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Original Article

Clinical usefulness of ankle brachial index and brachial-ankle pulse wave velocity in patients with ischemic stroke

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Abstract

Ankle brachial index (ABI) and brachial-ankle pulse wave velocity (baPWV) are widely used noninvasive modalities to evaluate atherosclerosis. Recently, evidence has increased supporting the use of ABI and baPWV as markers of cerebrovascular disease. This study sought to examine the relationship between ABI and baPWV with ischemic stroke. This study also aimed to determine which pathogenic mechanism, large artery disease (LAD) or small vessel disease (SVD), is related to ABI or baPWV. Retrospectively, 121 patients with ischemic stroke and 38 subjects with no obvious ischemic stroke history were recruited. First, ABI and baPWV were compared between the groups. Then, within the stroke group, the relevance of ABI and baPWV with regard to SVD and LAD, which were classified by brain magnetic resonance image (MRI) and magnetic resonance angiography (MRA) or computed tomography angiography (CTA) findings, was assessed. The baPWV was higher in the stroke group than non-stroke group (1,944.18±416.6 cm/s vs. 1,749.76±669.6 cm/s, $P < 0.01$). Regarding LAD, we found that mean ABI value was lower in the group with extracranial large artery stenosis ($P < 0.01$), and there was an inverse linear correlation between ABI and the grade of extracranial large artery stenosis ($P < 0.01$). For SVD, there was a significant correlation between SVD and baPWV (2,057.6±456.57 cm/s in the SVD (+) group *vs.* 1,491±271.62 cm/s in the SVD (-) group; $P < 0.01$). However, the grade of abnormalities detected in SVD did not correlate linearly with baPWV**.** These findings show that baPWV is a reliable surrogate marker of ischemic stroke. Furthermore, baPWV and ABI can be used to indicate the presence of small vessel disease and large arterial disease, respectively.

Keywords: ABI, baPWV, small vessel disease, intracranial artery stenosis, extracranial artery stenosis

Introduction

Ischemic stroke is a heterogeneous disorder with several pathophysiological mechanisms[1]. Atherosclerosis is one of the pathogenic mechanisms that can lead to ischemic stroke and cardiovascular disease. Carotid intima-media thickness (IMT), pulse wave velocity (PWV), flow-mediated dilation (FMD) of the brachial artery, and ankle brachial index (ABI) are widely used noninvasive modalities to evaluate atherosclerosis[2–5].

Among those, ABI is the ratio of blood pressure in the

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lower legs to blood pressure in arms which can readily be measured with Doppler. A low ABI is an independent marker for the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease[6]. Moreover, the subjects with low ABI had a significantly greater risk of developing stroke than those with normal values[7–8].

PWV, a widely used index of large artery compliance, is a measure of arterial stiffness[1]. Arterial stiffness reflects variations in vascular volume as blood pressure changes[9] and is evaluated by measuring the PWV between two sites along an arterial tree, with higher values indicating stiffer arteries[10]. Increased arterial stiffness is important in the pathophysiology of cerebrovascular disease[11]. Several studies have shown that aortic PWV is a predictor of cardiovascular events[10]. A recent study found that PWV was a prognostic factor for vascular damage as well as a marker of arterial stiffness[12]. Although PWV generally refers to carotid-femoral PWV, brachial-ankle PWV (baPWV) is more readily obtained because its measurement does not require specialized technical skills[10,13]. Several cross-sectional studies have shown that baPWV is useful for assessing large artery damage and peripheral arterial stiffness[14]. A study comparing aortic PWV, obtained using a catheter with a pressure manometer at the tip, and baPWV found that baPWV had excellent validity and reproducibility and was an acceptable marker of vascular damage[15]. Moreover, a recent study found that baPWV was related to silent cerebral infarction and intracranial stenosis[16]. Thus, baPWV is a novel marker of cerebrovascular risk, which may be more useful than conventional markers because it is readily obtained[17].

Studies have shown the predictive value of ABI and baPWV in ischemic stroke. Thus, screening tests that are easier to conduct, more economical, and reliable, like baPWV or ABI, would be of great use in identifying patients at risk of ischemic stroke and ultimately for the early prevention of ischemic stroke.

Additionally, whether ABI and baPWV are associated with ischemic stroke risk, by reflecting a large arterial disease mechanism (extracranial or intracranial large artery stenosis) or a small vessel disease mechanism (leukoaraiosis and lacune infarction), is important because the clinical management differs between the two etiologies, although these two mechanisms share the common pathophysiology of atherosclerosis. The main pathomechanisms of stroke, with the exception of cardioembolic stroke, are large artery disease and small vessel disease[18]. It is not clear whether atherosclerosis causes both conditions. Large artery disease is characterized by steno-occlusive lesions on the intra- and extracranial large arteries caused by primary atherosclerosis or rare conditions, such as arterial dissection, inflammatory disorders, infections, radiation, sickle-cell anemia, and moyamoya disease[19]. Small vessel disease is characterized by a syndrome of clinical, cognitive, neuroimaging, and neuropathological findings thought to arise from disease affecting the perforating cerebral arterioles, capillaries, and venules that cause cerebral white and deep grey matter damage. Although small vessel disease may arise from atherosclerosis, other pathologies, such as lipohyalinosis and fibrinoid necrosis may account for the condition. Arterial stiffness is a major contributor to small vessel disease[20]. baPWV is an accurate and reliable measure of arterial stiffness, and recent studies have found an association between baPWV and small vessel disease[10,21–22]. Furthermore, an investigation of ABI found that low ABI was associated with ischemic stroke caused by large artery atherosclerosis[23].

This study was conducted to determine whether there was any relationship between ABI and baPWV with ischemic stroke. With respect to the pathophysiological mechanism of ischemic stroke, this study also aimed to determine which pathology, large artery disease or small vessel disease, is related to ABI or baPWV.

Materials and methods

Subjects

In total, 121 patients with ischemic stroke (cerebral infarction (n = 107) or transient ischemic attack (n = 14), who visited the Department of Neurology at Chungbuk National University Hospital from January 1, 2007 to December 31, 2007 were recruited. All of the patients underwent neuroimaging studies (MRI and MRA or CTA) and measurement of ABI and baPWV.

Thirty-eight control subjects were recruited. Some of them were evaluated for organic causes of dizziness or headache, and others underwent a routine health check-up. None of them had a history or any clinical evidence of cerebrovascular disease. All of them underwent measurement of ABI and baPWV. Nineteen of them had an MRI. Seven of them had an MRA.

Assessment for risk factors of cerebrovascular disease and confounding variables for ABI/baPWV.

Hypertension, diabetes mellitus, history of smoking, and hyperlipidemia, defined as total cholesterol $\geqslant$ 230 mg/dL, triglycerides $\geqslant$ 150 mg/dL, or the use of lipid-lowering medications and history of cerebrovascular disease, were assessed by patient history and laboratory investigation[24].

Table 1 **Demographic features, cerebrovascular risk factors, and laboratory findings between groups**

Parameter	Stroke ($n = 121$)	Non-stroke ($n = 38$)	P value
Age (years)	66.56±10.99	63.07±9.59	0.045
Sex (male)	68(56.19%)	21(55.26%)	0.919
Hypertension	71(58.6%)	20(52.63%)	0.511
Diabetes	32(26.44%)	15(39.4%)	0.537
Smoking	41(33.88%)	16(42.1%)	0.357
Hyperlipidemia (cholesterol > 230 mg/dL)	11(9.09%)	5(13.2%)	0.467
Hypertriglyceridemia (TG > 150 mg/dL)	40(33.1%)	13(34.2%)	0.895

These data were used for confounding variables for each analysis. Continuous variables are expressed as mean±SD, SD standard deviation.

Neuroimaging assessment

MRI and MRA were performed with a 1.5-T Siemens magnetom Vision (Siemens, Germany). CTA was performed with a 64-channel Philips imaging system (Philips, Germany). The number of old lacunar infarctions on the fluid attenuated inversion recovery (FLAIR) image was counted, and a gradient echo image was used to exclude petechial hemorrhage. Lacunar infarction was defined as a hyperintense lesion between 0.3–1.5 cm in size on the FLAIR image located in the cerebral deep gray matter (basal ganglia and internal capsule) and the brainstem[16–17]. Periventricular white matter hyperintensities (PVWH) on the FLAIR images were considered as leukoaraiosis, if they were seen adjacent to the ventricle. Leukoaraiosis was graded as 0 = absent, 1 = "caps" or thin lining (< 0.5 cm), 2 = smooth "halo" (< 1 cm), and 3 = irregular PWMH extending into the deep white matter (> 1 cm) in accordance to the Fazekas scale[25–27].

Vessel stenosis on MRA or CTA was graded according to the following criteria: grade 1, normal or mild stenosis (up to 29% diameter stenosis); grade 2, moderate stenosis (30% to 69% diameter stenosis); grade 3, severe stenosis (70% to 100% diameter stenosis); grade 4, occlusion (100% diameter stenosis with rarefaction of the middle cerebral artery (MCA) distal to the stenosis)[28].

The conditions of the proximal MCAs, proximal anterior cerebral arteries (ACAs), proximal posterior cerebral arteries (PCAs), internal carotid arteries at siphon, basilar artery, and extracranial internal carotid arteries were assessed. The percentage of stenosis was measured by visual inspection in line with the principles established by the NASCET study. Each stenosis grade was given a score (grade 1 = 1.0, grade 2 = 2.0, grade 3 = 3.0 and, grade 4 = 4.0). The sum of each vessel's score was used to analyze the severity of stenosis. Stenosis that was too subtle or suspicious was given a score of 0.5 and was still included in the total.

ABI and baPWV measurement

Right and left baPWV were measured using the Form PWV device (VP-1000, Colin Medical Technology, Komaki, Japan). The subjects were examined in the supine position. Waveform data were obtained from volume plethysmographic sensors within the cuffs that were placed on the right brachium and both ankles. The time intervals between the wave detected at the right brachium and those at both ankles were measured. The distance between the brachium and the ankle for baPWV was automatically calculated according to the height of the subject. The average value of measurements from both left and right sides was used for analysis. ABI is a ratio of the systolic blood pressure (SBP) from the ankle to the SBP from the arm. The average values of bilateral ABI and baPWV were used in the analysis.

Statistical analyses

All continuous variable data were expressed as the mean±standard deviation (SD). To compare proportions across the groups, t-tests were used, and ANCOVA was used to compare the means of contin-

Table 2 **Comparison of ABI/baPWV between the ischemic stroke group and control group**

	Stroke ($n = 121$)	Non-stroke ($n = 38$)	P value
ABI	1.09±0.12	1.08±0.20	0.5390
baPWV (cm/s)	1,944.18±416.6	1,749.76±669.6	0.0079

Continuous variables are expressed as mean±SD. ABI: ankle brachial index; baPWV: brachial ankle pulse wavevelocity

uous variables across the groups. Logistic regression analysis was used to clarify the relationship between the presence of small vessel disease or large artery disease and baPWV. The correlation between the severity of small vessel disease or large artery disease and baPWV was tested using a multiple linear regression analysis. P values < 0.05 were deemed to indicate statistical significance. Age, presence of hypertension, diabetes, hyperlipidemia, and smoking were considered confounding variables. Analysis of the relationship between baPWV and large arterial stenosis/small vessel disease was limited in the ischemic stroke group only. All calculations were done using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows on a PC.

Results

In total, 89 males and 70 females aged (65.59±10.91) years were enrolled. The mean age of subjects was higher in the stroke group than in the non-stroke group (66.56±10.99 *vs*. 63.07±9.59). The stroke risk factors were not significantly different between groups. ***Table 1*** shows the clinical and demographic characteristics of the 159 subjects according to the presence or absence of ischemic stroke.

In analysis of the relationship between ABI/baPWV and ischemic stroke, there was a positive correlation between the baPWV value and ischemic stroke. A higher baPWV was positively correlated with the presence of ischemic stroke (1,944.18±416.6 in the stroke group *vs*. 1,749.76±669.6 in the non-stroke group; $P < 0.01$). ***Table 2*** shows the relationship between ABI/baPWV and presence of ischemic stroke.

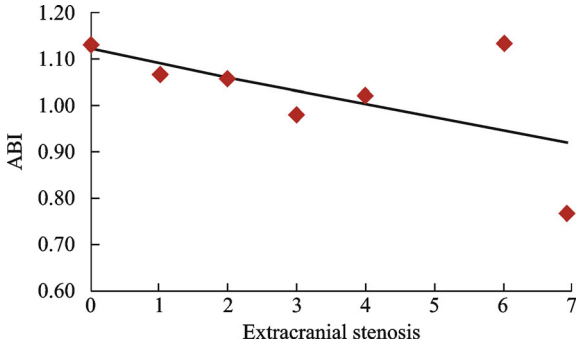

Fig. 1 **Relationship between ABI and severity of extracranial artery stenosis.** There is an inverse linear correlation between the ABI value and the grade of extracranial large artery stenosis (P = 0.0001, ß= – 0.301, calculated using linear regression analysis). Each dot indicates mean value of ABI. The line on the graph is a virtual trend line. ABI: ankle brachial index.

The analysis of large artery disease and ABI also revealed a positive relationship. Mean ABI value was lower in the group with extracranial large artery stenosis ($P < 0.01$; ***Table 3***). The optimal ABI cutoff value for the detection of extracranial large artery stenosis was 1.09, with 69% sensitivity and 52% specificity (area under the curve = 0.68±0.06, $P < 0.01$). Additionally, there was an inverse linear correlation between the ABI value and the grade of extracranial large artery stenosis ($P < 0.01$; ***Fig. 1***). The analysis of ABI and the severity of intracranial large artery stenosis revealed a weak inverse linear correlation with a low level of significance ($P = 0.07$; ***Fig. 2***).

With respect to baPWV, this study did not reveal any significant relationship between baPWV and large artery disease (***Table 4***). However, there was a strong

Table 3 **Relationship between ABI/baPWV and large artery disease**

	ABI	Number of subjects	*P* value
Extracranial stenosis			
Yes	1.04±0.09	31	0.005
No	1.13±0.16	90	
Intracranial stenosis			
Yes	1.11±0.12	91	0.420
No	1.12±0.12	30	
	baPWV(cm/s)	Number of subjects	*P* value
Extracranial stenosis			
Yes	2,019.3±537.95	31	0.427
No	1,963.9±456.88	90	
Intracranial stenosis			
Yes	2,001.2±455.86	91	0.747
No	1,908±539.21	30	

Continuous variables are expressed as mean±SD. Extracranial stenosis: the presence of extracranial large artery stenosis, Intracranial stenosis: the presence of intracranial large artery stenosis. ABI: ankle brachial index; baPWV: brachial ankle pulse wave velocity

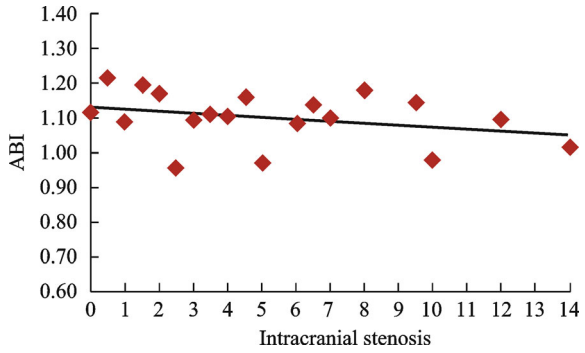

Fig. 2 **Relationship between ABI and severity of intracranial artery stenosis.** There is a weak inverse linear correlation between the ABI value and the grade of intracranial large artery stenosis ($P = 0.07$, ß=−0.171, calculated using linear regression analysis). Each dot indicates mean value of ABI. The line on the graph is a virtual trend line. ABI: ankle brachial index.

correlation between baPWV and small vessel disease. The overall presence of small vessel disease was associated with a high baPWV (2,057.6±456.57 cm/s in the small vessel disease (+) group *vs*. 1,491±271.62 cm/s in the small vessel disease (-) group; $P < 0.01$). However, the grade of the abnormalities detected in each of the subgroups of small vessel disease did not correlate linearly with the baPWV value ($P = 0.08$ in leukoaraiosis and $P = 0.181$ in lacunar infarction).

Discussion

Noninvasive imaging techniques offer a unique opportunity to study the relationship between surrogate markers of atherosclerosis and the development of atherosclerotic events. Studies have shown that baPWV and ABI are two such surrogate markers[24]. Because the majority of cerebral artery diseases are due to the development and progression of atherosclerosis, the use of noninvasive surrogate markers of atherosclerosis can aid in the diagnosis of cerebrovascular disease through the identification of subclinical cases. The present study showed that baPWV may be a more reliable marker in ischemic stroke than ABI. Although a few studies showed that a decrease in ABI may be a risk factor for ischemic stroke, other studies only revealed a relationship between ABI and atherosclerosis or ABI and cardiovascular disease, and subsequently postulated that atherosclerosis, which is detectable by ABI, may have an influence on ischemic stroke events[7]. However, another mechanism beyond atherosclerosis may account for the difference between stroke and cardiovascular disease. As the present study results show that low ABI is linearly associated with the large artery stenosis, ABI can reflect relatively large cerebral artery atherosclerosis, but not the entire spectrum of ischemic stroke mechanism, especially small vessel occlusive stroke. This observation is rather similar to the results obtained from a peripheral artery disease study wherein ABI testing identified macrovascular disease between the heart and legs[5].

The present study revealed a strong correlation between small vessel disease and baPWV as well as between overall ischemic stroke and baPWV. Several mechanisms may explain the association between increased PWV and stroke or cerebral small vessel disease. First, arterial stiffness may raise the occurrence of cerebrovascular events through an increase in central pulse pressure (PP). Increased arterial stiffness causes the early return of reflected waves from peripheral sites and leads to the augmentation of the central systolic pressure. This effect leads to inadequate increases in systolic blood pressure, relative decreases in diastolic blood pressure and a subsequent increase in PP. PP, an expression of arterial stiffness, is associated with ischemic SVD of the brain[29–30]. Second, coronary heart disease and heart failure, which are indicated by high PP and arterial stiffness, are also risk factors for stroke. Third, arterial stiffening can be caused by various phenomena, including fibrosis, medial smooth

Table 4 **Relationship between ABI /BaPWV and small vessel disease**

	ABI	Number of subjects	*P* value
Small vessel disease			
Yes	1.11±0.13	104	0.557
No	1.15±0.08	17	
	baPWV	Number of subjects	*P* value
Small vessel disease			
Yes	2057.6±456.57	104	0.001
No	1491±271.62	17	

Continuous variables are expressed as mean±SD. Small vessel disease: the presence of small vessel disease (leukoaraiosis or lacunar infarction). ABI: ankle brachial index; baPWV: brachial ankle pulse wave velocity

muscle necrosis, breaks in elastin fibers, calcifications, and diffusion of macromolecules within the arterial wall[31]. Moreover, the factors associated with increased PWV cause endothelial cell damage, which is a pathogenic mechanism of cerebral small vessel disease[32]. Finally, the vulnerability to ischemic insult may be increased in the distal portion of a vascular tree where cerebral perfusion pressure is relatively low[32]. Thus, although the degree of arterial stiffness is the same throughout the arterial system, ischemia is most likely to develop in the distal portion first causing small vessel disease. A recent study of small vessel disease has also shown that baPWV (arterial stiffness) is a reflection of cerebral small vessel (microvascular) disease[13].

Our findings are not consistent with those of previous studies showing a significant correlation between PWV and carotid IMT[2,33–34]. The present study did not show an association between carotid stenosis and baPWV. These negative results may indicate that increased IMT and carotid artery stenosis are governed by different pathophysiologic mechanisms. Increased IMT is associated with the pathophysiological mechanisms underlying small vessel disease, such as increased arterial stiffness, rather than with those of large arterial atherosclerosis.

In conclusion, this study focused on the usefulness of baPWV and ABI in the evaluation of ischemic strokes. Through this study, baPWV and ABI are suggested to be reliable, economical, and readily obtainable markers of cerebrovascular disease. In particular, baPWV is related to the presence of ischemic stroke and small vessel disease. Additionally, there is a relationship between ABI and extracranial large artery disease. Thus, if a screening test with ABI/baPWV shows abnormalities, more specific examination (brain MRI for abnormal baPWV, cervical MRA for abnormal ABI) should be recommended.

The present study has some limitations, including the retrospective design and the relatively small number of subjects recruited. In particular, non-stroke patients were excluded from the analysis of the ABI/baPWV relationship because few had undergone angiography. Thus, our results may not be generalizable to the general population. Furthermore, some inaccuracies may exist in the data due to the inclusion of cardio-embolic infarctions in the stroke group. More specific and detailed prospective studies on this topic are warranted.

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