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Association between Carotid Wall Shear Stress-Based Vascular Vector Flow Mapping and Cerebral Small Vessel Disease

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Aim: Wall shear stress (WSS) is the frictional force caused by viscous blood flowing along the vessel wall. Decreased WSS is associated with local vascular endothelial dysfunction and atherosclerosis. The vector flow mapping (VFM) technique detects the direction of intracardiac blood flow and WSS on the vessel wall with echocardiography. In this study, we examined carotid WSS by applying the VFM technique to the carotid arteries and evaluated its relationship with cerebral small vessel disease (SVD).

Methods: This is a single-center, prospective, observational study. We investigated the association between carotid WSS and SVD imaging, and cognitive outcomes in consecutive 113 patients with acute lacunar infarction.

Results: Carotid WSS was negatively associated with age (r=-0.376, $p<0.001$). Lower WSS was correlated with total SVD scores ($\rho=-0.304$, $p=0.004$), especially with enlarged perivascular space (EPVS) in the basal ganglia > 10 ($p<0.001$). The carotid intima-media thickness was not associated with the total SVD score ($\rho=-0.183$, $p=0.052$). Moreover, lower WSS was associated with executive dysfunction.

Conclusion: EPVS has recently been reported as a marker of early SVD imaging, and executive dysfunction is common in vascular cognitive impairment. These results suggested that decreased carotid WSS based on vascular VFM, which can be measured easily, is associated with imaging and cognitive changes in the early stages of SVD.

Key words: Wall shear stress, Carotid ultrasonography, Vector flow mapping, Cerebral small vessel disease, Enlarged perivascular space

Introduction

Wall shear stress (WSS) is a frictional force produced by viscous blood flowing parallel to the vessel wall. Animal studies on cardiovascular functions revealed that reduced WSS is associated with local endothelial dysfunction and atherosclerosis[1, 2]. Carotid bifurcations are particularly susceptible to atherosclerosis because of the complex turbulent blood flow in these bifurcations[2].

Computed flow dynamics (CFD)[3] and four-dimensional magnetic resonance imaging (MRI)[4] have been used to measure carotid WSS, but their application is limited in daily clinical practice. A previous report identified the relationship between carotid WSS calculated using the maximum velocity in carotid ultrasonography and atherosclerosis[5]. Another study showed that decreased carotid WSS was associated with increased cerebral white matter lesions and cognitive deterioration over time[6]. However, this measurement of WSS encountered a large error with CFD analysis[7]. As a result, the relationship between carotid WSS and cerebral small vessel disease (SVD) has not satisfactorily been

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investigated in daily clinical practice because of the complex measurement methods involved and the measurement errors associated with WSS.

The recently developed vascular vector flow mapping (VFM) is an application of the conventionally used echocardiographic intracardiac blood flow analysis technique[8] to carotid artery vessels. It is possible to visualize the direction and velocity of blood flow and calculate the WSS, using speckle tracking of the vessel wall, and conservation of mass law with two-directional echo beams. The WSS calculated by vascular VFM reflects the carotid artery wall geometry and motion and is comparable to particle image velocimetry measured using phantom modeling of the carotid artery[9]. Compared to conventional WSS measurement methods, we can easily measure WSS by vascular VFM at patient's bedside. It was shown that carotid WSS measured by vascular VFM inversely correlated with age and carotid mean intima-media thickness (IMT)[10]. Therefore, it is valuable to examine carotid WSS easily and accurately as an indicator of SVD.

Aim

This research aimed to understand the relationship between carotid artery WSS measured using vascular VFM technique and clinical features of cerebral SVD, such as imaging findings and cognitive function.

Methods

Subject Recruitment

This research was a single-center prospective observational study. The study complied with the Declaration of Helsinki for investigations involving humans. The study protocol was approved by the Ethics Committee of the Suiseikai Kajikawa Hospital (Hiroshima, Japan). We prospectively enrolled all consecutive patients with acute lacunar infarction within 7 days of onset admitted to Suiseikai Kajikawa Hospital from May 2020 to May 2021. We obtained the written consent from all patients or their families. Patients who had not undergone head MRI were excluded. Carotid WSS was measured by vascular VFM within 7 days of admission. We examined the relationship among the following clinical information: age, sex, body mass index, history of previous medical history or complications, smoking and drinking history, pre-morbid modified Rankin Scale (mRS), the score of National Institutes of Health Stroke Scale score at admission, head MRI findings, and cognitive and psychological tests. The data that support the findings of this study are available from the corresponding author on reasonable request.

Measurement and Analysis of Carotid WSS by Vascular VFM

A carotid artery ultrasound was performed by a neurologist (T, K) certified by the Japanese Society of Neurology with LISENDO880LE (Hitachi, Tokyo, Japan) with a linear probe (L441, Hitachi, Tokyo, Japan). Blood pressure was measured in the brachial artery before carotid ultrasonography to clarify the circulatory dynamics during WSS measurement. In the measurement, the carotid WSS was measured twice at 1 cm proximal to the bifurcation of the common carotid artery without stenosis or bending in the supine position. At least three heartbeats required for WSS analysis were saved as raw data in each measurement. The depth was less than 3.5 cm, and the common carotid artery was drawn close to the horizontal plane of the screen. The steering angle of the color Doppler flow mapping (CFM) was adjusted as large as possible in 5° increments between 0°–30° to keep a color signal close to the vessel wall and minimalize measurement error[9]. The frame rate was set at 11–13 Hz, the dynamic range and velocity range were kept as small as possible within the aliasing correction, and the echo gain was adjusted, as necessary. The crossbeam was automatically set within 20°–30° of the CFD and was adjusted by 5° increments to maximize the crossbeam Doppler signal in the vessel. The mean IMT of the common carotid artery was also calculated by automatically tracing more than 300 points at the same site of WSS measurement.

In the analysis, we traced the luminal edge of the high-echoic layer of the intima in the early diastolic phase as recommended by the manufacturer, with many tracking points especially near the two ends of the flow area to ensure accurate tracking. If the color signals of the CFM and crossbeam were reversed by exceeding the aliasing, they were corrected frame by frame. Speckle tracking automatically calculates the wall motion, and the blood flow vectors were calculated by the law of conservation of mass with the motion of the vessel wall and the blood flow on the three crossbeam lines as boundary conditions. WSS was calculated frame by frame in each distal and near walls measurement point. One heartbeat with the least WSS measurement deficit was selected from the two saved measurement values. Each heartbeat was divided into systolic, early-diastolic, middle-diastolic, and end-diastolic phases[11]. Since the duration of the diastolic phase of one heartbeat varies among different patients and measurement timings, we considered that the mean WSS for the whole cycle might be smaller

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because of the longer diastolic duration, which could result in measurement bias leading to underestimation. In addition, systolic WSS may be affected by the cardiac output or a particular heartbeat; therefore, the target of this study's analysis was end-diastolic WSS, referencing a previous analysis for WSS[11]. We used the end-diastolic mean WSS in the bilateral carotid arteries and combined the measurements of near and distal walls for the following statistical analysis.

Definition of Acute Lacunar Infarction and Evaluation of Cerebral SVD on Brain MRI

MRI was performed on admission with 1.5 Tesla (Avanto, Siemens Healthineers, Erlangen, Germany) or 3.0 Tesla MRI (Spectra, Siemens Healthineers). The imaging protocol consisted of diffusion-weighted imaging (repetition time (TR)=7000 ms and echo time (TE)=75 ms for spin echo, field of view (FOV)=22 cm, matrix size=98×140, slice thickness=5.0 mm, interslice spacing=1.5 mm), fluid-attenuated inversion recovery image (TR=12,000 ms and TE=87 ms for turbo spin echo, inversion time=2800 ms, FOV=22 cm, matrix size=226×384, slice thickness=5.0 mm, interslice spacing=1.5 mm), T2 star weighted image (TR=617 ms and TE=14 ms for gradient echo, FOV=22 cm, matrix size=224×320, slice thickness=5.0 mm, interslice spacing=1.5 mm), and three-dimensional time-of-flight magnetic resonance angiography (TR=22 ms, TE=3.69 ms, FOV=200 cm, matrix size=215×320, slice thickness=0.50 mm, interslice spacing=-6.0 mm). Acute lacunar infarction was defined as a single acute ischemic lesion less than 15 mm in diameter without more than 50% stenosis in arteries proximal to the territory of the ischemic area, in reference to the Trial of Org 10172 in Acute Stroke Treatment classification[12]. The imaging features of cerebral SVD were evaluated according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)[13], and white matter lesions were evaluated according to Fazekas classification[14]; periventricular hyperintensity (PVH) and deep subcortical white matter hyperintensity (DSWMH). The territory of old lacunar infarction was classified into the thalamus, medial capsule, corona radiata, basal ganglia, and brainstem according to a previous report[15]. Cerebral microbleeds (CMBs) were classified into deep (thalamus, medial capsule, corona radiata, basal ganglia), lobar (cortex, white matter), and infratentorial (cerebellum, brain stem) areas[15, 16]. Enlarged perivascular space (EPVS) was classified into one to three categories in each basal ganglia and centrum semiovale as follows: category 1 for 0 – 10 EPVS, category 2 for 11 – 25, and category 3 for 26 or more[17]. The total SVD score[15] was calculated as an imaging index of cerebral SVD. The score was rated on a scale of 0 to 4 for the following four items: the presence of old lacunar infarction, CMBs in deep territories, PVH of Fazekas 3 or DSWMH of Fazekas 2-3, and EPVS in the basal ganglia of category 2 – 3.

Measurement of Cognitive Function

We performed the following cognitive and psychological tests: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment-Japanese version (MoCA-J), trail making test (TMT), the Japanese version of the Patient Health Questionnaire-9 (PHQ-9)[18], and the Japanese version of the Apathy Evaluation Scale Informant version (AES-I)[19]. The MMSE calculated the sub-scores for orientation, memory, attention, language, and visuospatial skills. The MoCA-J calculates sub-scores for orientation, memory, attention, language, visuospatial skills, and executive function[20].

Statistical Analysis

Statistical analysis was performed using JMP® 16.0 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a p value <0.05. EZR[21] 4.1.3 was used for performing Spearman's rank correlation test. Continuous variables are presented as means (standard deviations) and were analyzed using the Student's t-test. Pearson's correlation coefficient (r) was used for the correlations between variables with bivariate normality. Continuous variables with non-normal distribution are expressed as medians and quartiles and were analyzed using Wilcoxon rank-sum test. Spearman rank correlation test (ρ) was performed to evaluate correlations. Comparisons of categorical variables were performed with the χ^2 test, while Fisher's exact test was used for the same comparison with small sample sizes. Receiver operating characteristic (ROC) curves were generated for WSS and IMT, and areas under the curve were compared. For imaging findings, we evaluated the association between carotid end-diastolic WSS and each of the SVD imaging findings and examined background factors associated with SVD score of ≥ 3 by logistic regression analysis. We also analyzed the association between carotid WSS and cognitive impairment, excluding patients with undeniable moderate depressive states of 14 points or more on PHQ-9 [18], with apathetic states of 46 points or more on the AES-I[19], and those without PHQ-9 or AES-I. Correlations of the WSS with the MMSE, MoCA-J, and TMT were analyzed. The difference between TMT parts B and A was defined as ⊿TMT.

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Results

A total of 117 patients with acute lacunar infarction were recruited. We analyzed 113 patients, excluding four patients who were finally diagnosed with non-lacunar infarction. The median measurement deficit was 0.97% per vessel per heartbeat. The intraclass correlation coefficients (ICC) for the WSS measurement were ICC (1,1)=0.931 and ICC (1,2)=0.976. Background factors, head MRI findings, and cognitive tests are shown in **Supplemental Table 1**. Of the total patients, 59.3% were men with a mean age of 71.3 years. **Table 1** shows a comparison of end-diastolic WSS with background factors, SVD imaging findings, and cognitive function tests. Age and WSS were negatively correlated (r=-0.376, $p<0.001$). The diastolic blood pressure at the time of WSS measurement did not correlate with diastolic WSS. Mean IMT and carotid end-diastolic WSS failed to correlate (r=-0.097, $p=0.307$). Scatter plots between IMT and WSS per phase of the cardiac cycle are included in **Supplemental Fig. 1**. Carotid WSS showed a negative correlation with the total SVD score ($\rho=-0.304$, $p=0.004$), PVH Fazekas grade 3 ($p=0.042$), and especially EPVS in the basal ganglia >10 ($p<0.001$). The mean IMT was not statistically significantly different from the SVD score ($\rho=-0.183$, $p=0.052$, shown in **Supplemental Fig. 2**). There was no significant difference between WSS and IMT in predicting SVD score ≥ 3 (shown in ROC curves in **Supplemental Fig. 3**). Low end-diastolic WSS was significantly associated with SVD score ≥ 3 in univariate analysis ($p=0.020$), but not in multivariate analysis (Odds ratio (OR) : 0.998, 95% confidence interval (CI) : 0.994 – 1.001, $p=0.249$, **Table 2**). Low WSS was not associated with SVD score ≥ 3 when the analysis was restricted to patients with the first acute lacunar infarction **(Supplemental Table 2)**. On the other hand, low end-diastolic WSS showed a significant association with EPVS in the basal ganglia >10 in multivariate analysis (OR: 0.996, 95% CI: 0.993 – 0.9996, $p=0.030$, shown in **Table 3**). WSS was also associated with EPVS in the post-hoc analysis (Effect Size 0.799, Power 0.987).

There was no association between WSS and MMSE, and WSS and MoCA-J respectively, even in each subgroup. However, WSS was negatively correlated with TMT-A, TMT-B, and ⊿TMT ($\rho=-0.470$, $p<0.001$; $\rho=-0.314$, $p=0.005$; $\rho=-0.262$, $p=0.021$; **Table 1**).

Discussion

This is one of the first reports showing the association between carotid WSS measured using vascular VFM and SVD while considering imaging findings and cognitive dysfunction. The measurement of vascular VFM-based WSS in daily clinical practice is easier than conventional WSS and reflects actual vascular morphology and hemodynamics. Previous cohort studies showed that EPVS is the most frequent imaging finding in SVD[15], and pathologically, EPVS appears early in the clinical course of SVD[22]. In this study, decreased WSS was associated with SVD imaging findings, especially EPVS in the basal ganglia region. These results suggest that carotid WSS, which has been considered the maker of the large artery atherosclerosis (LAA), may also be relevant for cerebral SVD.

It has been shown in previous reports that decreased WSS causes endothelial dysfunction, arterial stiffness, and pulse wave reflection[1, 2]. Reduced carotid WSS causes endothelial dysfunction in the carotid artery, which results in increased pulsatility to rich vascularized tissue and secondary carotid atherosclerotic changes such as increased IMT, carotid atheroma, and vascular remodeling[1, 2, 23]. Increased pulsatility in the basal ganglia arteriole causes the rupture of the brain-blood barrier. Consequently, extravasation occurs and interstitial fluid increases, resulting in progressive thickening and stiffening of the arteriolar wall, which limits vasodilation and inhibits normal perivascular fluid flushing[24, 25]. These pathological changes can be visualized as EPVS in brain MRI[24]. EPVS in the basal ganglia is common in cerebral SVD[26]. This is thought to be due to the basal ganglia region being the watershed area[27]. The increased pulsatility in the perforating branch region occurs because of the difference in caliber between the perforating branch and the middle cerebral artery[24]. Furthermore, increased local shear stress is caused by the large branching angle between the perforating branch and the middle cerebral artery[24]. In this study, we found an association between decreased carotid WSS and increased EPVS in the basal ganglia, an early SVD marker. This finding may indicate that mild large artery atherosclerotic change detected by VFM-based WSS is associated with significant early changes in the process of SVD progression.

The significant association between increased IMT and cerebral SVD imaging findings has been reported in the previous study[28]. Some studies have also shown the association between arterial stiffness of extracranial large arteries and cerebral SVD imaging findings[29, 30]. These findings indicated that the early stage of atherosclerotic changes in extracranial large vessels may affect cerebral SVD. The present study targeted patients with early stages of carotid atherosclerotic changes. In fact, the patients in this study had an average IMT of 0.805 mm **(Supplemental**

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Table 1. Comparison of WSS with clinical factors, SVD imaging findings, and cognitive function

	End-diastolic WSS (pa)	*P* value	Correlation coefficient (95% CI)
Background, NIHSS, blood pressure at the measurement of WSS, and IMT			
Age (years old)	-	<0.001	-0.376[r] (-0.525 – -0.206)
Male (N=67) vs female (N=46)	0.29 ± 0.13 vs 0.26 ± 0.14	0.214	-
Body mass index (kg/m^2)	-	0.288	-0.101[r] (-0.280 – 0.085)
HT (N=83) vs non-HT (N=30)	0.27 ± 0.14 vs 0.31 ± 0.12	0.173	-
DL (N=65) vs non-DL (N=48)	0.27 ± 0.13 vs 0.30 ± 0.13	0.212	-
DM (N=52) vs non-DM (N=61)	0.26 ± 0.17 vs 0.30 ± 0.14	0.090	-
CKD (N=30) vs non-CKD (N=83)	0.24 ± 0.14 vs 0.30 ± 0.13	0.025	-
Past stroke (N=29) vs non-past stroke (N=84)	0.25 ± 0.14 vs 0.29 ± 0.13	0.136	-
past symptomatic lacunar infarction (N=12) vs non-past symptomatic lacunar infarction (N=99)	0.28 ± 0.16 vs 0.28 ± 0.13	0.934	-
Habit drinking (N=48) vs non-habit drinking (N=64)	0.31 ± 0.11 vs 0.26 ± 0.14	0.027	-
Smoking (N=47) vs non-smoking (N=66)	0.30 ± 0.13 vs 0.27 ± 0.14	0.243	-
Past ischemic heart disease (N=7) vs non-past ischemic heart disease (N=106)	0.21 ± 0.13 vs 0.29 ± 0.13	0.154	-
Hospitalized NIHSS score	-	0.098	-0.157[ρ] (-0.332 – 0.029)
Diastolic blood pressure at the time of the measurement of WSS	-	0.317	0.096[r] (-0.091 – 0.277)
Mean IMT at the same site of WSS measurement	-	0.307	-0.097[r] (-0.277 – 0.090)
SVD findings in brain MRI findings in brain MRI			
PVH 3 (N=22) vs 0-2 (N=91)	0.23 ± 0.12 vs 0.29 ± 0.13	0.042	-
DSWMH 2-3 (N=47) vs 0-1 (N=66)	0.26 ± 0.12 vs 0.29 ± 0.14	0.219	-
old lacunar (N=82) vs non (N=31)	0.27 ± 0.13 vs 0.31 ± 0.13	0.237	-
deep MBs (N=46) vs non (N=67)	0.27 ± 0.14 vs 0.29 ± 0.13	0.588	-
EPVS in basal ganglia >10 (N=50) vs ≤ 10 (N=63)	0.23 ± 0.12 vs 0.33 ± 0.13	<0.001	-
Total SVD score	-	0.004	-0.304[ρ] (-0.434 – -0.090)
Cognitive and psychological test			
MMSE (N=77)	-	0.212	0.144[ρ] (-0.083 – 0.356)
Orientation	-	0.668	0.050[ρ] (-0.176 – 0.271)
Memory	-	0.648	-0.053[ρ] (-0.274 – 0.173)
Attention	-	0.085	0.198[ρ] (-0.027 – 0.404)
Language	-	0.116	0.180[ρ] (-0.045 – 0.389)
Visuospatial function	-	0.057	0.218[ρ] (-0.006 – 0.421)
MoCA-J (N=74)	-	0.794	0.030[ρ] (-0.195 – 0.253)
Executive function	-	0.729	-0.040[ρ] (-0.262 – 0.185)
Visuospatial function	-	0.913	0.012[ρ] (-0.213 – 0.235)
Language	-	0.896	-0.015[ρ] (-0.238 – 0.210)
Attention	-	0.754	-0.036[ρ] (-0.258 – 0.189)
Memory	-	0.960	0.006[ρ] (-0.218 – 0.229)
Orientation	-	0.986	-0.002[ρ] (-0.226 – 0.222)
TMT part A (N=74)	-	<0.001	-0.470[ρ] (-0.628 – -0.275)
TMT part B (N=72)	-	0.005	-0.314[ρ] (-0.503 – -0.097)
ΔTMT (N=72)	-	0.021	-0.262[ρ] (-0.459 – -0.040)
PHQ-9 (N=77)	-	0.161	-0.161[ρ] (-0.372 – 0.065)
AES-I (N=77)	-	0.872	0.019[ρ] (-0.206 – 0.242)

WSS indicates wall shear stress; SVD, small vessel disease; NIHSS, National Institutes of Health Stroke Scale; HT, hypertension; DL, dyslipidemia; DM, Diabetes Mellitus; CKD, chronic kidney disease; MRI, magnetic resonance imaging; IMT, intima-media thickness; PVH, periventricular hyperintensity; DSWMH, deep subcortical white matter hyperintensity; CMBs, cerebral microbleeds; EPVS, enlarged perivascular space; MMSE, Mini-Mental State Examination; MoCA-J, Montreal Cognitive Assessment-Japanese version; TMT, trail making test; PHQ-9, the Japanese version of the Patient Health Questionnaire-9; AES-I, the Japanese version of the Apathy Evaluation Scale Informant version; r, the Pearson correlation coefficient; ρ, Spearman rank correlation coefficient.

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Table 2. Analysis of factors associated with Total SVD score ≥ 3

	Univariate analysis			Multivariate analysis	
	SVD score ≥ 3 (N=50)	SVD score ≤ 2 (N=63)	*P* value	Odds ratio (95% CI)	*P* value
Age (per 1 year old)	75.8 ± 10.3	67.7 ± 12.3	<0.001	1.051 (1.011 – 1.093)	0.013
Body mass index (kg/m²)	23.2 ± 3.8	25.0 ± 4.6	0.030	-	-
Smoking	14 (28.0)	33 (52.4)	0.009	-	-
History of stroke	19 (38.0)	10 (15.9)	0.008	2.876 (1.115 – 7.417)	0.029
Hypertension	40 (80.0)	43 (68.3)	0.160	-	-
Diabetes mellitus	19 (38.0)	33 (52.4)	0.128	0.501 (0.214 – 1.173)	0.111
Chronic kidney injury	17 (34.0)	13 (20.6)	0.110	-	-
End-diastolic WSS (per 0.1 Pa)	0.25 ± 0.13	0.31 ± 0.13	0.020	0.998 (0.994 – 1.001)	0.249

In univariate analysis, each parameter of old age, lower body mass index, smoking, history of stroke, and lower WSS was associated with total SVD score ≥ 3. Variable selection was performed using the forward-backward stepwise selection method (threshold $p=0.20$) with variables with $p \leq 0.20$ in the univariate analysis, and logistic analysis was performed with WSS. Older age and history of stroke were associated with total SVD score ≥ 3. Lower WSS was not associated with SVD score ≥ 3 in the analysis of patients with first stroke (Supplemental Table 2). SVD indicates small vessel disease; WSS, wall shear stress; CI, confidence interval.

Table 3. Analysis of factors associated with enlarged perivascular space >10 in the basal ganglion

	Univariate analysis			Multivariate analysis	
	EPVS in BG >10 (N=50)	EPVS in BG ≤ 10 (N=63)	*P* value	Odds ratio (95% CI)	*P* value
Age (per 1 year old)	76.9 ± 10.5	66.9 ± 11.5	<0.001	1.071 (1.027 – 1.117)	0.002
Body mass index (kg/m²)	23.4 ± 3.7	24.9 ± 4.7	0.060	-	-
Habit drinking	16 (32.7)	32 (50.8)	0.054	-	-
Smoking	15 (30.0)	32 (50.8)	0.026	-	-
History of stroke	19 (38.0)	10 (15.9)	0.008	2.312 (0.840 – 6.366)	0.105
Hypertension	41 (82.0)	42 (66.7)	0.069	2.288 (0.794 – 6.590)	0.125
Chronic kidney injury	18 (36.0)	12 (19.21)	0.043	-	-
End-diastolic WSS (per 0.1 Pa)	0.23 ± 0.12	0.33 ± 0.13	<0.001	0.996 (0.993 – 0.9996)	0.030

In univariate analysis, older age, smoking, history of stroke, chronic kidney disease, and low WSS were associated with EPVS in the basal ganglia ≥ 10, respectively. Variable selection was performed using the forward-backward stepwise selection method (threshold $p=0.20$) with variables with $p \leq 0.20$ in univariate analysis, and logistic analysis was performed. Older age and lower WSS were factors associated with EPVS >10. WSS, wall shear stress; EPVS, enlarged perivascular space; BG, basal ganglia; CI, confidence interval.

Table 1), and the previously reported association between IMT and SVD imaging findings[28], was not detected. However, a slightly decreased WSS in the carotid artery without apparently detectable atherosclerosis changes was associated with SVD imaging findings and executive dysfunction in this study. Decreased carotid WSS is one of the factors contributing to arterial stiffness and increased IMT[1, 2, 23, 31]. We believe that the association between SVD findings and early atherosclerosis in the large vessels could be captured by the reduced WSS at an earlier stage than previously reported[28-30]. The negative correlation between WSS and SVD scores but the lack of correlation between IMT and SVD scores, and the absence of an increase in mean IMT in this study, suggest that lower WSS may reflect the early stage of LAA not detectable by IMT, which affected SVD via large and small artery crosstalk.

In this study, cognitive function tests such as MMSE and MoCA-J were not associated with end-diastolic WSS. Selection bias may have influenced the results because of the absence of higher brain function tests in patients with severe dementia or those discharged early from the hospital. However, WSS decline was associated with increased TMT. ⊿TMT, a more sensitive indicator of higher functions[32], also correlated with WSS, indicating the association of WSS with mild executive dysfunction in patients with early SVD but no cognitive decline. Since it has been reported that executive dysfunction is more pronounced in patients with vascular dementia[33], we hypothesized that our study was able to detect an association between early vascular cognitive dysfunction and WSS decline. Although a previous report showed

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a negative correlation between EPVS and executive functions[27], the present study did not show any such correlation with EPVS (not shown). Further large studies may be needed to clarify the associations between WSS, EPVS, and executive functions.

This study had some limitations. First, since this study is a single-center study of patients with acute lacunar infarction, it could have resulted in a selection bias. To generalize the results, it is necessary to perform WSS measurements at multiple centers, not limited to patients in the acute phase of cerebral infarction, which was difficult in this study due to medical resources and staffing requirements. Second, inter-rater reliability was not measured because of staff shortages. We were not able to evaluate the variability of WSS values in the same vessel by multiple examiners. The intra-rater error in multiple measurements of the same vessel by a single examiner is small, and we consider that the consistency of the measurement by a single examiner was maintained. Third, VFM-based WSS cannot be evaluated in calcified lesions because of the limitations of ultrasonography. Fortunately, none of the patients in this study had circumferential calcifications that precluded WSS. The color Doppler flow may not be able to properly delineate the blood flow in extremely slow-flowing or turbulently flowing vessels, and it may not be possible to measure WSS. The possibility of a measurement error remains in this study. Despite these limitations, WSS measurement using VFM is simpler than conventional WSS measurement and can be performed at the bedside.

Conclusion

This is the first report of an association between a lower WSS measured by vascular VFM and SVD imaging findings as well as cognitive impairment. Carotid WSS is negatively correlated with age and is associated with imaging findings of cerebral SVD, including EPVS in the basal ganglia, and with executive dysfunction. Decreased carotid WSS based on vascular VFM is associated with early cerebral SVD.

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

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Supplemental Table 1. Background factors, imaging findings, and cognitive function

Background factors and NIHSS (N=113)	
Age (years old)	71.3 ± 12.1
Male	67 (59.3)
Body mass index (kg/m^2)	24.2 ± 4.3
Premorbid mRS 0-1	88 (77.9)
Hypertension	83 (73.5)
Dyslipidemia	65 (57.5)
Diabetes mellitus	52 (46.0)
Chronic kidney disease	30 (26.6)
Stroke	29 (25.7)
Symptomatic lacunar infarction	12 (10.7)
Ischemic heart disease	7 (6.2)
Habit drinking	48 (42.9)
Smoking	47 (41.6)
Hospitalized NIHSS score (pt.)	2 [1-3]
Mean bilateral IMT (mm)	0.805 ± 0.160
Mean bilateral WSS in the whole cardiac phase (Pa)	0.520 ± 0.168
Mean bilateral WSS in the systolic phase (Pa)	0.855 ± 0.249
Mean bilateral WSS in the end-diastolic phase (Pa)	0.282 ± 0.133
Territory of acute lacunar infarction (N=113)	
Thalamus	19 (16.8)
Internal capsule	20 (17.7)
Corona radiata	22 (19.5)
Basal ganglia	9 (8.0)
Brain stem	31 (27.4)
Deep subcortical	12 (10.6)
SVD markers of head MRI (N=113)	
PVH Fazekas 3	22 (19.5)
DSWMH Fazekas 2-3	47 (41.6)
Old lacunar	82 (72.6)
Deep CMBs	46 (40.7)
EPVS in basal ganglia >10	50 (44.2)
Cognitive and psychological test	
MMSE (points, N=107)	28 [25 – 29] /30
Orientation	10 [9 – 10] /10
Memory	5 [5 – 6] /5
Attention	5 [2 – 5] /5
Language	8 [7 – 8] /8
Visuospatial	1 [1 – 1] /1
MoCA-J (points, N=91)	25 [20 – 27] /30
Executive	3 [2 – 4] /4
Visuospatial	4 [3 – 4] /4
Language	4 [4 – 5] /5
Attention	6 [5 – 6] /6
Memory	2 [0 – 3.8] /5
Orientation	6 [6 – 6] /6
TMT part A (sec, N=92)	45 [32 – 63.5]
TMT part B (sec, N=86)	117.5 [80.5 – 244.5]
ΔTMT (sec, N=86)	69.5 [44 – 166]
PHQ-9 (points, N=88)	5 [2 – 8]
AES-I (points, N=88)	29.5 [23 – 36]

N (%), median [Interquartile range]. ΔTMT is the difference between TMT part B and part A. NIHSS indicates the National Institutes of Health Stroke Scale; IMT, intima- media thickness; WSS, wall shear stress; mRS, modified Rankin Scale; SVD, small vessel disease; MRI, magnetic resonance imaging; PVH, periventricular hyperintensity; DSWMH, deep subcortical white matter hyperintensity; CMBs, cerebral microbleeds; EPVS, enlarged perivascular space; MMSE, Mini-Mental State Examination; MoCA-J, Montreal Cognitive Assessment-Japanese version; TMT, trail making test; PHQ-9, the Japanese version of the Patient Health Questionnaire-9; AES-I, the Japanese version of the Apathy Evaluation Scale Informant version.

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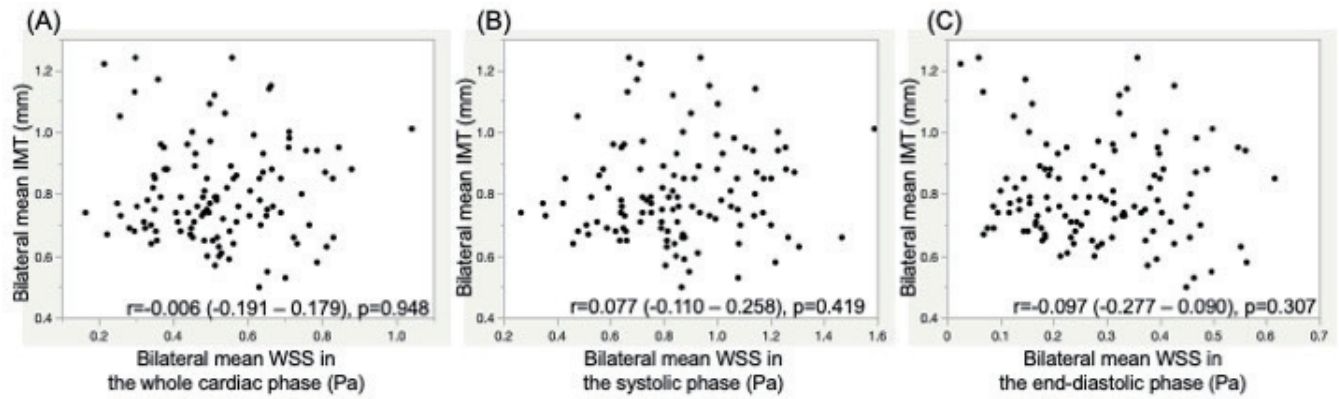
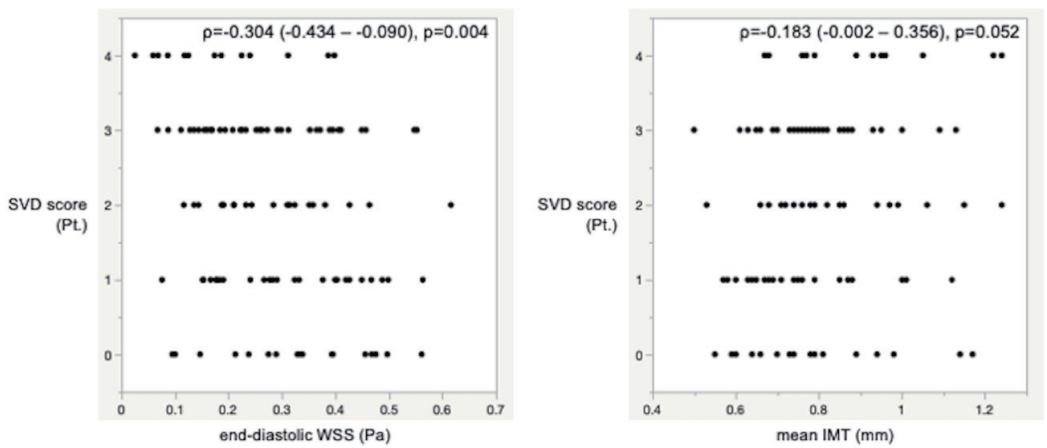


Supplemental Fig. 1. Scatter plots between IMT and WSS per phase of the cardiac cycle

(A) whole cardiac phase, (B) systolic phase, and (C) end-diastolic phase (r=-0.006 (95% CI -0.191 – 0.179), p=0.948; r=0.077 (-0.110 – 0.258), p=0.419; r=-0.097 (-0.277 – 0.090), p=0.307). Pearson's correlation coefficient (r) was used to analyze correlations.



Supplemental Fig. 2. Scatter plots of WSS and IMT against their respective SVD score

WSS and SVD scores were negatively correlated (ρ=-0.304 (95% CI: -0.434 – -0.090), p=0.004), but no significant correlation was found between IMT and SVD scores (ρ=-0.183 (95% CI: -0.002 – 0.356), p=0.052). WSS indicates wall shear stress; IMT, intimal medial thickness; SVD, small vessel disease; ρ, Spearman rank correlation coefficient; CI, confidence interval.

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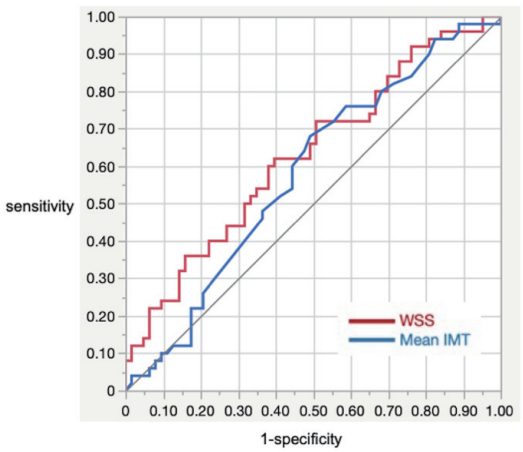

Supplemental Fig. 3. ROC curves for WSS and IMT in predicting total SVD score ≥ 3

The AUC of diastolic WSS was 0.629, versus the AUC of IMT was 0.579, which was not significantly different (p=0.503). The cutoff value of end-diastolic WSS for SVD score ≥ 3 was 0.272 (Pa), with a sensitivity of 62% and specificity of 60.3%. ROC indicates receiver operating characteristics; WSS, wall shear stress; IMT, intimal medial thickness; SVD, small vessel disease; AUC, areas under the curve.

Supplemental Table 2. Analysis of factors associated with SVD score ≥ 3 in patients with first- ever cerebral infarction

	Univariate analysis			Multivariate analysis	
	SVD score ≥ 3 (N=31)	SVD score ≤ 2 (N=53)	*P* value	Odds ratio (95% CI)	*P* value
Age (per 1 year old)	76.4 ± 11.4	66.9 ± 11.6	<0.001	1.077 (1.026 – 1.130)	<0.001
Body mass index (kg/m^2)	23.2 ± 4.3	25.4 ± 4.6	0.037	-	-
Smoking	8 (25.8)	28 (52.8)	0.022	-	-
Diabetes mellitus	19 (38.0)	33 (52.4)	0.128	-	-
Chronic kidney disease	11 (35.5)	9 (17.0)	0.067[§]	-	-
End-diastolic WSS (per 0.1 Pa)	0.270 ± 0.120	0.306 ± 0.132	0.218	1.000 (0.996 – 1.004)	0.895

Variable selection was performed using the forward-backward stepwise selection method (threshold p=0.20) with variables with $p \leq 0.20$ in univariate analysis, and logistic analysis was performed along with WSS. Chronic kidney disease was analyzed by Fisher's exact test ([§]). SVD indicates small vessel disease; WSS, wall shear stress; CI, confidence interval.

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