Original Article

Associations of Brachial-Ankle Pulse Wave Velocity and Carotid Atherosclerotic Lesions with Silent Cerebral Lesions

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Silent cerebral lesions are increasingly found in mass screenings using MRI and magnetic resonance angiography (MRA). The purpose of this paper is to assess the usefulness of two non-invasive clinical tests—carotid ultrasound examination and brachial-ankle pulse wave velocity (baPWV) measurement—for predicting silent cerebral infarction (SCI) and silent intracranial arterial stenosis. Data were collected on 480 asymptomatic adult subjects who participated in a brain screening program at a single hospital between April 2003 and March 2006. All participants underwent baPWV measurement, B-mode ultrasonography of carotid arteries, MRI, and MRA. Data on 476 (99.1%) subjects were included in the analysis. Among these, 273 (57.4%) were male and the mean age was 51.5 years; 161 (33.8%) had carotid plaque; 33 (6.9%) had increased intima-media thickness (IMT); 99 (20.8%) had SCI; and 7 (1.5%) had intracranial arterial stenosis. The multivariate analysis showed that age (odds ratio [OR]: 1.12; 95% confidence interval [CI]: 1.08–1.17), carotid plaque (OR: 2.69; 1.59–4.56), increased IMT (OR: 2.40; 1.02–5.65), and a history of hypertension treatment (OR 2.22; 1.11–4.43) were significantly associated with SCI. Also, increased IMT (OR 9.70: 1.48–63.71) was related to intracranial arterial stenosis. Brachial-ankle PWV was related to SCI ($p<0.01$) and intracranial stenosis ($p=0.01$) in univariate analysis but not in multivariate analysis. The presence of carotid plaque and that of increased IMT on ultrasound examination are useful for assessing the risk of SIC. Increased IMT is also predictive of intracranial arterial stenosis. (*Hypertens Res* 2007; 30: 767–773)

***Key Words*: atherosclerosis, brachial-ankle pulse wave velocity, ultrasonography, magnetic resonance imaging, magnetic resonance angiography**

Introduction

Carotid ultrasound examination is increasingly used in mass screening programs for lifestyle diseases as well as in daily clinical practice. Increased intima-media thickness (IMT) and atherosclerotic plaques in the carotid arteries have been reported to have associations with ischemic stroke (*1–8*), and therefore have been recognized as useful risk assessment tools for cerebrovascular diseases (*9*, *10*). Similarly, brachial-ankle pulse wave velocity (baPWV) has been investigated as a new method of assessing systemic atherosclerosis. This technique is increasingly available in clinical settings, particularly in Japan. Brachial-ankle PWV is calculated as the velocity of the pulse wave between two sites in the arterial tree, representing the degree of arterial stiffness. The clinical value of measuring baPWV has been assessed to some extent. A few studies, for example, indicated positive associations between baPWV and coronary heart disease (*11*), cerebral infarction (*12*), and cardiovascular death (*13*).

The technological development and wide distribution of MRI and magnetic resonance angiography (MRA) have

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increased the chance of finding small and silent brain lesions such as silent cerebral infarction (SCI) and silent intracranial arterial stenosis. Compared with symptomatic cardiovascular disorders such as stroke and coronary heart diseases, SCI and intracranial stenosis have been understudied in terms of their risks and consequences. Some studies showed SCI was associated with future stroke (*14–18*). However, the relationships among SCI, intracranial stenosis, carotid plaque, IMT, and baPWV are scarcely known. Because the carotid lesions and the increased baPWV are expressions of systemic atherosclerosis, they can be associated with these silent brain lesions, which are causally related to atherosclerosis in the brain. In light of the increasing availability in Japan of screening programs for cerebrovascular diseases using MRI and MRA in combination with carotid ultrasound examination and baPWV measurement, it would be beneficial to evaluate the associations between these non-invasive tests for atherosclerosis and silent brain conditions. In this study we therefore evaluated the power of these associations, and examined the value of carotid ultrasound and baPWV measurement as tools for assessing the degree of atherosclerosis in the brain.

Table 1. Characteristics of the 476 Study Subjects

Age (years)	51.5±7.8
Male sex (*n* (%))	273 (57.4)
Body mass index (kg/m^2)	23.8±3.3
Treated hypertention (*n* (%))	60 (12.6)
History of hyperlipidemia (*n* (%))	36 (7.6)
History of diabetes (*n* (%))	17 (3.6)
Systolic blood pressure (mmHg)	127.0±17.3
Diastolic blood pressure (mmHg)	78.3±12.7
Brachial-ankle pulse wave velocity (cm/s)	1,420.1±264.7
Carotid artery findings	175 (36.8)
Plaque (*n* (%))	161 (33.8)
Increased intima-media thickness (*n* (%))	33 (6.9)
MR findings	108 (22.7)
Silent cerebral infarction (*n* (%))	99 (20.8)
Intracranial stenosis (*n* (%))	7 (1.5)

Data are expressed as mean±SD, or number (%) where indicated. MR, magnetic resonance.

Methods

Data Collection

We collected data on the 480 asymptomatic adult subjects who voluntarily participated in the brain screening program at Mominoki Hospital, Kochi City, between April 2003 and March 2006. This is the so-called "brain dock" program, and each participant paid for his or her screening, which was completely outside the national health insurance system. It could thus be expected that the participants were wealthier and more conscious of their health condition than the general population in Japan. If a subject underwent a screening more than once during the study period, data from the first screening were used for analysis. At the time of screening, a self-administered questionnaire was given to each subject to obtain information on current and past history and treatment, including data on coronary heart disease, diabetes, and hypertension. The hospital staff coded the collected information in order to blind outside researchers to the identity of subjects. The hospital's ethics committee approved the study protocol as well as the procedures for obtaining informed consent and for protecting personal data.

Brachial-Ankle PWV Measurement

Brachial-ankle PWV was measured using a volume-plethysmographic apparatus (BP-203RPEII; Colin-Omron, Co., Ltd., Tokyo, Japan). This instrument records PWV, blood pressure, electrocardiogram data, and heart sounds simultaneously. The subject was examined in the supine position, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. After at least 5 min of rest, the subject's volume pulse form was detected. The time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle (ΔT_{ba}). The distance between each sampling point and the heart of the subject was calculated according to the subject's height. Brachial-ankle PWV was calculated as the difference between the ankle-heart distance and the brachium-heart distance subdivided by ΔT_{ba} (*19*).

Carotid Ultrasonography

B-mode ultrasonography of the carotid arteries was performed by one of the two trained clinical technicians who worked for the hospital, using a 7.5 MHz linear array transducer and the duplex scanner of a Toshiba Power Vision 8000 ultrasound system (Toshiba Medical Systems, Tokyo, Japan). Both the right and left common carotid arteries were examined. In this study, we measured carotid IMT in the common carotid arteries (CCAs), and detected plaques in the CCAs and at bifurcations. The IMT, defined as the distance between the media-adventitia interface and the lumina-intima interface (*20*), was measured by longitudinal 2-dimensional (D) ultrasound, using image magnification. Any focal thickening of the intima-media was excluded from the IMT measurements. IMT was measured at the point of maximal thickness in the walls of both CCAs, using the distance measurement tool in the ultrasound scanner. The measurement was performed to one decimal place in mm and imaged on the scanner display. We defined a thickened IMT as ≥1.0 mm existing in both carotid arteries. This value, 1.0 mm, is recommended as a cut-off point in some practice guidelines (*9*, *10*).

We also checked for the presence of atherosclerotic

Table 2. Characteristics of Subjects Classified According to the Status of Silent Cerebral Infarction (SCI)

	SCI (+) (n=99)	SCI (–) (n=377)	p*
Age (years)	57.6±8.9	49.9±6.6	<0.01
Male sex (n (%))	57 (57.6)	216 (57.3)	1.00
Body mass index (kg/m^2)	23.7±3.4	23.8±3.3	0.86
Treated hypertention (n (%))	23 (23.2)	37 (9.8)	<0.01
History of hyperlipidemia (n (%))	7 (7.1)	29 (7.7)	0.52
History of diabetes (n (%))	5 (5.1)	12 (3.2)	0.27
Systolic blood pressure (mmHg)	130.9±17.3	126±17.1	0.01
Diastolic blood pressure (mmHg)	80.5±12.6	77.8±12.7	0.06
Brachial-ankle pulse wave velocity (cm/s)	1,493.2±295.7	1,400.9±252.8	<0.01
Carotid plaque (n (%))	61 (61.6)	100 (26.5)	<0.01
Increased intima-media thickness (n (%))	16 (16.2)	17 (4.5)	<0.01
Intracranial stenosis (n (%))	3 (3.0)	4 (1.1)	0.16

*Fisher's exact test or Student's t-test. Data are expressed as mean±SD, or number (%) where indicated.

plaques, defined as localized lesions with protrusion into the arterial lumen, in CCAs or at bifurcations. We considered plaque to be present when it was found in either or both CCAs (*9*, *10*). Both thickened IMT and plaques were reconfirmed by re-examining the lesions on the printouts from the ultrasound scanner. No subjects had severe (50% or more) stenosis.

Brain MRI and MRA

Brain MRI was performed using a 1.5-T Signa Echospeed (GE Healthcare, Milwaukee, USA) to obtain T_2-weighted images and fluid-attenuated inversion recovery (FLAIR) images (T_2-weighted images: repetition time [T_R]=3,000 ms, echo time [T_E]=99.7 ms, body weight [BW]=15.6, 8 ch brain coil, field of view [FOV]=20 cm, 8 mm thickness/2 mm spacing, matrix=320×224, number of excitations [NEX]=1, and FLAIR; T_R=8,002 ms, T_E=107 ms, BW=15.6, 8 ch brain coil, FOV=20 cm, 8 mm thickness/2 mm spacing, matrix=256×160, NEX=1). Based on the guidelines of the Japanese Society for the Detection of Asymptomatic Brain Diseases 2003 (*21*), silent cerebral infarct was defined as a hyper-intense lesion less than 15 mm in diameter on conventional T_2-weighted images and on FLAIR images without any neurological deficit.

We used the 3D time-of-flight technique for brain MRA with gradient echoimaging (T_R=40 ms, T_E=6.8 ms, flip angle 20°, NEX=1, FOV=12.5×12.5 cm, matrix=128×128, and voxel size 0.9×0.9×1.0 mm). The slab was 64 mm thick and was parallel to the circle of Willis, demonstrating internal carotid, anterior cerebral, anterior communicating, middle cerebral, posterior cerebral, basilar, and vertebral arteries. Any degree of stenosis detected in the arteries was regarded as abnormal. MRI and MRA images were interpreted by a single board-certified neurosurgeon.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Tokyo, Japan). To compare characteristics of subjects with and without brain findings, Student's t-test was used for continuous variables and Fisher's exact test was used for categorical variables. Multiple logistic regression models were used to determine the independent contribution of each carotid lesion, baPWV, and other explanatory variables to the prediction of SCI and intracranial arterial stenosis. In the models, the effects of the explanatory variables were adjusted for three cardiovascular risk factors: age, sex, and history of hypertension. Odds ratios with 95% confidence intervals were calculated. A p-value <0.05 was considered statistically significant.

Results

Among the 480 subjects, 3 had cerebral infarction and one had cerebral bleeding on MRI with a clinical history of stroke. Thus, the remaining 476 subjects were included in the analysis. Characteristics of the study subjects and a summary of test results are shown in Table 1. The mean age was 51.5 years, and 57.4% were male. Ultrasound examination revealed that 33.8% of the subjects had plaques and 6.9% had increased IMT in the carotid arteries. SCI was found in 20.8% of the subjects on MRI and 1.5% had intracranial arterial stenosis found on MRA.

The subjects were divided into two groups: those with SCI and those without it, and the characteristics of both groups were compared in the univariate analysis. Table 2 shows the results of the comparison. The SCI group had a significantly higher values than the non-SCI group for of the following items: age, systolic blood pressure, baPWV, rate of carotid plaque, rate of increased IMT, and the rate of treated hypertension. We likewise compared subjects with and without intracranial arterial stenosis. The results are shown in Table 3.

Table 3. Characteristics of the Subjects Classified According to the Status of Intracranial Arterial Stenosis

	Stenosis (+) (n=7)	Stenosis (–) (n=469)	p*
Age (years)	52.6±7.2	51.5±7.8	0.72
Male sex (n (%))	5 (71.4)	268 (57.1)	0.70
Body mass index (kg/m^2)	24.5±3.1	23.8±3.3	0.54
Treated hypertention (n (%))	2 (28.6)	58 (12.4)	0.22
History of hyperlipidemia (n (%))	0 (0.0)	36 (7.7)	0.58
History of diabetes (n (%))	1 (14.3)	16 (3.4)	0.23
Systolic blood pressure (mmHg)	142.6±16.6	126.8±17.2	0.02
Diastolic blood pressure (mmHg)	83.6±12.4	78.2±12.7	0.27
Brachial-ankle pulse wave velocity (cm/s)	1,664.4±463.1	1,416.4±259.7	0.01
Carotid plaque (n (%))	2 (28.6)	159 (33.9)	1.00
Increased intima-media thickness (n (%))	3 (42.9)	30 (6.4)	<0.01
Silent cerebral infarction (n (%))	3 (42.9)	96 (20.5)	0.16

*Fisher's exact test or Student's t-test. Data are expressed as mean±SD, or number (%) where indicated.

Table 4. Multivariate Analysis of Factors Associated with Silent Cerebral Infarction and Intracranial Arterial Stenosis

	SCI			Stenosis		
	OR	95% CI	p*	OR	95% CI	p*
Age (1 year)	1.12	1.08–1.17	<0.01	0.94	0.83–1.07	0.11
Male sex	0.66	0.38–1.13	0.13	1.10	0.18–6.57	0.92
Treated hypertention	2.22	1.11–4.43	0.02	2.64	0.44–15.80	0.29
Systolic blood pressure (10 mmHg)	1.04	0.86–1.26	0.67	1.14	0.70–1.84	0.60
Brachial-ankle pulse wave velocity (100 cm/s)	0.93	0.82–1.05	0.25	1.28	0.90–1.81	0.17
Carotid plaque	2.69	1.59–4.56	<0.01	0.38	0.05–2.75	0.34
Increased intima-media thickness	2.40	1.02–5.65	0.04	9.70	1.48–63.71	0.02

*Logistic regression analysis. SCI, silent cerebral infarction; OR, odds ratio; CI, confidence interval.

The group with intracranial arterial stenosis had higher systolic blood pressure, baPWV, and a higher rate of increased IMT than the non-stenosis group.

Table 4 shows the results of the multivariate analysis for SCI and intracranial arterial stenosis. SCI had a positive association with age, carotid plaque, increased IMT, and treated hypertension. The group with intracranial arterial stenosis had a higher rate of increased IMT than the non-stenosis group.

Discussion

This study showed that carotid plaque and increased IMT were related with SCI independently of conventional stroke risk factors such as age and blood pressure. It also showed that increased IMT was independently related with intracranial arterial stenosis. Brachial-ankle PWV was associated with both SCI and intracranial arterial stenosis in univariate analysis, but the significance in the associations disappeared when adjustment was made for other risk factors.

Past cross-sectional and prospective studies have indicated that the ultrasound-detected carotid atherosclerotic lesions were associated with ischemic stroke (*1*, *2*) and coronary heart diseases (*22*, *23*), and that these lesions can help to estimate the risk of ischemic stroke (*3–8*). Our study showed the two types of carotid lesion were related with SCI. According to the criteria for SCI defined by the Japanese Society for the Detection of Asymptomatic Brain Diseases, the lesions must be 3 mm or more in greatest diameter (*21*). SCI generally is detected by MRI, and is thought to be a risk factor for stroke. The presence of SCI frequently is associated with symptomatic stroke (*14–18*), cognitive dysfunction (*24*, *25*), and both psychiatric and neurological disorders (*17*, *26*, *27*). Age, hypertension, smoking, diabetes, and atrial fibrillation are known as SCI risk factors. In addition, recent studies indicated carotid plaque and increased IMT are also risk factors (*28*, *29*). The results of our study support those findings and show that the carotid arteries can be a window into atherosclerosis in the cerebrovascular system.

In terms of intracranial arterial stenosis, MRA sensitivity and specificity were reported to be 85–100% and 96–97%, respectively, when conventional contrast angiography was used as the diagnostic standard (*30–32*). MRA is hence considered a good alternative to conventional angiography. In Japan, widely available mass screenings for intracranial arteries using MRI and MRA (brain dock) are increasingly uncovering cases of asymptomatic stenosis of main arteries in the

brain. Intracranial arterial stenosis was recently reported as a risk factor for brain infarction (*33*). Intracranial arterial stenosis is known to reflect systemic atherosclerosis (*34*). Therefore, it is expected that intracranial arterial stenosis is associated with systemic atherosclerotic indicators such as carotid plaque, increased IMT, and increased baPWV. However, as far as we know, no studies have evaluated such associations. The results of this study show that intracranial stenosis is associated with increased IMT but not with carotid plaque or increased PWV. Particularly, carotid plaque is an atherosclerotic change in arterial intima, and therefore its association with arterial stenosis was strongly expected. However, it had no association with intracranial arterial stenosis. The reason for this incongruence is unknown. There were only 7 cases of intracranial arterial stenosis in our study. This small sample size probably decreased the statistical power to detect associations. Further study with a larger sample size is needed.

The importance and value of measuring aortic PWV have been extensively studied. Aortic PWV was reported to be related with coronary heart diseases and stroke, even after adjustment for conventional coronary risk factors (*35–37*). Recently, the number of studies using baPWV, which is a simpler and less invasive way to measure PWV than the aortic method, has been increasing because of its wide availability in Japan (*38*). Brachial-ankle PWV was reported to have a high correlation with aortic PWV and is therefore considered a good alternative to aortic PWV (*39*). Recent studies have shown that baPWV is related to IMT, carotid plaque (*40*, *41*), calcification of the abdominal aorta (*42*), systemic vascular damage (*43*), and metabolic syndrome (*44*). In terms of its association with cardiovascular outcomes, baPWV was reported to correlate with coronary heart diseases (*11*), stroke (*12*), and overall cardiovascular death (*13*).

Despite the accumulation of epidemiological evidence on baPWV, little is known about its association with silent cerebrovascular diseases. The results of our study indicate that baPWV is associated with both SCI and intracranial arterial stenosis. However, the associations were strongly confounded by other stroke risk factors and were therefore recognized only in univariate analysis. In particular, blood pressure correlated strongly with PWV and offset baPWV's relationship with brain lesions. When we excluded blood pressure and history of hypertension treatment from the explanatory variables in the multivariate model, baPWV was significantly associated with intracranial arterial stenosis (odds ratio: 1.33; 1.01–1.75, data not shown in tables). We hence assume that PWV can be a predictor of these brain conditions, but the power to predict would be no more than that of blood pressure. However, because of the small number of outcomes in this study, we should be cautious about making conclusions about the value of baPWV as a predictor of silent brain lesions. Further studies are needed for that.

Although both carotid lesions and baPWV reflect atherosclerosis, the results of our study indicated that carotid lesions were more strongly associated with brain lesions. A possible reason for this is that carotid lesions and baPWV reflect different aspects of atherosclerosis. Brachial-ankle PWV, through the intermediary of pulse waves, represents physical stiffness of the arterial wall, while carotid lesions represent morphological changes that have occurred in the tunica intima and tunica media. Thus, it is expected that carotid lesions correlate better with arterial wall diseases. Another reason may be that, because carotid arteries are a part of the cerebrovascular system, carotid lesions reflect more specifically atherosclerotic changes of the cerebrovascular system than baPWV, which is a parameter of atherosclerosis in systemic arteries. Therefore, carotid ultrasound examination may be better than baPWV measurement in terms of its power to reflect cerebrovascular atherosclerosis. However, it is certainly true that baPWV is a convenient and non-invasive tool with which to obtain a rough overview of atherosclerosis in systemic arteries. Hence, each test should be used separately, depending on the purpose of the screening.

This study has some limitations. First, MRI interpretation by a single reviewer may produce detection bias, although the prevalence of SCI that we detected was comparable to that reported in another brain-screening–based study in Japan (*18*). Also, the validity of ultrasound findings is at issue because intra- and inter-observer variabilities of the two sonographers used in this study are unknown. Second, detailed characteristics of SCI and plaque-like size, shape, and location were not analyzed. Some of the lesions we recognized as SCI might have been état criblé, which corresponds to vascular ectasia and dilated perivascular spaces. Similar to infarcts, on T_2-weighted MRI état criblé appear as bright spots, but are said to be smaller than infarctions. A cut-off diameter of 3 mm was adopted according to the guidelines of the Japanese Society for Detection of Asymptomatic Brain Diseases and was also used in some epidemiological studies (*21*, *45–47*). In reality, however, it is quite difficult to clearly separate the two conditions. A Japanese study that used brain dock data with a population whose age and sex distributions were similar to those in our study, reported that 3% of SCI-like T_2-bright lesions actually were état criblé (*48*). Thus, in our study a similar proportion of SCI cases might have been état criblé and thus our results may have been diluted.

In conclusion, ultrasound examination of carotid arteries is useful for assessing the degree of atherosclerosis of the cerebrovascular system. Brachial-ankle PWV measurement is also useful for this purpose, but its association with atherosclerotic lesions in the brain seems to be confounded by blood pressure. Further studies are needed to confirm the value of measuring baPWV for screening for cerebrovascular diseases.

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