi JH, Moon JS, Kim HJ, Cha JK. Association between the severity of cerebral small vessel disease, pulsatility of cerebral arteries, and brachial ankle pulse wave velocity in patients with lacunar infarction. Eur Neurol 2010;64:247-252.

13. Xiong Y, Yang J, Wong A, Wong CH, Chan SS, Li HH, et al. Operational definitions improve reliability of the age-related white matter changes scale. Eur J Neurol 2011;18:744-749.

14. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-3421.

15. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985) 2008;105:1652-1660.

16. de Riva N, Budohoski KP, Smielewski P, Kasprowicz M, Zweifel C, Steiner LA, et al. Transcranial doppler pulsatility index: what it is and what it isn't. Neurocrit Care 2012;17:58-66.

17. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. Stroke 2012;43:2631-2636.