Association between Silent Brain Infarct and Arterial Stiffness Indicated by Brachial-ankle Pulse Wave Velocity

Naoki Saji¹², Kazumi Kimura¹, Hirotaka Shimizu² and Yasushi Kita²

Abstract

Objective The aim of this hospital-based cohort study was to clarify the independent association between silent brain infarct (SBI) and arterial stiffness indicated by brachial-ankle pulse wave velocity (baPWV) including the cutoff value for SBI.

Methods We studied 240 consecutive patients (mean age 69 years) with no history of stroke. We assessed the presence of SBI, white matter hyperintensities (WMHs), and risk factors. Arterial stiffness was evaluated using baPWV. We measured the intima-media thickness of the common carotid artery (CCAIMT) using carotid ultrasonography. We divided patients into two groups according to the presence or absence of SBI, and compared clinical characteristics between the two groups.

Results In multivariable analysis, increased baPWV [by 1 m/s; odds ratio (OR) 1.13, 95% confidence interval (CI) 1.02-1.25] was independently associated with SBI. The baPWV cutoff value for SBI was 17.49 m/s. Patients with baPWV ≥17.49 m/s had a higher possibility of the presence of SBI (OR 2.30, 95% CI 1.02-5.34) compared with patients with baPWV <17.49 m/s. Furthermore, the adjusted OR for the presence of SBI of the combination of baPWV ≥17.49 m/s and CCAIMT ≥1.1 mm (OR 2.73, 95% CI 1.24-6.11) was higher compared with that of baPWV ≥17.49 m/s (OR 2.47, 95% CI 1.11-5.65).

Conclusion Arterial stiffness is independently associated with SBI. Measurement of baPWV can indicate the presence of SBI, especially in patients with baPWV ≥17.49 m/s.

Key words: arterial stiffness, brachial-ankle pulse wave velocity, intima-media thickness, silent brain infarct, small vessel disease, white matter hyperintensities

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Introduction

Silent brain infarct (SBI) and white matter hyperintensities (WMHs) are risk factors for stroke, and are associated with cognitive impairment and poor functional outcome after stroke (1-15). The etiology of SBI and WMHs is related to cerebral small vessel disease (SVD) associated with arterial stiffness including age and hypertension (5-15). Although SBI and WMHs have similar clinical features and risk factors, their pathological findings are quite different. For example, the pathologic findings of SBI include gliosis and loss of myelin and axons, while those of WMHs include myelin pallor and dilatation of the perivascular spaces (8, 13-16). Furthermore, SBI is the highest risk factor (odds ratio (OR) 3.66) for stroke compared with marked periventricular hyperintensity (OR 2.08) and marked separate deep white matter hyperintense lesions (OR 2.73) (9).

We know from earlier work that arterial stiffness indicated by brachial-ankle pulse wave velocity (baPWV) can be used to assess the presence of WMHs and the baPWV cutoff value for WMHs is 18 m/s (5). Arterial stiffness is associated with microvascular early atherosclerotic changes, and is an independent predictor of cardiovascular deaths and events (3-8, 17-27). Previous studies demonstrated that baPWV cutoff values for increased intima-media thickness, cardiovascular events, and all-cause mortality were determined between 17 and 19 m/s (19-23). Although SBI is also

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associated with increased baPWV (3), the baPWV cutoff value for detection of SBI is not yet clear. In the present study, we investigated whether baPWV can be used to indicate the presence of SBI in our hospital-based cohort independently of age, gender, and other risk factors. Furthermore, we determined the baPWV cutoff value for SBI.

### Materials and Methods

#### Subjects

This was a single-center observational study approved by the Institutional Review Board at the Hyogo Brain and Heart Center at Himeji. Between October 2003 and March 2010, we enrolled consecutive patients who visited the clinic in the Department of Neurology at this hospital to request medical evaluation for a routine checkup or assessment of possible cerebrovascular diseases for reasons such as simple fear of stroke and positive vascular risk factors. The details of the inclusion and exclusion criteria have been described previously (5). In brief, patients were enrolled who had no history of stroke, transient ischemic attack, or dementia, no abnormality on neurological examination, no evidence of atrial fibrillation or atrial flutter, and no symptomatic and/or treated peripheral arterial disease. Informed consent was obtained from all patients. All MRI scans and other measurements were assessed blinded to any clinical information.

#### MRI assessment

All patients underwent a 1.5-T brain MRI scan (Intera, Philips Medical Systems, Best, The Netherlands), including diffusion-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging, and T2-weighted imaging (T2WI). The image acquisition parameters were as described previously (1, 5). SBI was defined as a focal lesion of at least 3 mm in diameter, with hyperintensity on T2WI and hypointensity on FLAIR (5, 9, 12). WMHs were defined as an irregular periventricular hyperintensity (Fazekas grade ≥3) and/or early confluent or confluent separate deep white matter hyperintense lesions (Fazekas grade ≥2) on T2WI and FLAIR, based on the rating scales of ischemic tissue damage due to arteriosclerosis (5, 9, 15, 28).

#### Carotid ultrasonography

We measured the far wall common carotid artery intima-media thickness (CCAIMT) using images acquired by high-resolution B-mode ultrasonography with a 7.5-MHz linear array transducer. We measured the maximal CCAIMT on both the left and right sides, and used the larger value for analyses (5). The maximal CCAIMT ≥1.1 mm was defined as increased CCAIMT (11, 29).

#### Measurement of ABI and baPWV

Ankle-brachial pressure index (ABI) and baPWV were measured using an oscillometric device (Form PWV/ABI®; Omron Colin Co., Ltd., Tokyo, Japan), which has been described in detail previously (18, 19). After examinations had been performed on both the right and left sides, we chose the lower ABI and the higher baPWV for analyses (5). ABI <0.9 was considered indicative of peripheral arterial disease (5).

#### Risk factors

Hypertension was defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg and/or by the use of antihypertensive agents. Hypercholesterolemia was defined as serum total cholesterol level ≥220 mg/dL and/or by the use of statins. Diabetes mellitus was defined as hemoglobin A1c level ≥6.5% and/or by the use of oral hypoglycemic agents or insulin, and/or a serum fasting blood sugar level ≥126 mg/dL. Ischemic heart disease was defined as a history of physician-diagnosed angina pectoris, evidence of prior myocardial infarction, or a prior coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass surgery). Current smoking habits were recorded.

#### Statistical analysis

Continuous variables are expressed as means and standard deviation and were compared using unpaired Student’s t-tests. Variables exhibiting skewed distributions are expressed as medians and inter-quartile range, and were compared using the Wilcoxon rank-sum test. Categorical variables are expressed as frequencies and percentages and were compared using χ² tests. Multiple logistic regression analyses were performed to identify the variables independently associated with SBI. Receiver operating characteristic curve analysis was performed to determine the cutoff value of baPWV for the presence of SBI. A two-tailed p<0.05 was considered to indicate statistical significance. ORs are presented with 95% confidence intervals (CIs). The data were analyzed using the JMP 8.0.2 software package (SAS Institute Inc., Cary, NC).

#### Results

#### Characteristics of the patients

A total of 240 patients were included in this study. Table 1 summarizes the characteristics of these patients. Among the 42 patients with SBI, 39 patients had a single infarct, whereas three patients had multiple infarcts and two of the three patients had both SBI and WMHs. Furthermore, 50% of the infarcts were located in the subcortical white matter (corona radiata, 24%; internal capsule, 17%; centrum semiovale, 9%), and 48% were in the basal ganglia (43%) or thalamus (5%). One patient had a cortical infarct.

#### Comparison between patients with/without SBI

Table 1 compares the clinical characteristics of patients with SBI and those without SBI. Patients with SBI had a significantly older age, increased baPWV and CCAIMT, and...
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n = 240)</th>
<th>SBI (+) (n = 42)</th>
<th>SBI (–) (n = 198)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>119 (50%)</td>
<td>23 (55%)</td>
<td>98 (50%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Age, years</td>
<td>69 (9)</td>
<td>72 (9)</td>
<td>68 (8)</td>
<td>0.01</td>
</tr>
<tr>
<td>CCAIMT, mm</td>
<td>1.5 (1.1–2.1)</td>
<td>1.9 (1.4–2.3)</td>
<td>1.4 (1.1–2.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>ABI</td>
<td>1.13 (1.09–1.18)</td>
<td>1.16 (1.05–1.20)</td>
<td>1.13 (1.09–1.17)</td>
<td>0.04</td>
</tr>
<tr>
<td>baPWV, m/s</td>
<td>17.11 (14.68–19.92)</td>
<td>18.84 (16.16–22.02)</td>
<td>16.71 (14.53–19.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMHs</td>
<td>82 (34%)</td>
<td>27 (64%)</td>
<td>55 (28%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>177 (74%)</td>
<td>36 (86%)</td>
<td>141 (71%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>140 (58%)</td>
<td>27 (64%)</td>
<td>113 (57%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>61 (25%)</td>
<td>16 (38%)</td>
<td>45 (23%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>40 (17%)</td>
<td>12 (29%)</td>
<td>28 (14%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoking</td>
<td>49 (20%)</td>
<td>7 (17%)</td>
<td>42 (21%)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Data are means (standard deviation), medians (inter-quartile range), or numbers (%). Abbreviations: ABI, ankle-brachial pressure index; baPWV, brachial-ankle pulse wave velocity; CCAIMT, intima–media thickness of the common carotid artery; SBI, silent brain infarct; WMHs, white matter hyperintensities.

A higher proportion of WMHs and ischemic heart disease compared with patients without SBI (Table 1). In multivariable analysis (Table 2), baPWV (by 1 m/s, OR 1.13, 95% CI 1.02–1.25) was independently associated with SBI (model 1). The baPWV cutoff value for detection of SBI was 17.49 m/s with 69% sensitivity and 60% specificity (area under the receiver operating characteristic curve; AUC=0.67±0.04, 95% CI 0.58–0.76, p <0.001). The possibility of the presence of SBI significantly increased in patients with baPWV ≥17.49 m/s (OR 2.30, 95% CI 1.02–5.34) compared with that of baPWV <17.49 m/s with the same adjustment applied (model 2). When patients were grouped according to quartiles of baPWV, the ORs of the presence of SBI increased with baPWV group with the same adjustment applied, although this analysis was not statistically significant (model 3).

The combination of baPWV and CCAIMT

As shown in Table 3, increased CCAIMT (both by 1 mm increase and ≥1.1 mm) was not independently associated with the absence of both SBI and WMHs, with the presence of SBI, and with the presence of SBI and/or WMHs. However, increased baPWV (both by 1 m/s increase and ≥17.49 m/s) was independently associated with those variables. Furthermore, combination of both baPWV≥17.49 m/s and CCAIMT≥1.1 mm had a higher possibility of the presence of SBI and the presence of SBI and/or WMHs compared with baPWV≥17.49 m/s (OR 2.73 versus 2.47, OR 3.14 versus 2.31, respectively).

Discussion

The main finding of the present study was that arterial stiffness indicated by baPWV is associated with SBI, independent of conventional vascular risk factors such as age, hypertension, and diabetes mellitus. We also confirmed the baPWV cutoff value for detection of SBI was 17.49 m/s, and the increased ORs of the combination of baPWV≥17.49 m/s and CCAIMT≥1.1 mm.

When arteriosclerosis is progressing, arterial stiffness of central artery increases and extension is attenuating. After that, microcirculation of peripheral artery is affected. Regarding small cerebral artery, vascular endothelial is damaged, and blood-brain barrier is failed, which should cause cerebral damage such as SBI and WMHs (8, 14, 24). Our results should be consistent with pathophysiological mechanisms.

The cutoff value of baPWV for SBI (17.49 m/s) in the present study is in agreement with that of previous studies (3, 7). Kim et al. reported a cutoff value of baPWV that represents the presence of asymptomatic subcortical ischemia (SBI and/or WMHs) of 17 m/s (7). Hatanaka et al. reported a mean baPWV of 18 m/s in patients with SBI (3). Considering the differences among subjects, our results are consistent with those of previous studies. Conversely, some reports suggested that baPWV was not independently associated with SBI (4, 30). Matsumoto et al. included état criblé in the definition of SBI, which encompasses vascular ectasia and dilated perivascular spaces, and is smaller than 3 mm (4). This contamination possibly affected their results. In our study, because SBI required a diameter ≥3 mm, état criblé was excluded. Nomura et al. reported that CCAIMT, but not baPWV (by 1 cm/s) was independently associated with SBI in patients with diabetes mellitus (30). However, change the unit of pulse wave velocity (PWV) from cm/s to m/s might be better to identify the relationship of PWV with outcomes and to simplify determination of the cutoff values of PWV (4, 27).

The baPWV cutoff value for SBI (17.49 m/s) was comparable to the cutoff for WMHs (18.29 m/s) in this cohort (5). This concurrence suggests that both WMHs and SBI are related to arteriosclerotic etiology because increased baPWV...
Table 2. Comparison between Patients with SBI and Patients without SBI by Univariable and Multivariable Logistic Regression Analyses

<table>
<thead>
<tr>
<th></th>
<th>Univariable Model 1</th>
<th>Multivariable Model 1</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
<td>1.33</td>
<td>1.17</td>
<td>1.22</td>
<td>1.22</td>
</tr>
<tr>
<td>Age (by 1 year)</td>
<td>0.68–2.64</td>
<td>0.51–2.73</td>
<td>1.05 *</td>
<td>1.02</td>
<td>1.03</td>
<td>1.03</td>
</tr>
<tr>
<td>CCAIMT, mm</td>
<td>1.01–1.10</td>
<td>0.97–1.08</td>
<td>1.51</td>
<td>1.19</td>
<td>1.23</td>
<td>1.30</td>
</tr>
<tr>
<td>baPWV (by 1 m/s)</td>
<td>0.99–2.30</td>
<td>0.74–1.90</td>
<td>1.17 †</td>
<td>1.13 †</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>baPWV &lt;17.49 (reference)</td>
<td>-</td>
<td>-</td>
<td>1.08–1.28</td>
<td>1.02–1.25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quartile 1 (&lt;14.68)</td>
<td>-</td>
<td>-</td>
<td>1.17 †</td>
<td>1.13 †</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quartile 2 (14.68–17.10)</td>
<td>-</td>
<td>-</td>
<td>1.08–1.28</td>
<td>1.02–1.25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quartile 3 (17.11–19.92)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quartile 4 (&gt;19.92)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.43 *</td>
<td>1.77</td>
<td>1.77</td>
<td>1.77</td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.35</td>
<td>1.37</td>
<td>1.33</td>
<td>1.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.69–2.76</td>
<td>0.64–3.03</td>
<td>0.63–2.90</td>
<td>0.61–2.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.09 *</td>
<td>1.81</td>
<td>1.79</td>
<td>1.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.74</td>
<td>0.68</td>
<td>0.63</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval. p shown when significant. *, p < 0.05; †, p < 0.001. The prevalence of SBI was the dependent variable. Variables (sex, age, CCAIMT, baPWV by 1 m/s, hypertension, hypercholesterolemia, diabetes mellitus, ischemic heart disease, and smoking) were entered into a logistic regression analysis using the forced entry method (model 1). Model 2 included baPWV categorized by the cutoff value and model 3 included baPWV categorized by quartile distributions with the same adjustment applied.

Table 3. Comparison of ORs for the Presence of SBI and WMHs among baPWV, CCAIMT, and the Combination of baPWV and CCAIMT

<table>
<thead>
<tr>
<th></th>
<th>SBI (–) and WMHs (–)</th>
<th>SBI (+)</th>
<th>SBI (+) and/or WMHs (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCAIMT (mm)</td>
<td>0.89</td>
<td>1.35</td>
<td>1.13</td>
</tr>
<tr>
<td>CCAIMT (≥1.1 mm)</td>
<td>0.81</td>
<td>2.34</td>
<td>1.23</td>
</tr>
<tr>
<td>baPWV (by 1 m/s)</td>
<td>0.41–1.60</td>
<td>0.95–6.71</td>
<td>0.62–2.44</td>
</tr>
<tr>
<td>baPWV (≥17.49 m/s)</td>
<td>0.86 †</td>
<td>1.14 †</td>
<td>1.16 †</td>
</tr>
<tr>
<td>Both baPWV ≥17.49 m/s</td>
<td>0.86 †</td>
<td>1.14 †</td>
<td>1.16 †</td>
</tr>
<tr>
<td>CCAIMT ≥1.1 mm</td>
<td>0.22–0.85</td>
<td>1.24–6.11</td>
<td>1.20–8.52</td>
</tr>
</tbody>
</table>

*, p < 0.05; †, p < 0.01
§, Adjusted-OR for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, ischemic heart disease, and smoking.

indicates arteriosclerotic change (2-8, 18-26). Although hypertension and age were independently associated with WMHs in that cohort (5), these risk factors were not statistically significant in the present study. Hence, WMHs and SBI are equally considered as SVD, but the etiology of WMHs could be more strongly affected by hypertensive arteriosclerosis due to hypertension and age compared with that of SBI.

The possibility of the presence of SBI was nearly two times higher in patients with baPWV ≥17.49 m/s than in
patients with baPWV <17.49 m/s, as shown in Table 2. Turin et al. demonstrated that baPWV ≥17 m/s is an independent predictor of all-cause mortality in a population-based prospective cohort study (19). Matsumoto et al. demonstrated that baPWV ≥18 m/s is the best cutoff value to identify increased CCAIMT in hypertensive patients (7). Furthermore, there is an opinion that a baPWV cutoff value should be 18 m/s, because baPWV is roughly 1.5-fold the magnitude of carotid-femoral pulse wave (cfPWV; conventional measurement of arterial stiffness) (8, 20). The cutoff value of cfPWV >12 m/s for total cardiovascular risk is recommended in the Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology (17, 20). Thus, the baPWV cutoff values of the present studies are consistent with these previous studies, although there are certain differences regarding subjects and outcomes. We recommend the use of brain MRI to detect SBI and/or WMHs in patients with increased baPWV (roughly ≥17 or ≥18 m/s), even if they are neurologically asymptomatic. Assessing baPWV may be reasonable, convenient, and cost-effective as an initial assessment tool to identify SBI and WMHs.

Increased CCAIMT is a surrogate marker for atherosclerosis and SBI, and is a risk for stroke (29, 30). Although CCAIMT was not significantly associated with SBI in the present study, the combination of baPWV ≥17.49 m/s and CCAIMT ≥1.1 mm strongly indicated the presence of SBI. Therefore, this combined factor might be a useful and non-invasive method to examine atherosclerosis.

There were several limitations of this study, as in our previous report (5). This study contains analyses of small numbers. Selection bias is possible because this was a hospital-based cohort study and we mainly enrolled patients who were relatively old and had cardiovascular risk factors. The causal relationships between the factors and SBI remain unclear because this is a correlational study. The location of infarcts such as corona radiate, internal capsule, or thalamus might suggest the possibilities of symptomatic cerebral infarction, because these infarcts can sometimes contribute to neurological impairment such as memory problem or subtle motor deficit (12, 13). Using a visual rating scale and integrating periventricular hyperintensity and separate deep white matter hyperintense lesions into WMHs may be less accurate than directly assessing WMHs. T1-weighted imaging in addition to T2WI and FLAIR images are desirable to more accurate detection of SBI, however, the averaged AUC for SBI in the combination of T2WI and FLAIR images (0.85) was similar to that of the combination of T1WI and T2WI (0.86), and three image types (0.95) (31). Other factors may also be associated with SBI, including alcohol habit, central systolic blood pressure, cerebral microbleeds, and chronic kidney disease (11-13, 32, 33). Further research is needed to validate an appropriate stroke prevention strategy for patients identified with SBI and/or WMHs.

In conclusion, arterial stiffness is independently associated with SBI. Measurement of baPWV can indicate the presence of SBI and may identify patients at risk of stroke.

**The authors state that they have no Conflict of Interest (COI).**

**References**

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http://www.naika.or.jp/imindex.html